Bengt Jönsson
Katarina Steen Carlsson

The Value of New Medicines

SNS FÖRLAG

THE VALUE OF NEW MEDICINES

Bengt Jönsson
Katarina Steen Carlsson

The Value of New Medicines

SNS FÖRLAG

SNS Förlag
Box 5629
114 86 Stockholm
Telephone: 08-507 025 00
Fax: 08-507 025 45
info@sns.se
www.sns.se

SNS – Centre for Business and Policy Studies – is a non-partisan and independent non-profit organisation that contributes to decision makers in politics, public administration and business being able to make well-informed decisions based on science and factual analysis. This is done through research, meetings and the publication of books.

The Value of New Medicines
The Swedish title: *Värdet av läkemedel*
Bengt Jönsson and Katarina Steen Carlsson
Translated by Maria Dalby

© 2014 The authors and SNS Förlag
Graphic design: Allan Seppa
Print: Stockholm 2014

ISBN 978-91-86949-60-0

Contents

Preface 6
Summary 8
Glossary 17
Introduction 20

1. New medicines – the result of investment in research and development 24

2. Making decisions on new medicines – what actors control the market 44

3. The value and cost of new medicines for society, the health care system and the industry 66

4. Utilisation determines value – what can we learn from regional variation? 96

5. From clinical trials to clinical practice – evaluating the efficacy and safety of medicines 114

6. How should new medicines be paid for? 134

7. Summary, conclusions and recommendations 157

Authors 179
Reference group 180
Review 180
SNS research programme The Value of New Pharmaceuticals 181

Preface

The cost of medicines in Sweden is expected to increase in the future as a consequence of an ageing population and the introduction of new drugs that are both more effective and more expensive. Not only are people living longer, but the number of conditions that can be treated effectively also is increasing. In part, this is due to new and more specialised medicines, which also tend to be more expensive. Used appropriately, such new medicines will improve overall health and contribute to social welfare. At the same time, however, society's resources are limited making prioritising necessary. The question is how to set priorities and what standards to apply. The benefits and costs of a particular medicine may occur across social sectors and at different points in time. As a result, the perceived value of a drug also may differ considerably, depending on which perspective is adopted.

The efficient use of new medicines, then, requires answers to difficult questions: What value is gained by the individual patient, the health care system and society as a whole? How do decision-makers go about determining value? How should benefits be weighed against costs? What approach should health care providers take to new medicines? What can different stakeholders do to optimize the potential value of new medicines?

The government and county councils are developing initiatives such as a national medicines strategy and revised procedures for introducing new drugs to the market. The crucial question of the value of medicines – especially new medicines – has yet to be addressed, however, much less answered. Against this background, in 2011 SNS launched a research programme, The Value of New Pharmaceuticals, with the encouragement and, in many cases, financial support of key stakeholders. The objective was to help improve the decision-making process about medicines by focusing on value, including how best to define and assess it.

The research programme includes a feasibility study, eleven specialised studies, and this final report. Academic health economists and epidemiologists have conducted the studies, usually in collaboration with medical experts. The research programme is described in detail in the concluding section of this publication, which also contains a complete list of study reports (most of them in Swedish) all of which can be downloaded from www.sns.se/forskning.

Professor Bengt Jönsson and Dr Katarina Steen Carlsson have prepared this final report, which is intended to summarise the issues addressed in the research programme and highlight important policy issues.

The research programme has benefited from the support of a very committed reference group chaired by Michael Sohlman, former Executive Director of the Nobel Foundation, and including representatives of government ministries and agencies, county councils, the Swedish Pharmaceutical Society and the pharmaceutical industry in Sweden. (A list of the reference group's members appears at the end of the report.) The reference group's discussions have provided invaluable insight and information.

The study reports and the final report have been reviewed by independent experts. However, neither the reviewers nor the reference group assume any responsibility for the content of those studies: the respective study authors are entirely responsible for the analyses, conclusions and policy proposals in each study.

SNS's mandate is to commission and present research-based analyses addressing key issues in society. It has adopted no official position on the issues and topics the studies addressed.

Johanna Lind, MD, led the research programme until the end of January 2013. Her participation is hereby gratefully acknowledged, as are the contributions of everyone involved in the project that was published in November 2013.

The translation has been made possible thanks to funding from AstraZeneca.

We are grateful to Nancy Mattison for editing the translation of the original Swedish version.

Stockholm, June 2014
Göran Arvidsson
PhD, Associate Professor, Research Director, SNS

Summary

This is the final report of the SNS research programme, The Value of New Pharmaceuticals, which was intended to inform decision-making about the marketing and use of new medicines. The focus of the programme, and this report, is on the overall value to society of medicines, particularly new medicines.

Decisions made by regulatory authorities on the licensing and reimbursement of new medicines, as well as decisions on the use of medicines for individual patients, involve a level of uncertainty that can be considerable. This uncertainty is reflected in the selection and funding of therapies by payers and providers, in Sweden several independent government bodies and the county councils, and in the pharmaceutical industry's decision about the development, introduction and pricing of medicines.

The purpose of this book is to stimulate reflection and discussion about the potential impact of value-based medicines policies on the use of medicines.

The current focus on the value of medicines in policy-making is the results of a number of factors.

- Patent expiry produces generic versions of innovative medicines that are available at much lower prices. As a result, any new medicine entering the marketing today must not only offer an advantage over existing therapy, but also be priced much more competitively than in the past.
- New drug development is becoming increasingly expensive; the current average cost of developing a new medicine exceeds 10 billion SEK (1.1 billion EUR).
- New medicines unquestionably have provided value for patients, health care providers and society as a whole. However, the health care system's ability to pay has not increased at the same rate as the costs of development.

- The pharmaceutical industry has become increasingly dependent on public health insurance and health care systems to pay for the new medicines it produces. Direct payments by patients account for a very small proportion.
- Entering the market is becoming more difficult for new medicines. More resources are required to document value to support market entry.
- Decisions about the pricing and use of medicines are increasingly based on formal assessments that weigh value against costs.
- The increasing cost of developing new medicines has resulted in a high degree of concentration within the pharmaceutical industry, with fewer and larger firms involved in drug development.
- Changes in the structure of the industry globally affect the pharmaceutical industry in Sweden. The export of pharmaceutical products from Sweden still exceeds imports, but the surplus has declined in recent years.
- Health system funding and the rate of uptake of new medicines in Sweden continue to make it an attractive location for developing and producing new medicines.

The value of a medicine can be summarised as the utility of providing health benefits to patients combined with productivity gains from increased ability to work. This cannot be measured or evaluated, however, without knowing how medicines are used because the value of any medicine, new or old, is created at the point of use. Assessing actual value, then, requires understanding both use in real-life clinical practice and the medicine's impact on health and welfare at the level of both the individual and society.

Decision-making

The criteria for assessing the value of medicines have changed over time. The efficacy and safety assessment made by the Medical Products Agency (LV) in Sweden (and its counterparts in other countries) determines whether a new product can be marketed at all. The Dental and Pharmaceutical Benefits Agency (TLV) assesses cost effectiveness and decides whether the medicine is eligible for reimbursement. Both assessments have become increasingly stringent and extensive as advances

in science allow more questions to be asked -- and more evidence to be collected and required. Other Swedish agencies that issue guidance and perform assessments also need data to document the clinical benefits of new health care technologies.

The most important consumer of information about new medicines today is not the patient or physician, but the health care system itself. To achieve efficiency and equity in the health care system, health care providers need to know which technologies will be the most therapeutically effective and most cost effective in clinical practice. Companies that develop new medicines also require data to help determine which new medicines health care providers are most likely to accept for reimbursement.

The roles and responsibilities of the Swedish government and the county councils in making decisions about medicines need restructuring. For example, the current split of the medicines market into separate markets for ambulatory and hospital medicines, with separate funding and decision-making procedures, no longer is appropriate. Government price regulation for ambulatory medicines is not functional now that county councils are responsible for payment and make the decisions about use, and as differential pricing by indication becomes increasingly important. Different rules for pricing and funding, that depend on where a medicine is used, artificially segments the market. Changing this would not require changing the co-payment system for prescribed medicines, but would require changing the pharmacy payment system.

Focusing on the patient

Could greater payer influence over the availability and use of medicines and other therapeutic options threaten the focus on the patient in clinical practice? Although this is possible, focusing on improvements in health care outcomes is in the patient's interest as well. Basing decision on cost effectiveness should ensure that resources are targeted to maximise health gains. Measuring and evaluating results based on outcomes that are relevant to patients clearly captures the patient's perspective. Basing decisions on objective and verifiable information, and making those decisions transparent, are essential to ensuring equitable access to new medicines for all patients.

Determining the value of a medicine

The principal prerequisite for assessing value is demonstrating treatment outcome. Medicines that affect survival can be assessed in terms of life-years gained. If the outcome is to include improvement in quality of life, quality-adjusted life-years (QALY) can be used to measure health gains. QALYs recognise that the quality of each life-year gained will vary, but QALYs also can capture improvements that result, for example, from fewer side effects, improved functioning, or reduced pain or anxiety. The primary advantage of this measure is that it allows comparison of health gains across treatments and diseases.

Medicines also may produce economic gains by reducing sickness absenteeism and early retirement due to illness. By reducing mortality in the working age population, medicines also may increase productivity. These societal gains, however, are offset by the increased cost of supporting people who live beyond working age. Finally, medicines also can help reduce the costs of other health care interventions.

Studies of the value of innovative medicines show that the most important benefit is improved quality of life and increased longevity, with breast cancers as an example. With respect to productivity, the greatest gains are from successfully treating conditions that affect younger people, such as type 1 diabetes and rheumatoid arthritis. Gains from reduced health care costs are particularly pronounced when a drug or vaccine cures or prevents a condition that otherwise would require prolonged or expensive treatment. A significant share of the value of innovative medicines is realised after patent expiry when the drug is no longer 'new' – for example, in the treatment of HIV/AIDS or cardiovascular disease.

The studies presented in chapter 3 show that new medicines can generate value that far exceeds the costs. Health economic analyses of the treatment of breast cancer, HIV/AIDS and hyperlipidaemia, for example, show that the amounts involved can reach into the billions over time.

Quality registries

For years, data on patients treated with a range of interventions have been recorded in Swedish quality registries – for example, surgery such as hip arthroplasty and medical therapies such as TNF-inhibitors for the

treatment of rheumatoid arthritis. They are called "quality" registers in Sweden, since a specific objective for collecting the data has been that they should contribute to improvements in quality of care and outcome. These registries often are referred to as 'gold mines' of information on diagnostic and therapeutic activities in the health care system and their impact on outcomes. Closer analysis, however, shows that this gold mine remains largely untapped and that the 'gold' must be refined to be useful and valuable.

The most important weaknesses of quality registries include a lack of information that allows assessment of the actual value of medical interventions, such as data on their impact on patient functioning and quality of life, and the level of health care resources consumed by different treatments. On the other hand, registries contain a great deal of detailed information that is important for improving health care services. Registry data can be used as the basis for assessments of value, however, only if they include information on treatments and outcomes for all patients, with no exceptions.

Value-based payment

Decision-making on medicines involves, amongst other factors, balancing expected value against cost. Because patients account for a declining proportion of the direct payment for medicines, this balancing act predominantly takes place within the broader health care system. This means that the public sector's willingness to pay for medicines is increasingly governed – or should be governed – by information on their value.

With the public sector being the principal decision-maker and payer for new and expensive medicines, payment is a key issue. The principle of value-based pricing, or rather value-based payment, has attracted interest. Uniform pricing of a new medicine is not a rational approach since the medicine's value will vary depending on how and where it is used. Nor is it a rational approach to set a high price per unit because this will prevent use of the medicine by those who wish to pay a lower price, but still contribute to the sunk fixed costs for R&D. Ability and willingness to pay will vary, for example, across countries and prices always have differed by type of customer in pharmaceutical markets. Events such as the emergence of the EU single market and appearance of international reference pricing systems did lead to a brief

period during which pharmaceutical companies attempted uniform international pricing.

The uniform pricing system is on its way out. In France, negotiations on price and volume have been part of the introduction and funding of new medicines for a long time. In England, recommended use is increasingly based on agreements on non-disclosed discounts off the list price. In Germany, decisions to include new medicines in the public reimbursement scheme now are to be followed by price negotiations. Extensive discounting of the approved list price has long been negotiated and required in public programmes in the United States.

The time has come for Sweden to adapt to the new reality and grant the health care system a wider remit to make flexible arrangements with pharmaceutical companies in order to improve patient access to new medicines in the face of limited resources. However, flexible pricing, or rather, agreements on pricing based on the number of patients receiving treatment, will not in itself resolve the issue of uncertainty about the value of medicines. For this reason, agreements increasingly will link a portion of the payment to observed treatment outcomes.

Regional differences

Regional variations in the utilisation of medicines and other health care technologies have been observed and debated for a long time. This has been perceived mainly as an equity problem; differences in treatment outcome also have been assumed to exist as a result. But this is not always the case, making it important to clarify both the causes and consequences of regional differences.

The observed variation is largely attributable to traditional local practice patterns. Whether and why this might be true requires analyses of how these local practice patterns have developed, whether they are based on scientific evidence, and how they can be altered.

Variations are more likely to be viewed as acceptable when indications and treatment outcomes are not well defined. Differences in utilisation are less acceptable if the indications and treatment outcomes are well defined or if the cost of treatment is high. One example is the treatment of breast cancer. The development of more precise indications and increasingly accurate prognoses about outcome have reduced the level of uncertainty. Trastuzumab, for example, is effective against

breast cancer in patients with a certain genetic marker (HER-2) and its effectiveness can be measured objectively. It is possible to determine whether all female patients were tested for that genetic marker, what the test results showed, and whether or not each patient was treated appropriately. Regional differences then can be measured and analysed, and the result used to inform policies aimed at reducing underuse or overuse. Differences also may exist in the duration of a specific treatment or, more commonly, duration before switching to another treatment. It is important that such variations also be documented and analysed to provide the information necessary for decisions that can optimise the value of the drug.

Assessment of whether regional differences are consistent with the criteria for a cost effective and equitable health care system requires patient-level data. Once such relevant data are available, it also will be possible to determine whether an observed regional variation has led to differences in outcomes. Such studies require additional data for description and analysis of treatment outcomes over time at the level of the individual patient. This applies to medicines as well as other health care treatment options.

National and regional level

Swedish health care policy is characterised by tension between centralised and decentralised decision-making, or in simpler terms, between the government and county councils. Policies will be most successful when the government and county councils are in tune with one another.

National practice guidelines allow the state to influence the use of health care technologies in the health care system. However, questions may arise about these guidelines because they are primarily based on results from international clinical studies, not on data from the Swedish health care setting. A further issue, suggested by observed regional variations, is poor adherence to the guidelines and lack of data for relevant follow up of the impact of the guidelines.

County councils will face a new situation as demands increase both for information about the value of new medicines and for greater transparency of decisions based on this information. Procedures and capabilities need to be developed to meet these new challenges. More importantly, to support objective and verifiable assessment of the value

of treatments at a population level, systematic documentation will be required for patients, treatments and outcomes. Developing payment systems that reward high-value interventions is also an important element of policy to support more efficient resource allocation in health care.

At present, medicines are partly financed by the government. To promote the use of innovative medicines, the state could use some of this funding to pay for them for a limited time. Such funding of innovative medicines outside regular county council budgets would facilitate and encourage their use. The impact on utilisation could be considerable and would certainly increase costs beyond current levels. This increase in expenditure, however, must be weighed against the benefits of the new medicines, which makes analyses of actual use important. Such information is essential to supporting decisions on the optimal utilisation of new medicines in the health care system.

Innovation and use – critical issues for Swedish health care providers and industry

The last ten years have seen Swedish pharmaceutical exports stagnate and Swedish participation in clinical studies evaluating new medicines decline. At the same time, the health care system is finding it increasingly challenging to remain at the international forefront in the use and assessment of new medicines.

Asking what can be done to improve Sweden's position in this sector of society is a legitimate question, since it is of crucial importance for both the future development of the health care sector and for the Swedish economy. Our observations and analyses, as well as those carried out in other countries, show that the health care sector plays a key role in any strategy for improving Sweden's position. The role of the health care system in funding innovative medicines, and thus determining and paying for their value, is of strategic importance for the future. The primary significance is not that using medicines generates revenues for pharmaceutical companies, but that paying for the appropriate use of medicines creates incentives for dynamic efficiency.

Information on the impact of new medicines in real-life clinical practice is therefore becoming an increasingly important part of the drug development process. Contributing to the development of this

evidence can create a strategic advantage for Sweden. The same data are necessary to guide modifications in the health care system and make it more efficient. Investments in health care information technology thus may serve dual purposes.

Proposals for action

What can be done to create a better framework for the development, introduction and evaluation of new drugs? We have devised five proposals, described in detail in chapter 7.

- Health care providers should be increasingly responsible for recording and compiling real-life clinical practice data to support decision-making on funding (price) and use of new medicines and other health care technologies.
- Analyses of regional variation increasingly should be based on patient-level data, which will allow research into the causes and consequences of overuse and underuse.
- Decisions on the funding (price) and utilisation of new medicines based on factors such as cost-effectiveness assessments should apply to all medicines, whether they are used in hospitals or prescribed in the ambulatory setting under the national pharmaceutical benefits scheme. In the longer term, such assessments should be extended to include diagnostics and other health care technologies that are frequently used with, or instead of, innovative medicines.
- Pharmaceutical price control should be abolished. State funding of the national pharmaceutical benefits scheme should be replaced with a budget for funding innovative medicines, diagnostics and other treatments based on cost-effectiveness assessments carried out by the TLV.
- Resources for assessment and introduction of innovative medicines (and other health care technologies) should be coordinated at the national level. County councils should develop capabilities for assessment, implementation and follow up.

Glossary

Agency for Healthcare Research and Quality (AHRQ) – an agency within the US Department of Health and Human Services tasked with improving quality, safety, efficiency, and efficacy in the health care system. Website www.ahrq.gov.

ARTIS – Antirheumatic Treatment in Sweden, a quality registry that records and publishes information on treatments and side effects relating to biological therapies on behalf of the Swedish Society for Rheumatology. Website www.svenskreumatologi.se/artis-gruppen-antireumatisk-terapi-i-sverige.

CER – Comparative effectiveness research is research on the relative effectiveness of health care interventions.

CMT – Centre for Medical Technology Assessment at Linköping University, a research centre tasked with developing methodologies, disseminating research findings, and assessing health care methodologies and procedures with respect to their medical, social, economic, and ethical impact. Website under www.imh.liu.se/.

DRG – diagnosis-related groups, a classification system used for the classification and reimbursement of health care interventions in secondary care.

EMA – European Medicines Agency, an agency within the European Commission located in London and responsible for conducting scientific assessments of medicines developed by pharmaceutical companies for use within the European Union. Website www.ema.europa.eu/ema/.

Eudravigilance – a network for handling the reporting and evaluation of suspected adverse events prior to and after marketing authorisation. Website under www.ema.europa.eu/ema/.

EUnetHTA – a network of national and regional HTA bodies in the EU countries, countries within the European Economic Area, EU candidate countries, and non-profit organisations. The aim is to promote collaboration among European HTA bodies. Website www.eunethta.eu.

Pharmacovigilance – information and activities relating to the identification, assessment, understanding, and prevention of drug-related injuries and disorders

FDA – Food and Drug Administration, an agency within the US Department of Health and Human Services with a broad regulatory remit that covers: the safety, efficacy and quality of drugs, vaccines and other biological agents and

medical devices, including those using radiation; foods and dietary supplements; cosmetics; animal health; and tobacco products. Website www.fda.gov.

HTA – health technology assessment, evaluation of the medical, social, ethical, and financial impact of the development, dissemination and use of health care technologies

Individualised health care – personalised medicine, precision medicine, stratified medicine, use of biomarkers that allow treatment to be tailored to the individual patient

Innovative medicine – a new original medicine that offers improved therapeutic efficacy and greater patient benefit compared with existing treatment options

ISPOR – The International Society for Pharmacoeconomics and Outcomes Research, an international research group focused on health economics and health outcomes evaluation that translates scientific research into information for decision-makers in the health care sector. Website www.ispor.org.

CML – chronic myeloid leukaemia

Life sciences – scientific research on living organisms, from microorganisms to human subjects, including related topics such as bioethics and technology development

LV – Läkemedelsverket (see MPA)

LYG – life-years gained, an outcome measure used in health-economic evaluations

MS – multiple sclerosis

NHS – National Health Service, the national health care system in the United Kingdom. Website www.nhs.uk.

MPA – Medical Products Agency (Läkemedelsverket). Website http://www.lakemedelsverket.se

NICE – National Institute for Health and Care Excellence, the British government agency that issues recommendations for reimbursement and use of medical technologies by the NHS in England and Wales intended to ensure quality and value for money. Website www.nice.org.uk.

New chemical entity (NCE) – new chemical or biological compound used to prevent, diagnose, alleviate or cure illness or symptoms of disease

Orphan drugs – medicines used for the treatment of rare conditions affecting less than 1/10,000 individuals (EU definition) or less than 200,000 (US definition)

P4P – pay for performance, health care provider remuneration based on predefined quality targets or treatment outcomes

Price discrimination – a microeconomics term, when a seller charges different buyers different prices for an identical product or service

PsoReg – quality registry for moderate and severe psoriasis eligible for systemic treatment. Website www.kvalitetsregister.se/register/ovriga_omraden/psoreg.

QALY – quality-adjusted life-year

RA – rheumatoid arthritis

RCT – randomised controlled trial, experimental clinical research study that involves human subjects

Reference pricing – when the price of a product or service is based on the price charged in another market, or on a (weighted) average of prices in other markets

Relative effectiveness – the extent to which a new intervention, such as a new medicine, is superior to existing alternative treatments available in clinical practice

SBU – Swedish Council on Health Technology Assessment (Statens beredning för medicinsk utvärdering). Website www.sbu.se.

SSATG – Swedish Arthritis Treatment Group register, an early registry for monitoring the use of biological therapies in Skåne county. Now part of the ARTIS registry (see above).

Stratified medicine – see individualised health care

STURE registry – registry for monitoring the use of TNF-inhibitor therapies in Stockholm, now part of the ARTIS registry (see above)

The thalidomide disaster – a little over 50 years ago, around a hundred Swedish children were born with birth defects after their mothers used a medicine known as thalidomide (branded Neurosedyn in Sweden) during pregnancy. In Germany, 10,000 children were affected.

TLV – the Swedish Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket). Website www.tlv.se.

TNF inhibitors – inhibitors of tumour necrosis factor alpha, a ubiquitous cytokine in the cells of the immune system

Translational research – research that aims to speed up the translation of the results of basic research into clinical use to improve outcomes.

UKPDS study – United Kingdom Prospective Diabetes Study, a research study that has been monitoring patients treated for type-2 diabetes since the 1970s. Website www.dtu.ox.ac.uk/ukpds_trial.

VBP – Value-based pricing – a method of pricing medicines and other products/services based on the anticipated benefit to the patient/consumer

Value-based payment – bundled payments, remuneration for a combination of interventions during an episode of care. This can be based on either costs or value.

Introduction

The cost of a medicine is fairly easy to determine. But how much is it actually worth? Knowing the answer to this question is the key to the rational use of medicines. Is the benefit of the medicine greater than that of existing treatment options? When and how should the medicine be used? Is it worth its price for the payer? Should its use be subsidised by the government? Will health care providers be willing to pay a price high enough to make its development profitable for the company and encourage future investments in development of new drugs? These are difficult questions with no simple answers. The situation is further complicated by the fact that the actual value of a medicine to society often is realised only long after the costs of its development have been incurred. In addition, the patient who benefits from a medicine rarely pays more than a very small proportion of the medicine's actual cost, if anything at all.

In order for a new medicine to receive regulatory approval that allows it be used by health care providers, it must be assessed for efficacy and safety. Such assessments are based predominantly on the results of clinical trials, which typically are limited to a few thousand patients in controlled settings, lasting months. What happens when these medicines then are used in actual clinical practice by a wide range of patients and perhaps for a prolonged period of time? What value may this generate for the individual patient, the health care system, and society as a whole?

We know surprisingly little about what happens once a medicine is

available for use in clinical practice. As a result, many decisions about the use of medicines are supported by insufficient information. We need more information about the real value of new medicines for a number of purposes: for government decisions about whether to approve the use of new medicines or discontinue use of older ones; for national decisions about whether to include a medicine in the national pharmaceutical benefits scheme; for county council treatment guidelines and budget decisions; for guiding doctors (and patients) in choosing between medicines or between a medicine and an alternative intervention, and so on.

The purpose of this book is to stimulate thought and discussion about the potential implications of value-based drug policy and practice. It provides examples to illustrate how knowledge about the value of medicines can support decision-making about medicines – by governments, as part of national pharmaceutical policy, in regulatory decisions, for county council treatment recommendations, and in routine clinical practice – but also in science and industrial policy decisions and within the pharmaceutical industry. The task is far too great to allow us to provide complete answers here. Our primary objective, then, is to contribute to answering these questions by provoking thought, suggesting what is possible, and explaining the importance of the challenge.

Understanding the benefits medicines can provide is very important to the rational use of drugs. The degree of benefit, or value, is determined by the effect of the medicine on individual health and welfare at the point of use. This frequently can be determined only over time and after use by a large number of patients, which means that thorough follow-up studies often are required. However, a number of important decisions must be made long before.

Decision-making by regulatory authorities on the introduction and reimbursement of new medicines, as well as decisions about the use of medicines in individual patients, thus involve uncertainty, which can be considerable. This lack of complete information is reflected in decisions about choice of medicine by health care providers, in decisions by county councils about which medicines to pay for, and in decisions by the pharmaceutical industry about which compounds to develop and what prices to ask.

Medical research and clinical studies provide vital, albeit incomplete, information about efficacy and safety, but reveal little about the relative

effectiveness of an intervention compared to alternative treatments or whether the value of a medicine outweighs its cost. Not surprisingly, then, the rate of introduction and the use of new medicines (and some older ones) vary substantially both across and within countries. Appropriate and inappropriate differences in use exist between Sweden and other countries, and within Sweden across regions, clinics, and individual prescribers.

Chapters 1–6 follow a themed outline and are based on the different reports for the SNS research programme, The Value of New Pharmaceuticals; other relevant published studies; and our many conversations and discussions with experts, some who were involved in the project and some who were not. This publication is neither a summary of the reports commissioned for the SNS research programme nor a complete research overview. It is intended to inform policy discussions and policy development.

Chapter 1 outlines the requirements for new drug development, the investment involved, and the continuing changes in the process of drug development and regulation. It discusses the numerous decisions made by a broad range of regional, national and international stakeholders prior to the introduction of a new medicine. Chapter 2 identifies the primary stakeholders and describes the evidence base required for decision-making, highlighting the critical role of the health care system in decisions about the use of new medicines. Chapter 3 provides examples that illustrate the value of medicines based on actual health gains, the impact of medicines on productivity, implications for health care resource utilisation, and the cost to society of using new medicines. The examples mainly involve highly successful new medicines, but examples of those that have failed to meet expectations also are included.

Chapter 4 is based on the assumption that the value of a new medicine is determined by how it is used in actual clinical practice. We use results from SNS studies showing variations in use to argue that there is much to learn from regional variation including its extent, its underlying causes, as well as the potential societal gains from reducing any unwarranted variation. Chapter 5 highlights the importance of analysing the value generated by the use of new medicines in real-life clinical practice. It notes that studies on the relative effectiveness of new medicines constitute an essential evidence base for decisions by pay-

ers. Although such comparative studies can face a number of practical challenges, they nevertheless can add to the evidence base about the best use of new medicines and help reduce the uncertainty about their value. Chapter 6 discusses the financing of the use medicines and current trends for funding the use of new medicines. A set of principles for the financing of new medicines are devised using a comparison between public financing for the construction of a new bridge and the development of a new medicine.

Chapter 7 consists of two parts. Part one is a self-contained summary of the main messages delivered in the preceding chapters; part two comprises the authors' policy conclusions.

1. New medicines – the result of investment in research and development

New medicines are the result of investment in research and development (R&D) that generate new insights into diseases and how to treat them. Such investment is made by both the public and the private sector. The main product of these investments is knowledge, which occasionally takes the form of a new medicine, but may also contribute to information about appropriate use. Knowledge is a public good in the sense that once it has been produced and become widely available, it is available to everyone and its worth is not reduced by its use. To generate incentives for developing new medicines and to preserve value, knowledge may be kept confidential for a period of time under patent protection (exclusivity) laws.

Creating optimal incentives for the development of new drugs is one of the most complex challenges for economic and health care policy makers at both the national and international levels. New medicines have become global products, but their value differs by country and health care system.

History

The development of new medicines based on biomedical research is a relatively new phenomenon. The ethical pharmaceutical industry as we know it did not emerge until about fifty years ago, in the aftermath of the thalidomide disaster. Until then, drug development had been largely unregulated and the share of public payment for medicines was

small. Tighter regulation that required documentation of efficacy and safety prior to introducing new medicines produced a brief drop in the number of new medicines reaching the market. However, rather than stifling drug development as some had feared, this marked the beginning a drug development process that has resulted in the introduction of hundreds of new medicines with considerable benefits for patients and health care providers and payers. Calculations of the value of some of these medicines are shown in detail in Chapter 3.

The definition of a 'new' medicine is not straightforward. The regulatory authorities that license medicines for use consider a new medicine to be one that is a new chemical or biological entity. Figure 1.1 shows the average annual number of new medicines approved during the five-year periods between 1990 and 2010. It shows that the number decreased by about 25% by 2005–2009. This decline is comparable to that seen in the 1960s following the implementation of stricter drug control regulations in the US. During the period 2010–2012 the US Food and Drug

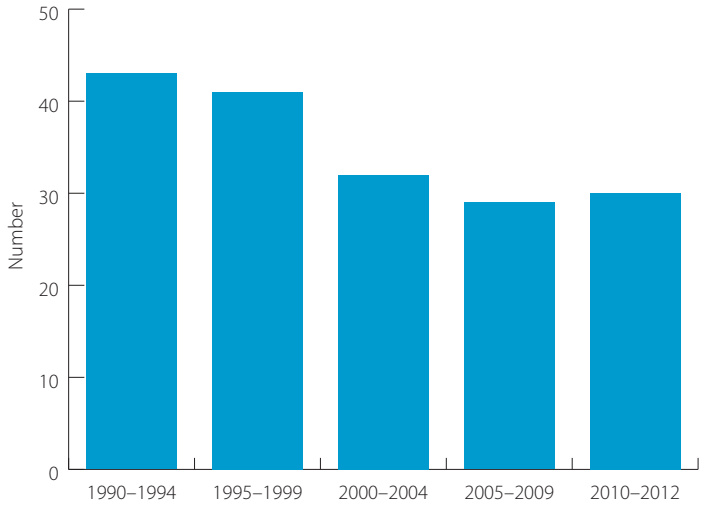


Figure 1.1 Global approval rate of new medicines 1990–2012. Average for each period. Source: Mestre-Ferrandiz et al (2012) for 1990–2009, authors' own estimates for 2010–2012.

Administration (FDA) and the European Medicines Agency (EMA) respectively approved on average 30 and 22 new medicines annually. In 2012 the FDA approved 39 new medicines, which was the highest number in 13 years, although this does not necessarily indicate a trend towards increasing numbers of yearly approvals.

Drug development also can be characterised by the level of financial investment in R&D. Annual investment increased between 1990 and 2011, from 8 billion to 27 billion EUR in Europe and from 7 billion to 40 billion USD in the US. However, the rate of increase in R&D investment has gradually declined from approximately 10% annually in the late 1990s to just over 5% during the early- to mid-2000s, and to between 2% and 3% since.

Figure 1.2 shows that total R&D expenditure by the pharmaceutical industry increased from 20 billion USD in 1990 to more than 90 billion USD in 2010. As the number of new drugs fell from 40 to 30 in the same period, this means the cost of each new medicine increased from 0.5 to 3 billion USD.

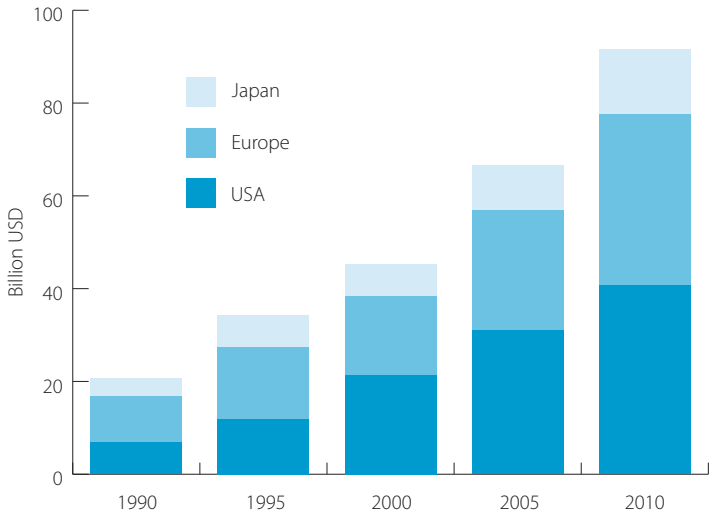


Figure 1.2 Pharmaceutical industry annual R&D expenditure 1990–2010, in billions of USD. Source: Authors' own estimate based on European Federation of Pharmaceutical Industries and Associations (EFPIA) data (2012).

As is also evident from the Figure 1.2, investment increased at a slower rate in Europe, which lead to a gradual decline in its share of the global market. The US, Europe and Japan together account for 80% of the global pharmaceutical market and account for nearly all investment in R&D.

Detailed estimates of the cost of taking a new medicine to market shows a rate of increase similar to those noted above, although differences in methodology preclude direct comparisons. The most recent cost estimate is approximately 1.5 billion USD, equivalent to just over 10 billion SEK (Mestre-Ferrandiz et al, 2012). The reasons behind increasing costs and declining productivity have been discussed at length (Boston Consulting Group, 2011; Paul et al, 2010). Mentioned most often are more stringent regulatory requirements and the increasing cost of conducting clinical studies. No matter what the reason, however, new medicines are increasingly expensive, reflecting the increasing cost of R&D for the pharmaceutical industry.

How did an innovative pharmaceutical industry develop? The most important explanation, of course, is that scientific progress has generated sufficient knowledge. Many new medicines are based on biomedical discoveries about the mechanisms of disease that have provided the scientific basis for developing a new medicine. A common explanation for the perceived decline in productivity in the pharmaceutical industry is that existing knowledge is being exhausted and not enough new knowledge is being created.

A second factor was economic conditions favourable for investment in basic science, scientific research education, and expansion of the health care system. Each of these three has been crucial to the success of the pharmaceutical industry. A high level of investment has been encouraged by macroeconomic conditions that have supported high rates of economic growth, including a young, economically-productive population. The US and Western Europe have been the principal markets for new medicines because of their high economic growth rates and their willingness to spend substantial amounts on health care.

A third factor behind the development of the innovative pharmaceutical industry was what may be classified loosely as organisational advances. Pharmaceutical companies successfully integrated different fields of scientific knowledge in the R&D process and invested in

marketing to ensure successful commercialisation.

A fourth success factor in the development of the pharmaceutical industry was a cooperative relationship between the pharmaceutical industry and the health care system, both in terms of clinical research and in introducing new products. Regulatory authorities and pharmaceutical companies worked together to formulate workable requirements for the design and evaluation of pivotal clinical studies and to define criteria for market authorisation.

Sweden's role

Sweden has been an important actor in the development of the pharmaceutical industry. Economic growth was exceptionally strong during the 1950s and 1960s and although it slowed in the 1970s, Sweden by then had established itself as one of the world's wealthiest nations. Its investments in biomedical research were on a par with other wealthy nations. Investment in higher education and biomedical research created the pool of qualified individuals necessary for successful drug R&D. Other important factors included the expansion of the health care services, a vast increase in the number of doctors, highly competent regulatory authorities, and a positive relationship between the pharmaceutical industry and the health care system.

It is thus not surprising that the Swedish pharmaceutical industry became a vital part of the Swedish economy. A number of internationally successful products have been developed by the Swedish pharmaceutical industry.

Figure 1.3 shows trends in Swedish pharmaceutical exports and imports. Sweden maintains a highly positive trade balance in medicines, although a gradual decline has occurred since 2006, from 40 billion SEK to 26 billion SEK in 2012. Exports in recent years have declined, especially to countries within the EU. Swedish pharmaceutical companies invest around 10 billion SEK annually in R&D; of this amount, around 6 billion is spent on clinical research. The number of clinical research studies has declined in recent years, however, and the cost of clinical research has stagnated. This negative trend in what has been described as a 'growth industry for the future' in the Swedish economy was analysed in an earlier SNS report, Medicine for Sweden,

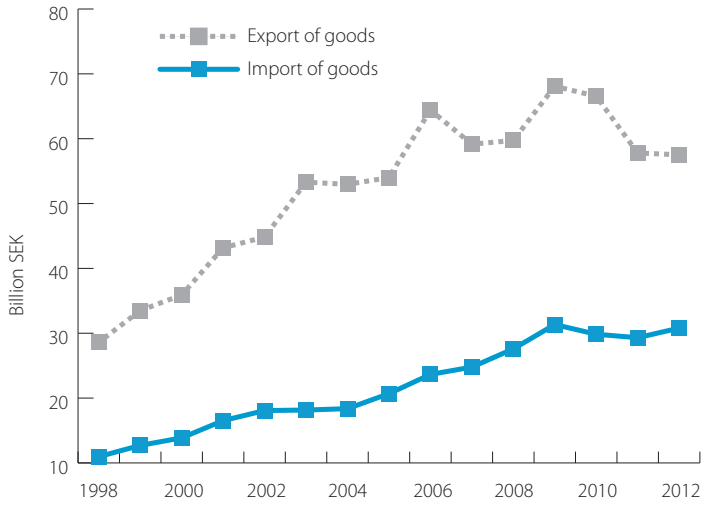


Figure 1.3 Annual Swedish imports and exports of medical and pharmaceutical products, billions of SEK annually. Source: Statistics Sweden (www.scb.se/HA0201). Classification SITC 54.

Arvidsson et al (2007). The measures taken to date have not been able to stop this decline. Sweden may rely on new medicines developed in other countries, of course, but economic growth in other parts of the economy will be necessary to finance their purchase.

It is highly advantageous for any country to be successful in the type of business that is expanding at an international level, employs highly qualified staff, and pays comparatively high wages. The pharmaceutical industry is such a business and is a core component in the interplay between economic growth, health care development and public health.

WHAT HAS BEEN DONE IN SWEDEN IN RECENT YEARS TO STRENGTHEN THE BIOMEDICAL BUSINESS SECTOR?

The national innovation strategy – a government initiative to enhance innovative capabilities within the public sector

The national drug strategy – a national procedure that includes managed drug entry

The research and innovation law – increased government expenditures for the life sciences and an institute for process development
The Swedish Research Council and Karolinska Institute – investments in bio banks (BBMRI) and chemical biology (CBCS)
Science-for-life lab, with an annual turnover of 1 billion SEK, a collaboration between the Swedish Royal Institute of Technology (KTH), Uppsala University, Stockholm University and the Karolinska Institute

What is the problem?

The development of an innovative pharmaceutical industry is a success story in which Sweden has played a central role. However, the current debate, both in Sweden and internationally, focuses heavily on emerging problems and the perceived need for a new 'model of success'. The problems cannot be described simply because, like success, they depend on a number of interrelated factors.

One important factor is diminishing productivity and the consequent increase in the cost of taking a new medicine to market. A common explanation is that investment in new drug development increasingly focuses on potentially high-return indications such as cancer and diseases of the brain, areas that also involve a higher degree of risk of failure (see Pammolli and Riccaboni, 2007, and Pammolli et al, 2011). Other, more established therapeutic areas such as cardiovascular diseases, where the chances of success may be greater, offer lower returns on investment because a large number of highly effective medicines at low cost already are available. Previous successes thus mean that renewed success can be achieved only at ever-increasing cost. This puts the question of the value of a new medicine right at the heart of the argument: the increasing cost of developing new medicines must be accompanied by increasing value (and revenue) to justify the investment.

An important incentive for new drug development is patent protection to ensure a higher price and predictable income for a known period of time. Although patent protection does provide a vital incentive for innovation, it may not be enough.

Today, opportunities for collaboration between stakeholders during the innovation process constitute an additional crucial success factor, and the relative decline of the European pharmaceutical industry has indeed

been explained by the lack of 'clusters' that encourage innovation. Some also question whether patents can steer innovation towards valuable medicines – patentable medicines are not necessarily valuable. New models for collaboration known as 'open innovation' are being explored to stimulate innovation, including collaboration between companies and the public sector, and collaboration between companies.

Scientific progress brings new opportunities, but also new challenges. In the past, drug development relied on screening a large number of compounds to identify a handful with the potential for becoming successful medicines. This 'quantitative model' now has been abandoned in favour of a model based on vastly more detailed knowledge about the indication and the potential targets before developing a treatment. This allows more accurate estimation of efficacy and safety, and uses genetic markers to determine which patients are most likely to benefit from the treatment. Greater awareness of the value of measuring and assessing biological differences between patients is growing and that may influence choice of therapy.

The trend towards individualised care (personalised medicine, precision medicine, stratified medicine) means patient populations for a particular indication will become both better defined and smaller. In addition, health care providers will incur new costs for molecular diagnostics in determining which patients are eligible for treatment, monitoring treatment, and modifying treatment including withdrawing or switching therapies. One way of describing these changes is to say that the use of many new health care technologies will require the vertical integration of interventions. Viewing treatment as a single intervention is fast becoming outdated. Treatment decisions are more complex and must integrate a series of therapeutic interventions, rather than focusing on each component separately. As a result, health care systems must procure, and pay for, a service, rather than a specific product.

The macroeconomic situation recently has been unfavourable in the major pharmaceutical markets – the US, Europe and Japan. Increased sales in countries with rapid economic growth, such as Brazil, Russia, India and China, have compensated for this to some extent. Per-capita income and health care expenditure in these countries, however, remains comparatively low and economic growth has not been sufficient to support the increases in R&D costs. Although improvement in the global

economic climate would favour the global pharmaceutical industry, its fundamental problems would remain.

The pharmaceutical industry faces another, crucial change: companies must increasingly rely on private and public third-party payers to purchase the products they have developed. The principal customers now are health care systems, which base decisions about purchasing medicines on how well they fit cost and expenditure goals. This is a marked difference from the past when patients paid for their own medicines, supplemented to some extent by insurance, and the decision to use a particular medicine was made by the patient with the advice of the physician, who wrote the prescription. Not surprisingly, activities intended to market a new drug by targeting prescribers have declined dramatically. Unless purchase of a medicine is funded by public payers, moreover, few patients will be willing, or able, to use it. Health care payers' assessments of cost and value, or price and value, then, will have a critical impact on the future of the pharmaceutical industry.

The question of value and price also must be considered from a global perspective. Until the EU single market was created by the Maastricht Treaty 20 years ago, pharmaceutical markets in Europe were in effect national. Today's European pharmaceutical market spans 28 countries with widely varying incomes and health care systems. The differences across countries in income and access to health care are even greater globally. Innovative medicines now are disseminated rapidly around the globe, although access to them is uneven.

These changes offer the pharmaceutical industry important new opportunities. At the same time, however, the traditional business model is shifting away from one where the lion's share of development costs is borne by the US market with support from Western Europe, Japan, and a handful of other countries. This adds a layer of complexity as development costs will need to be spread across markets with widely varying abilities to pay, different health care systems and divergent regulatory frameworks. Moreover, it will be neither economically feasible nor, in most cases, politically acceptable, to sell only to a private market where access is limited to individual patients who are able to pay. Instead, the main customer will be the public health care and national insurance system in each country. These authorities will assess the value of new medicines, both in relation to what they can afford to pay and with

respect to cost-effectiveness compared with alternative options.

The value of innovative medicine will thus become, or already is, a defining issue for global drug development. The process of determining value, and the decisions based on evidence of value, will determine the future of pharmaceutical markets and public health care systems, with important implications for public health.

Localisation of drug development investments

New medicines mean increased expenditure for health care systems; however, this expenditure will generate equivalent income for the companies and countries where the new drugs are developed and produced. An important question for the future is where these investments will be located. Will Sweden be able to remain a net exporter of medicines and thus generate sufficient income to more than cover the anticipated increase in the cost of pharmaceutical imports? Will Sweden be able to remain a leader in medical science and innovative drug development? Competition among countries is fierce, and several have already taken steps to improve their positions. New entries such as South Korea and Malaysia have ambitious growth programmes. China and India already have significant pharmaceutical production facilities and aspire to develop innovative medicines as well (see Boston Consulting Group, 2011).

A year ago, the UK government introduced a strategy for life science development that aims to increase the academic knowledge base, but also sets clear targets for growth (see Bloor et al, 2011). Like Sweden, the UK has a much larger medical research base than is suggested by the size of its population; the experience of the UK and its current initiatives, then, are particularly relevant for Sweden. Issues addressed in the UK strategy include encouraging advances in biomedical research, dealing with increasing pressures on the public health care system, identifying investment opportunities for the UK in fast-growing economies, and adjusting the regulatory framework for introducing new medicines in Western Europe.

The core of this new strategy is improved collaboration involving academia, industry and the health care system, with the patient at the centre (see Figure 1.4).

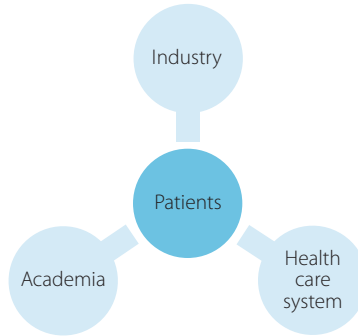


Figure 1.4 Actors and interactions in the British Life Science model.

The UK strategy report contains 200 recommendations. Five of these are particularly relevant to Sweden: the development of translational research, the use of population data, creating clusters of scientific excellence, modifying the regulatory framework, and making optimal use of the public health care system as part of the innovation process.

A crucial aspect of new drug development is translating scientific research into clinical practice. This process is changing dramatically with the evolution towards individualised care based on molecular diagnostics. The ability to define specific targets for new medicines, and to use markers to identify which patients can benefit from them, offer unprecedented opportunities for drug development. Ensuring that the health care system effectively uses the new medicine developed also requires new approaches and resources.

Access to bio banks is an important factor in progress towards targeted medicine. A decision was made recently to invest the equivalent of over 1 billion SEK in collecting genetic DNA from 100,000 individuals in the UK. The aim is to gain more knowledge about cancer and rare diseases to help develop better treatments. Such data can help to shorten clinical studies, with fewer patients, although additional evidence will be required from clinical practice to help determine the value of the new treatment options.

The growing interest in collecting and analysing population data is linked to translational research, but has also emerged from increas-

ing demands for safety and efficacy documentation for new medicines as used in real-life clinical practice. Numerous studies have shown that new medicines are used differently, and with different results, in clinical practice than during the original clinical research. Once a new medicine is marketed, it may be used to treat patient populations not included in clinical trials, such as patients with multiple co-morbidities or concomitant medications, each of which may influence outcomes. Adherence to the treatment regimen also differs from that in clinical trials, which affects both costs and outcomes

Follow-up studies in actual clinical practice thus are becoming an increasingly important part of the overall development process. Such studies also may capture important information from clinical practice that leads to new options and strategies for the use of the medicines.

Studies of the process of innovation have demonstrated the importance of geographic clusters that allow experts from industry and academia to collaborate easily, enhancing the drug development process. It is not clear exactly how successful clusters are formed, but the idea is to encourage multidisciplinary collaboration and provide equal access for companies of all sizes. The public health care system also may be part of such clusters, given that is both a buyer and user of health care technology. Medicon Village (www.mediconvillage.se) in Lund in the south of Sweden is an example of a cluster that includes academia, health care providers and industry and is intended to create optimal conditions for innovation in the life sciences.

Market entry regulations for new medicines are evolving in response to changes in biomedical science and demands from governments, health care systems and the general population for information about efficacy and safety. The speed at which a new medicine reaches the market, and at what price, is influenced primarily by new rules for reimbursement set by the public health care system and by requirements for documenting cost effectiveness. Relatively new types of regulatory bodies, such as National Institute for Health and Care Excellence (NICE) in the UK and the Dental and Pharmaceutical Benefits Agency (TLV) in Sweden, have become increasingly important. Sweden's Medical Products Agency has been mentioned before as a significant factor in the past successes of the Swedish pharmaceutical industry. It is now obvious that agencies and regulations governing

the funding of new medicines will become equally significant for the innovation process in the future.

National regulations and decision-making for market entry of new medicines may thus become important means of competition for countries in attracting pharmaceutical industry investment. Note, however, that the pharmaceutical market is global and Sweden's options are limited to some extent by EU rules. In the future, evidence requirements for proving the value of new medicines are likely to be harmonised in the same way that European drug regulation has been centralised under the EMA. Decisions on pricing and use, however, will be made nationally as long as financing of health care remains a national competence.

Health care systems play a key role in creating a favourable climate for innovation. Traditionally, research, development and innovation within the public health care system in Sweden has been the concern of the national government, rather than the county councils. A major change is underway, however, that will see health care payers and providers play an increasingly important role in the development process because of the demand for patient-level data and the importance of the criteria applied in decisions about the funding and use of new medicines.

In the history of the development of a successful Swedish pharmaceutical industry, interaction with physicians, both as researchers and as professionals responsible for patient care, was an important source of information for the pharmaceutical industry. Going forward, physicians will continue to be important, but their expertise must be supplemented by collaboration with the health care system in order to integrate economic and administrative considerations. Changes in translational research require new approaches to the design and conduct of clinical trials and follow-up studies.

The UK strategy illustrates how important it is for countries to be part of medical innovation. It also indicates that success cannot be taken for granted. Sweden is a small player compared to the UK. In the future, competition will come to a significant extent from large countries such as China and India that have considerable capacity for biomedical research and innovation as well as large potential markets for the medicines developed. However, in a vast global market, even small successes may contribute importantly to the economic growth of a small player. Developing policies and strategies for improving the

probability of success is an obvious step for Sweden and, with this in mind, approaches for valuing medicines are crucial.

The role of medicines in health care

The cost of medicines is part of health care expenditure, and thus a target for savings in times of cutback. Table 1.1 shows the rise in medicine costs in Sweden as a proportion of overall health care costs.

In 2011, the overall cost of medicines, including medical consumables, was 40 billion SEK. Approximately 12% of total health care costs, this share has decreased somewhat in recent years due to stagnating sales. Prescription medicines account for most of the medicines budget (72%); out of this approximately 18 billion SEK is paid through the national pharmaceutical reimbursement scheme and just over 7 billion is paid directly by patients. In addition, patients pay over 3 billion for over-the-counter drugs resulting in total out-of-pocket expenditures of 10.5 billion SEK (see Carlsson and Tinghög, 2013, and Chapter 6).

There is widespread debate about medicines expenditures and how these can be reduced. The recent agreement between the pharmaceutical

Table 1.1 Health care expenditure as a proportion of gross domestic product (GDP). Medicines and medical consumables expenditure, with prescription medicines listed separately. Current prices, billion SEK. Source: Health care accounts, Statistics Sweden, http://www.scb.se/NR0109.

Health care spending	2001	2005	2008	2009	2010	2011*
GDP at market price	2,348	2,769	3,204	3,106	3,338	3,500
Total health care expenditure	208	251	296	309	316	331
Per cent of GDP	8.9	9.1	9.2	9.9	9.5	9.5
Medicines and other medical non-durable/consumer goods	29.1	33.5	38.2	39.3	39.4	40.0
Per cent of total health care expenditure	14.0	13.4	12.9	12.7	12.5	12.1
Prescription medicines	22.4	25.4	27.9	28.4	28.6	28.9
Per cent of total health care expenditure	10.8	10.1	9.4	9.2	9.0	8.7

* Data for 2011 are based on preliminary annualisations of national accounts.

industry and the government is a typical example (Swedish Ministry of Health and Social Affairs, 2013). The agreement involves price cuts on medicines older than 15 years and is expected to generate a cost saving of 800 million SEK during 2014–2017. This followed an earlier proposal to introduce international reference pricing (see Chapter 6).

Of course, these savings are welcomed by the government as the principal funder of the national pharmaceutical reimbursement scheme, and the agreement avoids potential problems that would have been created by a reference pricing system. However, the cost of medicines in Sweden is low compared to other countries, both as a proportion of overall health costs and in absolute terms. Spending trends are not cause for concern as the spending on medicines is a declining share of overall health care expenditure. Focusing on costs and the pricing of older products will lead to very small cost savings, less than half of 1% of the total cost of medicines during 2014–2017, and will address none of the key questions about the value and cost-effectiveness of new medicines.

The focus in this book is on medicines as a production factor in health care, that is, how the use of new medicines in combination with other diagnostic and therapeutic resources can contribute to improved treatment outcomes. Table 1.2 shows sales figures for 2008–2012 for medicines that entered the market in the previous five years.

The main focus of attention in recent years has been the cost of new medicines, or rather the pricing of them. As seen in the table, sales of

Table 1.2 Sales of new original medicines introduced during the previous five years. Pharmacy wholesale price (AIP) in million SEK, excluding medicines for veterinary use and parallel imports. Source: Swedish Association of the Pharmaceutical Industry (2013) p 19.

Year of introduction	Year of sale	Sales of new medicines	Per cent
2004–2008	2008	2,470	8.5
2005–2009	2009	2,271	7.6
2006–2010	2010	2,051	6.9
2007–2011	2011	2,121	7.0
2008–2012	2012	2,531	8.4

new medicines amount to between 2 and 2.5 billion SEK, equivalent to 8% of total sales of prescription medicines; from a cost point of view, this is a comparatively modest amount. However, it is not the overall cost of new medicines that is being called into question, but rather their cost effectiveness.

Table 1.3 displays the sales of cancer drugs entering the market during 2007–2011. As the table shows, cancer drugs introduced during the previous five years accounted for 14% of total cancer drug sales in 2011. This greater share of sales for new drugs is hardly surprising given the high degree of innovation and the large number of new market entries in this therapeutic area; at least one third of total investment in new

Tabell 1.3 Sales of cancer medicines in Sweden during 2011 by year of introduction. ATC-code 1+2A+2B+thalidomide+lenalidomide. Source: Jönsson and Wilking (2013).

Medicine	Year of introduction/first sale	2011 sales (million SEK)	Accumulated sales of cancer medicines (million SEK)	Accumulated share of total sales	Cost of medicines by month of treatment* (thousand SEK)
Abiraterone	2011	13	13	0.5	34
Eribulin	2011	4	17	0.6	30
Ipilimumab	2011	4	21	0.8	74
Cabazitaxel	2011	13	35	1.2	70
Ofatumumab	2010	2	37	1.4	60
Pazopanib	2010	12	49	1.9	30
Vinflunine	2010	3	52	2.0	55
Azacitidine	2009	30	82	3.1	65
Temsirolimus	2009	3	85	3.3	30
Everolimus	2008	22	108	4.0	38
Lenalidomide	2008	110	218	8.0	52
Panitumumab	2008	18	236	8.7	30
Thalidomide	2008	23	259	9.5	8
Trabektedin	2008	12	271	9.9	58
Dasatinib	2007	42	313	11.4	41
Clofarabine	2007	3	316	11.5	58
Lapatinib	2007	11	327	12.7	26
Nilotinib	2007	33	360	13.9	26

*Authors' estimate. Rounded figures.

medicines is currently targeting the cancer field. However, most of the difference is because of a single medicine, lenalidomide, for the treatment of myeloma (a form of blood cancer), which had sales of over 100 million SEK, more than a quarter of total sales of new cancer drugs.

Another important observation is that most new cancer drugs have very low sales. Only six new cancer drugs have achieved annual sales exceeding 20 million SEK, and more than half have annual sales below 10 million SEK. These do not impose a significant cost burden on health care providers, nor do they generate large profits for the pharmaceutical industry. Some of these medicines may be of great value for individual patients, but seen from a wider perspective, a small number of medicines are responsible for generating both value and costs. It is for these medicines that appropriate decision-making on value, price and use becomes especially important.

Table 1.3 also shows estimates of the cost of medicines per month of treatment. These are estimated costs that may vary; they are shown here merely to give an idea of the order of magnitude. New targeted cancer treatments frequently cost around 30,000–70,000 SEK per month of treatment, and the cost per month of treatment has increased dramatically over time.

This increase in the price of cancer drugs reflects the increased cost of introducing new medicines outlined earlier in this report. One implication of the increase in price is that only a few individuals with either high incomes or considerable personal wealth can afford to pay the price by themselves. A further consequence is that the opportunity cost to health care providers of using new medicines has increased dramatically. The monthly cost of medicines may well exceed the monthly salary of a nurse or physician who is also essential to the cancer treatment.

Balancing the allocation of resources so that all patients can receive adequate treatment throughout the entire course of their illnesses is therefore both difficult and important. The dominant item of expenditure for cancer patients has been hospitalisation; however, this is changing due to the introduction of new cancer drugs. Whilst this is a positive development, health care payers and providers are still faced with difficult decisions, both in terms of how much additional resource can be made available for cancer services in both the short and longer term, and how to balance the use of medicines against the need for

additional staffing to meet the demands of improved cancer care for all patients at all stages of the disease.

These choices can be discussed from several points of view – ethical, political, and financial. Decision-making in public health care systems must be transparent and based on non-biased information. Under the Swedish Health and Medical Services Act, resources must be directed primarily to those patients with the greatest need. This means the outcome for the patient is the most important factor when estimating the value of a new medicine. The price and the costs must therefore be weighed against any health benefits in the form of increased survival and/or improved health-related quality of life that may result from using the medicine. Such balancing acts have become a key element in resource utilisation control within health care systems. This means that the value of new medicines has assumed a central position in health care policy making.

Summary and conclusions

New drug development is a success story for both health care policy and the pharmaceutical industry. It is the result of joint efforts by public and private stakeholders. Developing, manufacturing, marketing and using new medicines is a complex process. Although this success has not been without obstacles, these have been overcome and form the basis for future development.

There are many signs that we have now reached a situation where new drug development must find alternate routes to be successful.

- As before, advances in medical science are an important driver of change. However, these advances cannot as easily be translated into new medicines and new technologies.
- Economic growth, another key driver, has slowed and incomes have stagnated in major drug markets.
- New medicines now must enter markets where health care systems are facing serious financial pressures.

Globalisation of the pharmaceutical market has changed the terms of supply and demand, and it is currently difficult to predict in which countries new drug development will be occur in the future. However,

most countries view the biomedical sector as a future growth industry and are willing to be competitive in this sector.

Despite widespread agreement on the importance of future success both for improved health and national economic growth, the best paths are not obvious. New drug development involves a high degree of risk, and Sweden is a prime example of the difficulty in retaining a successful pharmaceutical industry over a prolonged period of time. However, we know what factors are important, and investments to create opportunities for becoming a global leader in the biomedical sector are an important element of innovation policy.

Decision-making about the price and use of new medicines is one of the major areas of change that will have important consequences for new drug development. The traditional model of decisions being made by the patient and physician with the public funding body having a passive role is history. Decisions made by payers are of vital importance not only for the efficiency of the health care system and the health of the patients, but because they influence which new medicines will be developed, and how. Renewed and refined collaboration between health care providers and the pharmaceutical industry is a key success factor for the future of both health care services and the biomedical industry.

We are in the midst of a process of change wherein the value of a medicine – and evidence of value relative to price – is becoming increasingly important to health care policy makers and individual patients. The following chapters provide detailed descriptions and analyses of decisions made by health care systems about the use and funding of new medicines.

References

Arvidsson G., Bergström H., Edquist C., Högberg D., Jönsson B. (2007). Medicin för Sverige! Nytt liv i en framtidsbransch. Stockholm: SNS Förlag.

Bloor C., Sriskandarajah R., Croxfod V., White H. (2011). Strategy for life sciences in the UK. London: Department for Business Innovation & Skills.

Boston Consulting Group (2011). Life sciences R&D. Changing the innovation equation in India. Delivering affordable innovation through global partnerships. Boston Consulting Group. Available from http://www.bcg.com/.

Carlsson P., Tinghög G. (2013). Läkemedel – när är det rimligt att betala själv? Stockholm: SNS Förlag.

European Federation of Pharmaceutical Industries and Associations (EFPIA) (2012). The pharmaceutical industry in figures. Available from http://www.efpia.eu/.

Jönsson B., Wilking N. (2013). Värdering och implementering av nya läkemedel – med exempel från cancerområdet. Stockholm: SNS. See also Jönsson B WN. Evaluation, Implementation and Access to New Cancer Drugs in Sweden. Journal of Cancer Policy, 2014.

Swedish Association of the Pharmaceutical Industry (2013). 'Fakta 2013'. Available from http://www.lif.se/.

Mestre-Ferrandiz J., Sussex J., Towse A. (2012). The R&D cost of a new medicine. London: Office of Health Economics, OHE.

Pammolli F., Magazzini L., Riccaboni M. (2011). 'The productivity crisis in pharmaceutical R&D', Nature Reviews Drug Discovery 10 (6), s. 428–438.

Pammolli F., Riccaboni M. (2007). Innovation and industrial leadership. Lessons from pharmaceuticals. Washington DC: Center for Transatlantic Relations, Johns Hopkins University.

Paul S.M., Mytelka D.S., Dunwiddie C.T., Persinger C.C., Munos B.H., Lindborg S.R., Schacht A.L. (2010). 'How to improve R&D productivity: the pharmaceutical industry's grand challenge', Nature Reviews Drug Discovery 9 (3), p. 203–214.

Socialdepartementet (2013). Utvecklad takprismodell för vissa äldre läkemedel och krav på laga kraft av beslut om sanktionsavgifter. Stockholm: Socialdepartementet. S2013/6586/FS. Available from http://www.regeringen.se/sb/d/16824/a/224934.

2. Making decisions on new medicines – what actors control the market

This chapter focuses on decisions about market entry of new medicines, describes how this has changed over time and identifies issues that are relevant to policy making. The pharmaceutical market is subject to strict regulation, but most innovations originate from decisions made by private pharmaceutical companies. Regulation of the medicines market has been intended both to stimulate innovation, for example through patent and orphan-drug legislation, and to set standards for market entry, including criteria for safety, efficacy and quality. Although the trend has been towards more and increasingly strict regulations, policy makers also seem more aware of the importance of tempering the effect by also implementing measures intended specifically to stimulate innovation. A key issue is how much control can be exerted over the market without discouraging innovation.

In this chapter, we focus on the links between the development, market entry and use of new medicines and the concept of the 'value' of a new medicine. Other aspects of the decision-making process are noted only when necessary.

Incentives for private companies to develop new medicines

New medicines are developed by private companies that compete for and on a market. The prospect of profit usually is considered to be the main driver, or incentive, for innovation. In practice, however, profit-

ability is just one of the drivers, and is by itself insufficient as an explanation of why medicines are developed. Decisions about investing in R&D are based largely on a company's strategic considerations; the choice of which therapeutic areas of research to explore is influenced by other factors as well, including the opportunity to perform research that is both interesting and meaningful. Selecting areas for investment that have been identified as important in studies or in public debate is attractive because the probability of making a profit is greater. Examples include initiatives for encouraging the development of new antibiotics, one focus of Sweden's presidency of the EU in 2009 (see Mossialos et al, 2009). Decisions about which drug to develop, however, also are constrained by the funding available. Survival for any pharmaceutical company depends on generating the revenue needed to fund new drug development over the long-term.

To mitigate the risk inherent in drug development, companies may favour an R&D portfolio with a range of projects. Concerns about risk and increasing development costs also clearly have led to company mergers, which have concentrated R&D in a fewer, but larger, companies. Such mergers have not necessarily made research more efficient and, at least in the short term, can result in transaction costs and loss of qualified staff.

The importance of generating enough income to fund continuing investment in R&D is prompting pharmaceutical companies to carefully monitor what its customers will pay for. Over the longer term, what the pharmaceutical industry produces must coincide with what its customers want. What customers – patients and health care insurers – choose to pay for now are important signals that set parameters for the scope and direction of new R&D. However, the ability of payers to 'financially manage' development choices is limited; payments are only one means of influencing R&D direction, albeit an important one. Examples exist of both successful new medicines with serendipitous origins, and failure of R&D investments aimed at specific therapeutic areas. Some investments targeted to specific diseases have been very successful in producing results – medicines developed for the treatment of HIV/AIDS, for example, which is discussed in more detail in Chapter 3.

Penicillin is said to have been discovered accidentally, but behind its discovery was a research focus that recognised the importance of

observations made in the laboratory. Similarly, the development of insulin for the treatment of diabetes nearly 100 years ago might be considered accidental. But several scientists had been searching for a way to replace insulin in patients with type 1 diabetes since the early 1800s. The target was known; finding the treatment required many attempts and numerous failures.

Controlling new drug development and controlling the global financial sector, or the business cycle, possess certain similarities. Matching means and ends is an uncertain process. This is complicated by the difficulty of accurately measuring progress toward the goal and the impact of different factors over time. Despite uncertainty about how to effect desired change, the goal of any policy for the pharmaceutical industry is a drug development process that maximises the probability of 'good' accidental or chance discoveries. Innovation policy also can provide a climate favourable to long-term R&D. It is particularly important to note that health care systems will play a critical role in the future of drug development by creating, analysing and sharing knowledge on the use of new medicines and integrating this into clinical practice.

Patents and orphan drugs

Patent protection is an intangible entitlement that increases the chances of making a profit and recouping investments in the development of, for example, new medicines. During the patent exclusivity period, the manufacturer is guaranteed exclusive rights to sell the product for a defined period of time before other manufacturers may enter the market and compete, for example, by reducing the price.

The legislation on orphan drugs is another example of public policy intended to create incentives for innovation. The focus is on medicines intended to treat rare diseases, which by definition will have a low volume of sales. Orphan drugs in the EU are granted exclusivity for a period of ten years following marketing authorisation. During this time, no other marketing authorisation will be granted for a similar medicine for the same indication. Some exception applies, for example, if the manufacturer is unable to supply sufficient quantities.

Patent protection and orphan drug legislation do not invariably steer R&D investment to areas that will produce maximum value for

society. A vital medicine may not be developed, for example, because of ambiguities in patent status. If orphan drug incentives cause companies to devote unreasonable large amounts of resources to products for small patient populations, this may mean that medicines that could benefit larger patient populations are not developed. The effect of legislation may be quite different in a private market where patients pay for their own medicines than in a market where medicines are paid for by public funds. In a private market where the patients themselves are paying directly, the manufacturer sets the price. Patients can choose, with the advice of the prescriber, whether to acquire the medicine at the asking price.

The trend towards new medicines being paid for mainly by private or public health insurers has led to a change in the nature of the market. In a fast-growing economy with a young population, insurance coverage can help support the price set by the manufacturer – at least for a period of time and with the help of co-payments – because total expenditure still will be low in relation to the ability to pay. The situation in the Western world today, however, is the opposite – low economic growth and an ageing population produce tight funding, which is a limitation. In this climate, pharmaceutical companies must negotiate price and volume. The company is expected to prove that its new medicine is cost-effective and estimate the likely budget impact on health care services. The value of patents is limited unless the medicine is used and paid for by the public health care system. Legislation such as that for orphan drugs that differentiates among medicines based on the size of the target patient population are unnecessary when all medicines are publicly funded. This will become just one of several factors when determining price. The trend towards individualised stratified or personalised medicine also will render orphan drug legislation obsolete because so many target populations will be comparatively small.

The recent Swedish government report on pricing and access to medicines offered no proposals for addressing the issues in its interim report 'Pris, tillgång och service – fortsatt utveckling av läkemedels- och apoteksmarknaden [Price, supply and service – continued development of the pharmaceutical and pharmacy market]' (Swedish Government Official Reports [SOU] 2012:75). The report stated that there are grounds for considering special rules for the pricing of medicines for the treat-

ment of rare and very severe conditions, and that this issue will be revisited in a future report. An appendix to the report, however, notes that the desirability of preferential measures for medicines with small target patient populations is not obvious – potential benefits must be weighed against the potential drawbacks of directing development towards this objective. Equity should be considered an important part of the overall assessment, but the size of the patient population is just one of many aspects that should be taken into account in decisions about reimbursement.

New instruments for the management and regulation of the market for medicines

The evolution of pharmaceutical markets has begun to make traditional means of stimulating innovation obsolete; new approaches must be developed. The single most important new policy instrument is public funding, or reimbursement. The concept of 'value' plays a vital role in this context since the price and cost (price times quantity) of a medicine will be considered in relation to its value when deciding whether to pay for it. The challenge will be to determine this value objectively and establish decision-making processes that also take into account those aspects that cannot be determined objectively. The central decision maker will be the 'payer', and the roles of the patient and physician in choosing among alternative treatments will be reduced (Figure 2.1).

Until relatively recently, decisions on the use and funding of medicines were the prerogative of the patient and the prescriber. The extent of 'third-party funding' was limited, costs were born by the patient directly, and limits on available funds minimised the risk of excessive use. Direct payments by the consumer still play a significant role in the funding of prescription medicines, but their relative importance has diminished over time. In the case of most new medicines, the choice of patient and physician is limited to what the buyer/health care provider has decided to fund.

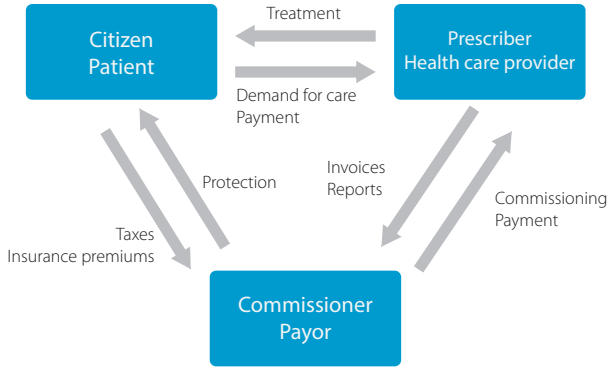


Figure 2.1 The pharmaceutical market – a three-way relationship.

Drug regulation and the value of new medicines

During the 1900s, national and international bodies were established to assess the efficacy and safety of new medicines based on scientific data. The US Food and Drug Administration (FDA) is the most influential of these bodies since it controls access to the world's largest pharmaceutical market. In Sweden, the Medical Products Agency has been responsible for regulatory approvals since 1990. Following the establishment of the European Medicines Agency (EMA) in 1995, however, scientific assessment of new medicines in Europe has gradually moved away from national bodies. Market authorisation decisions now are made by the European Commission, based on the EMA's recommendation, and are binding in the majority of European countries.

Regulation of which products may be marketed both protects patients and provides important information on safety and efficacy for patients and physicians. It is obviously extremely important that medicines seriously lacking in safety, that is, those with a high incidence of adverse events, be prohibited from entering the market. Similarly, medicines approved for marketing also must have been proven effective. What is less obvious is what the balance between efficacy and safety should be and this may differ from one treatment to another. What is clear is that the traditional model for marketing authorisation –

with rigorous and comprehensive randomised controlled clinical trials (RCTs), but no systematic follow-up once marketing commences – is in need of reform.

Market authorisation does not necessarily mean that the medicine will be available to all patients. The decision whether the medicines will be reimbursed, a decision made after marketing authorisation, is critically important for patients' access to the medicine. Regulatory assessment of efficacy and safety is merely one step on the route to patient access to a medicine; it is necessary, but not sufficient, to ensure access. Drug regulatory activities must be more involved in defining the value of medicines if regulatory agencies are to remain separate from those that decide on pricing and reimbursement. Market authorisation and reimbursement decisions for new drugs are based largely on the same data as licensing, but evaluated using different criteria. Regulatory evaluation of new medicines does include criteria for 'clinically relevant effectiveness', but the data collected rarely are enough to support decisions about reimbursement. The latter requires evidence of value that can support the asking price, for example, prolonged survival and/or improved quality of life. Methods for estimating the value of new medicines are discussed in more detail in Chapter 3.

The safety and effectiveness of a medicine depends not just on its chemical makeup, but also on its actual use in clinical practice. Medicines are not used in the same way in clinical practice as they are in the pivotal clinical studies upon which evaluations of safety and efficacy are based. Regulatory assessments are based on clinical studies that, to meet their objectives, must be restricted to defined patient populations that are closely monitored and managed. They cannot be expected, then, to reflect how patients are treated in the real world, outside the clinical trial setting. The results of clinical trials alone are inadequate for estimating the full range of benefits and risks associated with the use of a drug.

Regulatory bodies have a long history of collecting data for identifying rare adverse events that occur after a drug reaches the market. This is discussed, for example, in the SNS study by Gyllensten and Steen Carlsson (2013). Weighing risk against benefit in actual use, however, requires collection of data on efficacy in actual clinical practice. We are entering an era in which efficacy data increasingly will be gathered in a systematic way (European Commission 2012). In practice, such data

have been collected routinely for years – Swedish quality registries are an example. For the most part, however, data collection has not been carried out systematically, nor have the registries been used systematically as the basis for decisions. We return to this subject in Chapter 5 and discuss the potential for such studies in Sweden.

Clearly, then, both the criteria for assessing new medicines and the data required for decision-making are changing. Increasingly, the focus is on the benefit for patient health, relative to price and cost, in actual clinical use. Experimental clinical trials that test hypotheses on efficacy and adverse side-effects remain a core element of new drug development. We must be sure that new medicines work as intended. Determining value, however, requires knowledge about the therapy's effect on patient health in the real world as compared to available alternatives. Such studies may be called by different names – relative effectiveness assessments (REA) or comparative effectiveness research (CER) – but their objectives are the same: to establish the extent to which a new medicine is superior to medicines already in use in the health care system (Luce et al 2012, Jönsson 2011).

This trend towards changing the evidence base from RCTs to clinical data collected from clinical practice applies to all health care technologies and interventions, not just medicines. However, since innovative medicines play a key role in the development of new treatments and treatment strategies, it is also particularly relevant in the development, documentation and evaluation of new medicines. Examples of real world studies of the value of new drugs appear in Chapters 3 and 5.

The EMA is one of the more successful institutions within the EU and Sweden has played an important role in ensuring its success. The main challenge for the EMA today is to determine what its role should be given new standards for evidence for evaluating medicines.

Decisions on reimbursement are made nationally and the ability to pay for new drugs varies dramatically from one European country to another. At the same time, however, EU Directives now are in place to make it easier for its citizens to seek medical care in any EU country they choose. To avoid serious differences in quality of care, this requires agreement on the value of various health care interventions, including medicines. To address this major issue, the EU has been working for a number of years to create a mechanism for exchanging information

on health technology assessments (HTA), which are evaluations of medical treatments and interventions. On 26 June 2013, the European Commission ruled that a network of national HTA bodies should be established, citing as a basis the 2011 ruling that any patient has the right to seek medical care in any EU country and have it paid for by their home country.

HTA has become a core health care policy tool in many countries. As with drug regulation, Sweden has played a key role in Europe, setting up HTA entities early on, including the Centre for Medical Technology Assessment (CMT), established at Linköping University in 1985, and the Swedish Council on Health Technology Assessment (SBU), established in 1987. Because HTA will be an increasingly important approach to assessing the value of all health care technologies, including medicines, understanding both its strengths and weaknesses is important.

Health Technology Assessment (HTA)

The development of HTA since its beginnings in the 1970s has been based on the observation that the use of medical technologies – diagnostics, surgery, medicines, and so on – varies considerably within the health care system and that scientific data that can guide appropriate use often are lacking (see Chapters 4 and 5). In a now-famous book published in 1972, English physician and epidemiologist James Cochrane asserted that the health care system would have enough resources for everyone if the use of inefficient methods could be eliminated (Cochrane 1972).

HTA initially focused on diagnostics and surgery, for which there was no systematic review process equivalent to that for medicines. Early HTA studies of drug therapies often focuses on treatments that had been available on the market for a long time, but had come to be used in a way that raised concern about overuse or underuse. As an example, SBU initiated a large project on medical treatment of hypertension based on a hypothesis of overuse, whilst a study on oestrogen (HRT) was based on a hypothesis of underuse. The final reports were unable to confirm either hypothesis, but the systematic review of the available evidence was important, particularly for provoking informed discussion about the use of these technologies given the available scientific evidence.

The benefit of studying established technologies is that extensive documentation and experience from clinical use may be available. The development of HTA in Sweden over the past three decades has produced studies that have improved care and reduced costs in the health care system (Swedish Council on Health Technology Assessment, 2012a). However, whilst HTA has become accepted as a valuable instrument for systematically organising and understanding what is know, it also now is used to provide guidance when the scientific evidence base is much narrower. The evaluation of new medicines is an example. HTA has become the dominant methodology for providing the basis for decisions about pricing and reimbursement after a new medicine has been approved by the EMA or by a national regulatory body. Since public funding determines whether patients will be able to access the medicine in most cases, and thus whether the company will be able to sell it, HTA has become a new and important instrument for drug policy makers. As such, it now greatly influences new drug development, patient access to new medicines, and pharmaceutical company revenues.

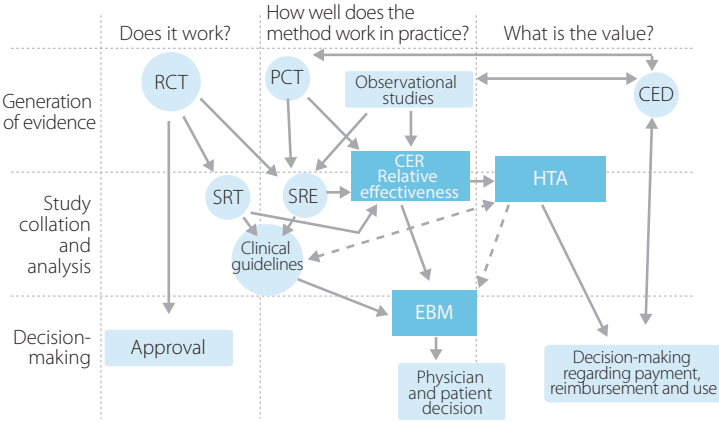
The primary approach of HTA is a systematic review of the scientific literature on a particular medical intervention or technology (Swedish Council on Health Technology Assessment, 2012b). In the case of new medicines, evidence on effectiveness is derived from the same clinical studies on which the regulatory authority bases its assessment. However, the questions asked are different, which means the conclusions reached also often are different. The aim of HTA is to quantify the positive and negative outcomes for the patient in relation to existing treatments. The available studies may not include all relevant patient populations or comparator products. Moreover, the efficacy documented in clinical studies is often not directly relevant for estimating the value of the medicine: any endpoints that are used for assessing the efficacy of new medicines, such as various biomedical or radiological markers, for example, cannot be directly translated into patient benefit. This is an increasingly important challenge in gathering evidence to guide decisions about the appropriate use of a new medicine.

Determining value is the core of the HTA process, which calculates the economic implications of the technology, expressed as an estimate of its cost effectiveness. This is a crucial criterion for payer funding and, in Sweden, for coverage under the national pharmaceutical benefit

scheme. It is determined by dividing the net cost – the direct cost of the intervention minus any cost saving – by a measure of effectiveness, such as the number of life-years (LY) or quality-adjusted life-years (QALYs) gained. Cost effectiveness thus may be expressed as the cost-per-LY or cost-per-QALY of an intervention. To be meaningful, the calculations should be for a specified treatment in a well-defined patient population. The cost-effectiveness of a medicine, then, is dependent on how it is actually used and will vary accordingly.

Data from controlled clinical studies form the basis for HTA and 'evidence-based' medicine. Clinical studies also are pivotal to the EMA's marketing authorisation decisions. However, the definition of evidence is wider in HTA; it includes systematic reviews, but goes beyond those to consider effectiveness and costs in real-life clinical practice.

Figure 2.2 shows the relationship between some of the concepts that have been developed and applied in the increasingly complex process of determining the value of a new medical technology, such as a new medicine.



RCT – randomized controlled trial; PCT – pragmatic clinical trial; SRT – systematic review of trials; SRE – systematic review of evidence; CER – comparative effectiveness research; HTA – health technology assessment; EBM – evidence based medicine; CED – coverage with evidence development.

Figure 2.2 The new evidence panorama. Adapted from Luce et al (2010).

The figure is two-dimensional: the vertical axis indicates the generation of evidence, the compilation and evaluation of evidence, and decision-making. The horizontal axis presents three questions:

1. Does the technology work?
2. How well does it work in real-life clinical practice?
3. Is it worth the cost?

COMMENT ON FIGURE **2.2**

Clinical studies that test hypotheses about efficacy constitute the main evidence base for regulatory decision-making about marketing authorisation. This is illustrated by the line from RCTs to regulatory assessment and decision-making about marketing authorisation at national or EU level.

'SRT' is systematic review of clinical trials. This may include indirect comparisons and meta-analyses in which data from different studies are compiled and analysed. 'PCT' is pragmatic clinical trials, such as randomisation of patients in a registry follow-up study. Non-randomised observational studies also can be used to gather information on the effectiveness of an intervention in real-life clinical practice. 'SRE' is systematic review of evidence from both clinical trials and other types of studies. Relative effectiveness assessment (REA) and comparative effectiveness research (CER) include both new studies and reviews of existing study. These reviews may provide support for clinical treatment guidelines health technology assessment (HTA) that assess costs and outcomes. Clinical guidelines are the basis for evidence-based medicine (EBM) which guides decisions about treatment for individual patients and, to a certain extent, groups of patients – see the overlap with the 'value' column. Increasingly, results from REA/CER and HTA are included in the development of guidelines for EBM.

In addition to the outcomes of therapy, HTA studies also include economic, ethical and administrative aspects of providing health care. Such studies are used in making decisions about public or private insurance coverage. CED, coverage with evidence development, is increasingly common because of the sometimes substantial degree of uncertainty about outcomes and value at the time a drug is first marketed.

Decisions on marketing authorisation are based on data from clinical trials and consider the efficacy of the medicine or technology relative to the potential for adverse events, based on clinical trials. To answer the question of how well a medicine works in actual use, data from clinical

trials are supplemented by information from systematic reviews of published studies and, after marketing begins, additional studies in real-life clinical practice. Clinical decision-making mainly is about the treatment of individual patients, but also includes the development of treatment guidelines. HTA is based on systematic analyses of treatment options for groups of patients with a certain disease or within an indication.

Data and methodologies for documenting real-life clinical effectiveness (real-world evidence)

HTA is intended to help direct health care resources towards uses that result in maximum benefit. Data from clinical trials provide the basic outline for evidence-based medicine, but observing actual outcomes in clinical practice provides additional information that may be more relevant to choices that must be made in practice.

The demand for and funding of new medical technologies now is driven by the health care system which, as a result, is exerting increasingly influence on the process of innovation. Health care payers and providers are increasingly interested in what new medicines are being developed and what documentation is available for supporting decisions about clinical use. For example, both NICE and TLV are involved in advising pharmaceutical companies about the development of new drugs. At the European level, advice about the data needed for HTA soon will routinely supplement regulatory advice on companies' drug development plans (see EUnetHTA, website www.eunethta.eu). Individual pharmaceutical companies already gather information from payers to guide internal decisions about development (Backhouse et al, 2011).

In the future, data originating from clinical trials will be designed to better meet the needs of the health care system. The number of pivotal studies that can be done during the development phase of a new medicine, however, is limited. The only real option is to collect additional on evidence about outcomes from actual clinical practice.

Sweden has a long tradition of maintaining data registries on the use of new drugs, for example, in the therapeutic areas of rheumatoid arthritis (RA) and multiple sclerosis (MS). Data from these registries were used in several studies for this project (see Chapters 3 and 5). To

date, these registries have been created primarily to answer medical and epidemiological questions and so contain only limited data for assessing the efficacy, value and cost-effectiveness of medicines.

In recent years, a number of registries have begun including important parameters for economic analysis. An example are local and national registries of RA patients that realised at an early stage the importance of including patients' estimates of quality of life, alongside medical parameters, when new biologic agents were introduced as therapeutic options (for example, the South Swedish Arthritis Treatment Group, SSATG; the STURE registry in Stockholm; and the national registries, the Swedish Rheumatology Quality Register and ARTIS, which monitor the use of biological agents). Another example is PsoReg, a registry of patients with psoriasis who receive 'systemic' treatment using conventional and/or biological medicines. Begun in 2007, PsoReg was designed from the beginning to allow HTA follow-up studies as well as safety monitoring.

The trend is towards disease registries increasingly including economic variables. Ensuring that this is done in a more comprehensive and systematic way is a core challenge. Much would be gained from implementing methods for collecting this data in an efficient low-cost way and making it available to all stakeholders. We discuss registries in more detail in Chapter 5.

The movement towards individualised medicine, using molecular diagnostics for targeting treatment, holds great promise. By reducing uncertainty about the treatment benefit for an individual patient, this offers significant opportunities for improvement in outcomes and can encourage more cost-effective provision of care. Individualised medicine, however, demands more data than ever before. Modern information technology allows vast amounts of data to be gathered and processed at a reasonable cost in very different ways, but it also creates a number of ethical issues, particularly around privacy protection, that must be addressed.

Increasing amounts of data about the real-life use and effectiveness of new medicines and other health care technologies will present new opportunities for allocating resources and improving outcomes. It also will greatly improve access to information on the effectiveness of new medicines. Data on actual clinical use will become part of a process of

translational research, which can make both health care delivery and new drug development more efficient.

Swedish health care providers already are collecting and publishing a wealth of data on regional differences in treatment patterns. This has been important for creating awareness of differences and stimulating thought and analysis; however, the data itself provide no information on overuse or underuse, or on what measures should be taken for improvement.

The Swedish model – collaborative decision-making at national and regional level

The pharmaceutical market is an example of the national and local (regional) division of responsibilities that is characteristic of the Swedish model of political and administrative governance. The government controls centralised bodies, such as the Medical Products Agency and TLV that decide on the use of medicines in the Swedish market. The Swedish Council on Health Technology Assessment (SBU) and the National Board of Health and Welfare conduct studies that are used in the development of guidelines on the use of medicines. The government also is involved in health care funding – through both direct co-funding of prescription medicines and state grants to county councils. It is the county councils, however, that actually pay for the medicines used in health care system.

The policy objective of the Swedish model (Figure 2.3) is national parity and minimum regional variation, whilst allowing municipalities and county councils to make their own decisions based on local conditions and requirements. It is hardly surprising that conflicting objectives arise in such a system – the surprise is that it has worked as well as it has for so long.

Changes in the pharmaceutical market are putting the Swedish model under pressure. For several decades, the market has evolved towards county councils assuming complete responsibility for the health care of all citizens in the region with diminishing central government oversight and control. This development towards a 'single payer' is rational in terms of cost control and allocation of resources. Flexibility about who is responsible for delivering health care and separating

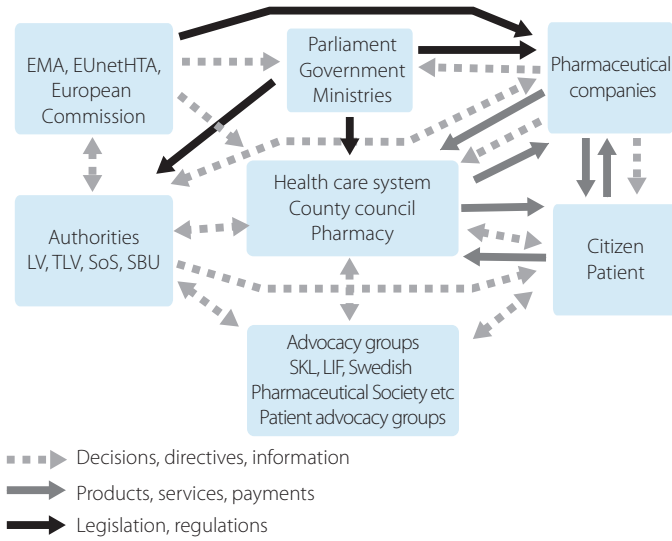


Figure 2.3 Actors and stakeholders (EMA – European Medicines Agency; EUnetHTA – European Network for Health Technology Assessment; LV – Medical Products Agency; TLV – Dental and Pharmaceutical Benefits Agency; SoS – National Board of Health and Welfare; SBU – Swedish Council on Health Technology Assessment; SKL – Swedish Association of Local Authorities and Regions; LIF –Swedish Association of the Pharmaceutical Industry).

purchasers from providers within the system have made it possible to compensate for weaknesses in the model, such as low productivity and ineffective management. The only part of the health care system not fully under county council control is prescription medicines. These are governed by the national pharmaceutical benefits scheme and national pricing of prescription medicines. Medicines are funded under a separate agreement between the government and the county councils.

Developments in the pharmaceutical market have made the separation of ambulatory and hospital medicines irrelevant -- and to some extent even dysfunctional. Controlling the use of a medicine based on whether it is prescribed and funded through the national pharmaceutical benefit scheme or paid for directly by the hospital is not a rational approach.

An excellent example of this dysfunction is in the therapeutic area of oncology. In principle, cancer patients can get access to new cancer drugs in two different ways. One way is through TLV for drugs prescribed and distributed through pharmacies. TLV is undertaking an assessment of cost-effectiveness as a basis for the decision about reimbursement. Most new medicines are designed to benefit patients by improving treatment. For serious diseases such as cancer, this may mean replacing existing treatments with those that are more effective or that have fewer unpleasant side-effects. It could be argued, then, that once an innovative medicine has been approved by the Medical Products Agency, it should be covered under the national pharmaceutical benefit scheme, in accordance with two of TLV's guiding ethical principles – human dignity, and needs and solidarity. The fact that the treatment may be of critical, if not life-saving, importance for at least some patients is nearly always obvious. In practice, cost effectiveness is the decisive criterion in TLV decisions. The decision will be simple only in cases where the proposed treatment is no better, and the asking price higher, than for existing alternatives – the clear choice then would be to exclude the treatment from the national pharmaceutical benefit scheme. However, in the vast majority of cases, the balance between the treatment and its value is far less obvious. Since the value depends on the effectiveness of the new treatment, a balance must be found between the effect, which likely is still uncertain, and the price or cost, which is likely to be higher than therapies the new treatment might replace. The higher the price of the new treatment, the greater the estimated value must be to justify the additional cost.

Decision-making on public funding of medicines under the national pharmaceutical benefit scheme is associated with a number of problems. Firstly, the process only applies to some medicines (prescription medicines dispensed through pharmacies). Many cancer drugs are administered as injections or infusions and will therefore not undergo TLV assessment. This leads to a non-rational sub-classification of cancer drugs, and other medicines as well, which obscures the overall picture.

The second issue is that in principle TLV approves a specific product for reimbursement, rather than approving its use in a specific indication or patient; however, decisions often include provisions that restrict use based on indication or patient characteristics. Although the value of a

medicine is dependent on its use, and the use may vary, TLV cannot specify different prices for different uses in its reimbursement decisions.

A third issue is that, as part of the TLV decision, the price becomes public. This may affect the price level that can be maintained by the pharmaceutical company in countries that impose an international reference pricing system.

The other route by which a patient may receive a cancer medicine is via the county council through the funding of hospital-based cancer care. There is no formal process for assessing the cost-effectiveness of medicines funded through clinical budgets; instead, hospital clinics decide themselves whether to use a medicine. Many county councils operate a system in which clinics are responsible for all medicines used, including medicines prescribed for dispensing through pharmacies, making them ambulatory drugs with respect to funding and cost. The county councils also can decide whether to use and fund medicines not assessed by TLV. In a number of instances, pharmaceutical companies have elected to negotiate directly with county councils, rather than approach TLV. County councils also may reach informal agreements with individual pharmaceutical companies; the scope of these, however, is currently under discussion.

Two problems associated with the 'county council route' have become apparent. The first is that these agreements may result in undesirable regional differences in health outcomes. Regional differences in the use of new medicines are documented, but there is no evidence as to whether observed differences have resulted in different health outcomes. With respect to survival rates for particular cancers, the Northern regional health care authority is at the bottom of the league table in outcomes, despite having been at the top in use of medicines for the last ten years (Wilking and Jönsson 2013; see also Chapter 4). It is thus not possible, based on currently available data, to substantiate the assertion that the county council route promotes health inequality.

A second potential problem with the decentralised approach is that it may put county councils with smaller health care budgets at a disadvantage when negotiating with pharmaceutical companies. This is relatively unlikely because county councils are grouped in to six regional health care authorities for delivering cancer care, increasing their bargaining power. Other opportunities exist for collaboration across

regions in health care. Finally, the freedom for patients to choose health care providers will also put pressure on county councils to collaborate.

The decentralised approach may present a third problem, namely that local-level decisions will be dominated by budgetary considerations. This is mitigated to a large extent by the fact that the county council is responsible for the funding and provision of effective and equitable health care. County councils also may negotiate on pricing and quantities, which avoids the inefficiency of having to set a national price, then followed by negotiating volume at a regional level.

TLV, created specifically to decide about the pricing and reimbursement of prescription medicines, has been conducting its responsibilities in a commendable fashion since its creation in 2002. The position of TLV as the national administrator of price control, however, clearly is untenable in a market in which county council decisions determine the use of new medicines. Nor is it reasonable to limit the remit of the TLV to prescription medicines only (and decisions about coverage under the national dental benefits scheme and certain consumer goods). TLV should be given a broader responsibility that encompasses all medical technologies requiring cost-effectiveness analysis. The current trial assessment of hospital medicines is a step in this direction (Vårdanalys 2013).

Developments in the pharmaceutical field are challenging the Swedish model by focussing attention on balancing the objectives of local autonomy and national parity. Regional differences in the utilisation of new medicines are interpreted, rightly or wrongly, as differences in the quality of care.

Centralizing decisions at the national level about the use of all medicines may seem an obvious solution for overcoming regional differences. However, drugs often only constitute part of a treatment regimen; some obvious problems are associated with employing specific funding mechanisms for different health care 'production factors'. Nevertheless, a national funding scheme can be designed that both simulates innovation and provides an incentive for county councils to use medicines cost effectively. We review this in more detail in Chapters 6 and 7.

Health care and the innovative pharmaceutical industry

In Chapter 1, we highlighted the crucial role of the health care system in creating incentives that can promote the growth of an innovative pharmaceutical industry. Traditionally, Swedish county councils have considered R&D a national government responsibility. If the Swedish biomedical industry is to continue to be successful, however, this attitude needs to change. There are signs that such a change is underway, but much more needs to be done. Structures and mechanisms must be put in place to allow for closer collaboration between the health care system and the pharmaceutical industry based on a win-win strategy.

The market entry of new medicines, as well as other health care technologies, should be considered as an opportunity for improving and increasing the cost-effectiveness of health care. This will provide incentives for developing medicines that will be attractive for export markets as well being important to health care within Sweden.

Summary

This chapter has outlined how the criteria for assessment of new medicines, and the data that support decisions about the value of medicines, have changed over time. The determination of whether a new medicine is allowed on the market at all is based on scientific evaluation by the drug regulatory authority of its efficacy and safety. Such assessments have changed over time, becoming increasingly exacting and extensive in response to the emergence of new medical knowledge and analytic methodologies. Moreover, clinical trials during the development phase are designed increasingly to also meet the requirements of the health care system for data to support decisions about pricing and reimbursement.

At the same time, and apart from the drug development process per se, demands are increasing for evidence about which approaches to preventing diagnosis and treatment are the most effective in actual clinical practice. Such evidence supports efforts to improve both health care outcomes and cost effectiveness. The growing importance of real-life clinical effectiveness data also is clear in assessments of the efficacy and safety of medicines.

The evolving criteria and requirements for scientific evidence about relative effectiveness and cost effectiveness will require changes in the decision-making processes. The current separation of the medicines market into segments for ambulatory and hospital medicines, each with its own separate funding and decision-making process, is no longer workable. Adapting to these new realities are imperative. The powers and responsibilities of the government and county councils should be revised to ensure open and transparent decision-making that involves all stakeholders.

Since decisions about value must be based on relevant and reliable information, data generation will become a critical task. Good data are the essential for achieving the efficient and equitable provision of care. But they are equally essential to the future of innovation because they underpin the decisions about pricing and reimbursement that signal to the pharmaceutical industry what new medicines the health care system is likely to use in the future.

References

Backhouse M.E., Wonder M., Hornby E., Kilburg A., Drummond M., Mayer F.K. (2011). 'Early dialogue between the developers of new technologies and pricing and reimbursement agencies: a pilot study'. Value in Health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 14 (4), pp 608–615.

Cochrane A. (1972). Effectiveness and efficiency. Random reflections on health services. London: Nuffield Provincial Hospitals Trust.

European Commission (2012). Delegated act on post-authorisation efficacy studies (Article 10B of Regulation (EC) No 726/2004 and Article 22B of Directive 2001/83/EC). Brussels: Directorate General for Health and Consumers.

Gyllensten H., Steen Carlsson K. (2013). Nya läkemedel och läkemedelsrelaterad sjuklighet. Analysmöjligheter i svenska registerdata, Stockholm: SNS.

Jönsson, B. (2011). 'Relative effectiveness and the European pharmaceutical market', The European Journal of Health Economics 12 (2), pp 97–102.

Luce B.R., Drummond M., Jönsson B., Neumann P.J., Schwartz J.S., Siebert U., Sullivan S.D. (2010). 'EBM, HTA, and CER: clearing the confusion', The Milbank quarterly 88 (2), pp 256–276.

Luce B.R., Drummond M.F., Dubois R.W., Neumann P.J., Jönsson B., Siebert U., Sanford Schwartz J. (2012). 'Principles for planning and conducting compara-

tive effectiveness research', Journal of Comparative Effectiveness Research 1 (5), pp 431–440.

Mossialos E., Morel C., Edwards S., Berenson J., Gemmill M., Toyama D. (2009). Policies and incentives for promoting innovation in antibiotic research. London: London School of Economics.

Swedish Council on Health Technology Assessment (SBU) (2012a). SBU påverkar vården. Ett försök att värdera effekterna av kunskapsspridning. Available from www.sbu.se.

Swedish Council on Health Technology Assessment (SBU) (2012b). Utvärdering av metoder i hälso– och sjukvården – en handbok. Available from www.sbu.se.

Swedish Government Official Reports (2012). Pris, tillgång och service – fortsatt utveckling av läkemedels- och apoteksmarknaden. SOU 2012:75.

Wilking N., Jönsson B. (2013). "Hur kostnadseffektivt används cancerläkemedel idag?", Onkologi i Sverige (1), pp 60–68.

Vårdanalys (2013). Vad är nyttan med hälsoekonomiska bedömningar av klinikläkemedel? Interim report. Stockholm: Swedish Agency for Health and Care Services Analysis.

3. The value and cost of new medicines for society, the health care system and the industry

The introduction of a new medicine represents a change in available technology and a new tool in the pursuit of better health. This change is the product of the translation of new knowledge about how to cure or alleviate disease into a usable product – delivered as a 'pill' or through other routes of administration such as infusions or injections. New medicines used in primary or specialist care have a direct impact on patients and on the health care system, but also have an indirect impact on other stakeholders. In this chapter, we move on from the previous chapter's overview of who makes the decisions about the value of medicines to discussing the costs and added value of new medicines to three key stakeholders: citizens/patients, health care providers, and the pharmaceutical industry. We define costs and value and provide examples of how these have been calculated for a number of innovative medicines.

Society benefits when new medicines improve the health of its citizens. Members of the community also finance the bulk of health care through tax payments or purchase of health insurance. With this in mind, then, citizens should take an interest in ensuring not only that new technologies are effective and relatively safe, but that they also are used cost effectively.

Health care providers play a key role in decisions about whether new medicines are prescribed to patients and in what quantities. They also are responsible for discontinuing the use of outdated technologies when better ones become available.

Pharmaceutical companies drive and fund the development of new

medicines and also are responsible for producing, marketing and pricing. Examples in this chapter illustrate the size and distribution of the profits and costs associated with new medicines in different market segments and to different stakeholders in the short and long term.

New medicines and health care technologies may generate value in several dimensions. The patient may derive value from the treatment through increased wellbeing and having more energy. Healthier people of working age also may have a greater capacity for work and be more productive. Both these values are commonly captured in health economic evaluations and are highlighted in our examples. However, values that accrue to family members who are also affected by a patient's condition and treatment are less commonly quantified because of data limitations. Some studies, however, have included such values and categorized the distribution of the burden of health care interventions as 'formal' or 'informal care'. Formal care is organised and/or funded by public or private providers and controlled by laws and regulations. Informal care is unremunerated and is usually provided by family members or friends, or by volunteers from charitable organisations. These studies address both the extent of care given and who bears the cost of it. 'Value' is expressed in terms of reducing the burden of care or, for individual stakeholders, by shifting the burden elsewhere. In addition, new medicines may generate value by freeing resources within the health care system, and other sectors, that otherwise would be used in the treatment of the specific condition.

Below we present the results of studies carried out as part of the SNS research programme on the value of new medicines, as well as other published studies. All are based on data on the use over time of new medicines in a real-life clinical practice setting and demonstrate outcomes in specific patient populations.

The value of new medicines – examples

A number of studies have been published in recent years that have estimated the value of new drug treatments when administered to specific patient populations with clearly defined diagnoses and health problems. Here we present a selection of these studies, mainly set in Sweden. The aim is to show how value can accrue to society from new technologies.

In what way have new medicines generated value in the treatment of diseases such as cancer, diabetes, rheumatoid arthritis, HIV/AIDS, and cardiovascular disease? What can we learn from studies that have determined the value of introducing new technologies for use in these patient populations? What values were included and what values could be measured using data from empirical observations? We demonstrate how these estimations could and should be done. As estimations of this type are becoming increasingly important for health care policy making, we also discuss how these experiences may be used in future analyses for earlier and more efficient implementation.

Table 3.1 shows the types of values of new medicines as determined in a total of eight studies, seven of which are set in Sweden and one in the US. These studies have been selected to demonstrate the type of data required for determining the value of new medicines and the need for capturing different aspects of value. The selection has also been guided by a wish to illustrate multiple aspects of the value of new technologies and the fact that several years of follow-up data were available for the particular medicines analysed. This means the analyses have been performed retrospectively and are based on actual use in a clinical practice setting. They may also serve as a guide to the feasibility of making adequate estimates of costs and health benefits at an early stage of new drug development.

Six of the eight studies included statistical analyses of life years gained. Prolonged survival is a result of improved treatment and thus an important measure of better health. Another example is HIV/AIDS. When HIV/AIDS was first diagnosed 30 years ago and its severity became evident, huge research investments were made to find treatments that could cure the disease or at least attenuate its progress. One study (Philipson and Jena, 2005) estimated the average remaining life expectancy of a person who developed AIDS in 1984 to be three years. This was before the launch of the first antiretroviral drug in 1987. A series of antiretroviral drugs with somewhat different and more effective mechanisms of action followed in 1995, 1996, and 2003. The life expectancy for anyone developing AIDS in 2000 was estimated to have increased to 16.5 years.

A similar positive trend in expected survival has been observed amongst people who develop chronic myeloid leukaemia (CML) which

Table 3.1 The value of new medicines as shown in eleven studies of the HIV/AIDS, cancer, cardiovascular disease, rheumatoid arthritis, and diabetes.

Disease/condition Study	New medicine (year of approval) Design and year of study	Values	Data sources
HIV/AIDS Philipson and Jena (2005)	Antiretroviral drugs (1987, 1995, 1996, 2003) Model analysis of patients contracting HIV during 1979–2000	Life years gained following successful treatment of patients who have developed AIDS. Life-years gained by delaying disease progression to AIDS for patients who are HIV-positive.	Registry data Meta-analysis of published studies
Breast cancer Lundqvist et al (2013b)	Tamoxifen (1977) Model analysis of incident cases during 1979–2004 Trastuzumab (2001) Model analysis of incident cases during 2001–2011	Life-years gained Quality of life Increased productivity	Registry data Published studies
Chronic myeloid leukaemia Lundqvist et al (2013a) Ohm et al (2014)	Imatinib (1999) Model analysis of a year cohort	Life-years gained Quality of life Increased productivity	Registry data Published studies
Cardiovascular disease Lundqvist et al (2012)	Several medicines for primary and secondary prevention were introduced during the 1980s and 1990s Counterfactual analysis, had the mortality due to ischaemic heart disease remained unchanged between 1980 and 2010	Life-years gained Quality of life Increased productivity	Registry data Published studies
Cardiovascular disease – hyperlipidaemia Lindgren and Jönsson (2012)	Simvastatin (1987) Model analysis 1987–2028	Life-years gained Quality of life	Registry data Published studies

Disease/condition Study	New medicine (year of approval) Design and year of study	Values	Data sources
Rheumatoid arthritis Neovius (2013)	TNF inhibitors (from 1999 onwards) Observational cohort study 1999–2007 Registry-enhanced randomised clinical trial (2002–2006)	Increased productivity (reduction in number of work days lost)	Registry data
Rheumatoid arthritis Kalkan et al (2013)	TNF inhibitors (from 1999 onwards) Repeated cross-sections 1990–2010	Health care costs primarily due to rheumatoid arthritis Increased productivity (reduction of number of work days lost)	Registry data
Diabetes Steen Carlsson et al (2013)	Insulin 1921+ continued progress; sulphonylureas and biguanides 1950s; glitazones 1990s, meglitinides 1998, novel incretin mimetics 2007, GLP-1 analogues 2006, 2010 Model analysis	Life-years gained	Registry data Published Swedish studies on relative mortality

affects around 90 people annually in Sweden (corresponding to about 1 per 100 000 in the population). Thirty years ago, the average life expectancy was three years for a person diagnosed with CML. In 1999, the first tyrosine kinase inhibitor, imatinib, was launched, which acts by suppressing the growth of cancer cells. The benefit of this treatment was recognized early and Swedish data up to 2008 showed that, on average, 75% of CML patients were treated with imatinib and the mean survival rate had increased to 18.5 years (Björkholm et al, 2011; Lundqvist et al, 2013a). To date, no new medicine has been capable of curing HIV/AIDS or CML outright (Ohm et al 2014), but in both cases a high-mortality condition has been transformed into a chronic

illness that can be managed for a significantly increased number of years with regular treatment.

Another patient population that has seen an equally dramatic improvement in survival prospects is children and adolescents with type 1 diabetes. In the early 1900s, there was no effective method of managing the absence of endogenous insulin production. Anyone stricken by diabetes prior to 1920 could hope to survive for possibly another two years. In January 1922, a 17-year-old boy from Canada became the first human subject to receive an injection of human insulin, and he survived for another seven years. Throughout the 20th century, the gap in remaining life expectancy between people with type 1 diabetes and the general population has gradually narrowed down.

Around the time of the Second World War, the gap in remaining life expectancy between a person developing type 1 diabetes at the age of 10 and an average of other children of the same age had narrowed from 52 to 17 years. Following this initial dramatic increase, life expectancy changed little until the late 1970s (Weiderpass et al, 2001 and Steen Carlsson et al, 2013). This also meant that the gap vis-a-vis the general population increased during this period. In the last 30 years, the gap in life expectancy compared to the general population has again narrowed (Figure 3.1).

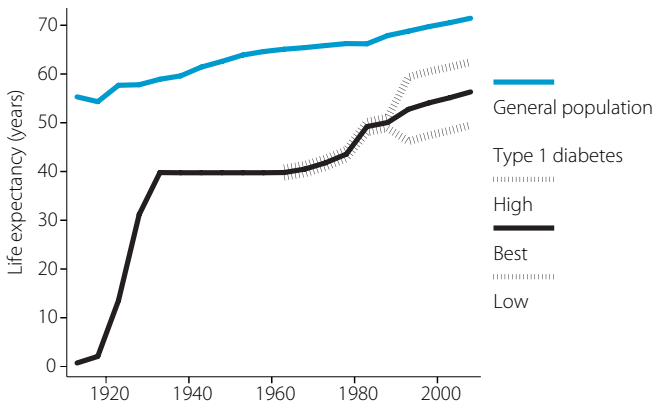


Figure 3.1 Life expectancy for a patient who developed type 1 diabetes at the age of 10 years during 1910–2010. Source: Steen Carlsson et al (2013).

In addition to continuously improving insulin treatment by, for example, developing new types of insulin with different characteristics (such as short-acting and long-acting insulin analogues) that improved the insulin molecule, technological developments also have resulted in improved methods of administration and self-management tools for people with diabetes. In addition, developments in preventive treatment of cardiovascular disease have been crucially important for prolonging the survival of people with diabetes. However, estimates of life-years gained with preventive treatment in diabetes are marred by uncertainty and are likely to be conservative. Cohorts that are now aged 50–60 years and developed type 1 diabetes as children or adolescents have not had access to modern diabetes treatments throughout their disease. This means that studies published to date have not yet been able to monitor modern diabetes treatments for sufficiently long periods of time to be able to conclusively determine the full value of the treatment.

Life-years gained is also a key component in studies that have determined the value of tamoxifen and trastuzumab for the treatment of breast cancer, as well as lipid-lowering and antihypertensive treatments administered as primary and secondary prevention in cardiovascular disease, as shown in several studies (Table 3.1; Lindgren and Jönsson 2012, Lundqvist et al 2012, and Lundqvist et al 2013b). In addition, these studies have also included estimates of quality of life improvements and thus provide a more detailed view of the value of new medicines.

There are at least two reasons why capturing quality of life is important for determining the value of new medicines. Firstly, there are a number of treatments that can improve health status and well-being but have no effect on survival as such, for example in the treatment of many chronic illnesses. Focussing on life-years gained alone will mean that the analysis will not capture benefits that are important to patients. Secondly, estimations that only show life years gained without taking into account the patient's actual state of health may actually overestimate the treatment benefit. It is thus important that the analysis should be capable of ranking health benefits, so that a life year gained without any pain or restrictions of function is rated higher than a life year with pain, anxiety or impaired function.

Lundqvist et al (2012) compared actual mortality rates due to ischaemic heart disease during 1980–2010 with a hypothetical scenario in

which age-specific mortality remained at the 1980 level. Using Swedish statistics on cause of death for relevant age groups, the authors estimated that a total of 401,000 deaths had been prevented or postponed amongst people aged 45–84 years during the 30-year study period. The authors then estimated the life-years gained by adjusting for shorter life expectancy amongst people with cardiovascular disease (in total 3.3 million life-years gained). Finally, the adjusted life-years were weighted for quality of life and the total health benefit was found to be 2.4 million QALYs. Referencing an epidemiological model analysis by Björck et al (2009) of factors that may explain the reduced cardiovascular mortality during this time, a total of 693,000 QALYs gained were attributed to new medical technologies during this period. In monetary terms the value of these health benefits was estimated at 762 billion SEK based on an estimate of the monetary value of a QALY as 845,000 SEK.

An important contribution of this study is the demonstration of how the value of new technologies accumulates over time. The analysis of risk-factor treatment will need long-term follow-up by definition. This was demonstrated by new technologies introduced in cardiovascular care over the past 30 years that have aimed at reducing risk and postponing serious conditions such as myocardial infarction and stroke. Prolonged follow up may be required to capture the value of treatments that affect risk factors with any degree of certainty. This is particularly evident for treatments where serious events do not occur until after many years of risk exposure. One example of this is insulin therapy for controlling blood glucose levels in patients with diabetes. Another example is lipid-lowering therapy using statins.

Lindgren and Jönsson (2012) estimated the value of lipid-lowering therapy using simvastatin from its launch in Sweden in 1987 until 2008, based on registry data, and forecasted its continued use to 2028. This study showed a steep increase in the number of individuals commencing treatment with simvastatin shortly before the patent expired. Once generic substitution became an option, the price fell by 90%. A similar steep increase in total value of annual sales was seen shortly before patent expiry, only to have been more than halved a few years later.

The consumer surplus for simvastatin for the entire study period was estimated at 1,083 EUR per head. It is of interest to note that according to the authors' estimates, 95% of this value occurred after the patent of

the branded product had expired. There were two main factors behind these results. Firstly, the number of statin prescriptions filled during the first ten years after approval was modest compared with current levels. As is often the case, medicines are often prescribed cautiously during the early introductory phase. This can be explained partly by uncertainty about the real-life clinical effectiveness of the medicine; many clinicians may prefer to prescribe trusted established therapies, especially if the price of the new alternative is significantly higher. Patent protection is effective only during a small portion of the total life cycle of a medicine. The estimations by Lindgren and Jönsson were based on the assumption that statins will continue to be used until 2028, which means 16 years with patent protection and 26 years with generic competition. Statins may conceivably be replaced by other medicines by then, but it is also possible that they may continue to create value. This has been the case in the next example, tamoxifen, which has been used for the treatment of breast cancer in Swedish health care for more than 30 years.

The SNS study by Lundqvist et al (2013b) analysed two targeted therapies for the treatment of breast cancer, tamoxifen and trastuzumab. When tamoxifen was introduced in breast cancer care in the late 1970s, it was originally prescribed for metastatic breast cancer. Tamoxifen is used in the treatment of women with breast cancer tumours that respond to hormonal treatment (ER-positive), which accounted for approximately 80% of cases in 2010 according to the Regional Cancer Centre Stockholm-Gotland (2011). It was obvious from an early stage that tamoxifen is also effective as an adjuvant to chemotherapy and radiation. Over time and as new scientific data have become available, the treatment duration for adjuvant tamoxifen was extended from one to two years, and later to five years. A recently published study supports continued treatment for up to ten years in women with ER-positive breast cancer (Davies et al, 2013).

In the SNS study, the estimation of the realised value of tamoxifen was limited to the first 25 years of use in Sweden, 1979-2004, and before more recently introduced medicines made registry data more difficult to analyse and interpret. Table 3.2 summarises the study's estimates of the number of patients treated, the health benefit, measured as QALYs, and a monetary expression of value. The report determined that over 75,000 women had been treated with tamoxifen in total. Together they

Table 3.2 Number of patients treated, aggregate health gains measured as QALYs, and monetary value of health gains (million SEK) from tamoxifen in Sweden during 1979–2004. Source: Lundqvist et al (2013b).

	Patients treated Number (%)	Aggregate health gains QALY (%)	Monetary value Million SEK (%)
Disseminated disease	19,500 (26)	8,100 (18)	6,800 (18)
Adjuvant therapy	55,700 (74)	37,500 (82)	31,700 (82)
Of which			
1 year	4,900	2,000	1,700
2 years	16,400	8,800	7,500
5 years	34,300	26,700	22,600
Total	75,100	45,600	38,500

QALY – Quality-adjusted life-year. Rounded figures.

were estimated to have received nearly 46,000 QALYs at a monetary value of just below 39 billion SEK.

The number of women who received tamoxifen for metastatic disease during the 25-year-long period of analysis was stable at around 750 women per year. About 18% of the total value derived from 25 years of use of tamoxifen in breast cancer care in Sweden was attributed to this group in more advanced stages of the disease. As is seen from the distribution of health benefits and value in Table 3.2, patients receiving tamoxifen as adjuvant therapy accounted for a majority of the total value, 82%. One explanation for this is that nearly three times as many women received tamoxifen as adjuvant therapy (n=55,700) than received it for the metastasized disease (n=19,500). In addition, the health benefit per woman treated was greater when the drug was used in adjuvant therapy than after the cancer metastasized.

Tamoxifen is an example of how the use in clinical practice produces a gradual increase in knowledge that allows more patients to be treated and more potential value of the technology to be realized. In the early phase, around 500 women received adjuvant tamoxifen annually until the mid-1980s. As new scientific results were published and awareness

of the value of tamoxifen grew, the number of women with breast cancer who were treated with tamoxifen in Sweden rose to around 2,000 annually by the second half of the 1980s. During the 1990s the number of treated women rose further and was equivalent to around 4,000 women annually by the early 2000s. This increase was mainly a result of extending the recommended time period for adjuvant treatment from one to two years and subsequently to five years.

The analysis showed that more than 70% of the total health benefit of adjuvant tamoxifen therapy occurred during the last ten years of the twenty-five-year treatment periods. The increased health benefit in terms of life-years gained was due more to a greater number of women treated than to increased treatment duration. The marginal utility of prolonged treatment was lower, but nevertheless cost-effective thanks to the reduction in price over time. In fact, a recently published study recommends adjuvant tamoxifen therapy for ten years, and new data have also been published that show benefit from using tamoxifen for primary prevention (Davies et al, 2013). In Chapter 5 we revisit the observation that realised values gradually increase with use and the importance of this for successful health care policy making.

The second targeted treatment for breast cancer, trastuzumab, was introduced more recently and is used for the treatment of HER2-positive breast cancer (Lundqvist et al 2013b). Trastuzumab was approved in Sweden for the treatment of metastatic breast cancer in 2001; adjuvant use began in 2005. According to Wilking et al (2010) approximately 14% of women with early breast cancer and 25% of women with metastatic breast cancer are HER2-positive. The Lundqvist et al study determined the value of introducing trastuzumab based on available data from a period of eleven years from 2001 to 2011. In total, the report determined that around 6,500 women had been treated with trastuzumab and achieved a total of 6,800 QALYs at a monetary value of 5.8 billion SEK (Table 3.3).

Data on the use of trastuzumab was available for a shorter time period, 11 years, compared with 25 years for tamoxifen. Hence the proportion of the overall treatment period during which the drug was used for a smaller indication and in more severely ill patients is greater for trastuzumab than for tamoxifen. It is clear that this shorter period of observation – particularly the shorter time period during which the

Table 3.3 Number of patients treated, aggregate health gains measured as QALYs, and monetary value of health gains (million SEK) from trastuzumab in Sweden during 2001–2011.

	Patients treated Number (%)	Aggregate health gains QALY (%)	Monetary value Million SEK (%)
Disseminated disease	3,300 (51)	3,300 (48)	2,800 (48)
Adjuvant therapy	3,200 (49)	3,500 (52)	3,000 (52)
Total	6,500	6,800	5,800

QALY – Quality-adjusted life-year. Rounded figures.

authors monitored use as an adjuvant to chemotherapy and radiation – meant that only some of the value of this new medicine was captured in the study. Time will show how much more value may be realised. The results in Table 3.3 show that, until 2011, the health benefit and associated value were almost equally divided between use of trastuzumab for metastasized disease and its use as an adjuvant. Our interpretation of the results is that, in the future, benefits for trastuzumab will follow a value trajectory similar to that for the older medicine, tamoxifen. In the final year of the study, around 1,000 women received trastuzumab, 600 as adjuvant therapy. Trastuzumab was patent protected during the entire 2001–2011 study period.

The two examples above – simvastatin for lipid-lowering treatment and hormonal treatment of breast cancer using tamoxifen – show that a greater number of patients received the medicine after patent protection had expired and price competition increased. Future use of trastuzumab will depend, amongst other things, on the number of women with HER2-positive breast cancer, the proportion of this population receiving treatment, and the duration of treatment for each patient. However, estimating benefits will become increasingly difficult as new medicines are introduced and used either concomitantly or sequentially with other treatments such as tamoxifen.

Five of the studies shown in Table 3.1 estimated the impact of change in health on productivity loss due to disease. Two of these studies, Neovius (2013) and Kalkan et al (2013), used longitudinal data from Swedish

registries to analyse labour market participation rates amongst patients with rheumatoid arthritis (RA). RA is an autoimmune inflammatory disease that affects 0.6–0.8% of the adult population in Sweden.

RA treatment has long focused on symptomatic treatment and pain relief using anti-inflammatory and pain-relieving drugs including NSAIDs and cortisone. About 20 years ago, methotrexate was introduced as the first conventional disease-modifying drug for the treatment of RA. Methotrexate had been used for the treatment of cancer since the 1950s. It works by suppressing the immune system and thus reducing RA symptoms such as stiffness, pain, swollen joints and fatigue. Generic methotrexate was already available by the time the indication was extended to include treatment for RA.

In 1999, the first so-called TNF inhibitor was introduced for the treatment of RA; this class of medicines is based on antibodies, often referred as 'biological' treatments. The treatment indications for TNF inhibitors have gradually expanded to include other rheumatoid conditions (such as anchylosing spondylitis, spondyloarthropathy, psoriatic arthritis, and juvenile arthritis) as well as treatment of psoriasis, Crohn's disease and inflammatory bowel disease. Several studies have demonstrated quality of life gains for RA patients treated with TNF inhibitors (Lindgren et al, 2009; Gulfe et al, 2010; and Karlsson et al, 2011); here, we highlight methods for estimating the value of reductions in productivity losses and freeing up resources within the health care system.

Kalkan et al (2013) reported on trends for 1990–2010 in the cost of sickness absenteeism and disability pensions where RA was reported as the primary cause. The authors noted a reduction in productivity losses at an aggregate national level. The greatest difference was found in disability pensions. In the early 1990s, RA was given as the primary cause in 3% of all disability pensions, compared to 1.5% in 2010. A similar reduction was seen in the number of newly granted disability pensions, from 2% to 1%.

The aggregate data set on which the above study was based showed parallel trends; however, data were insufficient for drawing conclusions about a causal relationship. One of the SNS studies includes a discussion of methodologies for highlighting the burden of illness and monitoring actual effectiveness using quality registry data in combination with national health registries (Neovius 2013). The author used TNF-inhibitor

treatment of RA with the outcome of workdays lost as a case in point. The report addresses three issues relating to outcomes and the feasibility of monitoring clinical effectiveness in the clinical practice:

4. What are size of the productivity losses associated with established RA?
5. How does the number of workdays lost change with the diagnosis of newly-onset RA?
6. How does the number of workdays lost change with biological treatment of established and new-onset RA, respectively?

Neovius (2013) found significant loss of productivity amongst people with established RA. Working-age RA patients lost twice as many work days annually as matched population-based controls. The total loss of productivity due to RA was estimated at 2.3 billion SEK in 2008 (Neovius 2013, Figure 4, p 17). Consistent with previous research, Neovius also detected a pattern of rapidly increasing loss of productivity prior to RA diagnosis and a reduction following the start of disease-modifying antirheumatic therapy. One year after the diagnosis, RA patients lost on average six additional work days each month compared to individuals of the same age, sex, and level of education (11 versus 5 work days lost per month).

The RA patient group was not homogenous; a small group of patients accounted for a large proportion of the overall loss of productivity. The statistical analysis showed that four years after diagnosis, on one side of the distribution 19% of patients were on full-time sick leave or disability pension and, on the other side, 46% had not registered any sick days with the Swedish Social Security Agency [Försäkringskassan] at any point. A small proportion, 8%, had lost 1–49 work days whereas a slightly larger proportion, 21%, had been away from work for 50–199 days; 7% of patients had been away from work for 200–364 days. It is clear that society incurs significant costs due to RA as a consequence of reduced work capacity, and new and more effective treatments may reduce it.

Biological treatments have been hailed as a treatment revolution in rheumatology. Sales statistics indicate a tenfold increase in total sales during 2000–2009. In 2012, TNF inhibitors accounted for more than 7% of the total cost of medicines. In Sweden, three of the top five selling medicines that year were biologics.

At the same time, the statistics in Neovius (2013) indicate a trend similar to that seen with the introduction of the breast cancer medicines tamoxifen and trastuzumab. The first patients to be offered a new medicine will be those whose illness is the most severe, also true for RA. Patients who started biological treatment in 2005 experienced a gradual increase in the number of annual sick days, up to an average of nearly 200 days in the year that treatment was started. These patients were diagnosed more than six years earlier (median duration). Once biological treatment began, sickness absenteeism stabilised in this group in comparison to a continuing upward trend amongst matched population-based controls. A study of patients with new-onset RA during 2006–2008 showed that more than 90% were treated with conventional disease-modifying drugs or cortisone alone (Neovius, 2013 p 24, Figure 11). Biological treatments were prescribed mainly for younger patients (30% of patients aged 18–29 years and 4% of patients aged 70–79 years).

A further study analysed treatment effectiveness in terms of disease activity in patients with new-onset RA during 2002–2006. Patients who did not achieve satisfactory health improvements on methotrexate alone where randomised to receive either a biological or a non-biological disease-modifying drug as an adjuvant to methotrexate. Even in this group of relatively new-onset RA patients, a sharp rise was seen in the number of days of sick leave before adjuvant treatment began. In both the biological and non-biological adjuvant therapy group, patients experienced a reduction in days of sick leave, from approximately 17 days per month at the time of randomisation to approximately 13 days per month after one year (Neovius 2013). The difference in clinical outcomes based on disease activity was statistically significant, but no statistically significant difference was observable in the number of days on sick leave after one year in this study of 258 patients. Overall, the results indicated small differences in outcomes in the selected patient population, whilst the difference in treatment costs was large.

RA clearly imposes a significant cost burden on society as a consequence of reduced capacity to work. Just over 20 years ago, a label extension for methotrexate provided clinicians with an additional tool in the fight against health and productivity loss due to RA. Around ten years later, TNF inhibitors brought about a therapeutic revolution, initially in rheumatology and subsequently in a wider range of indica-

tions. Good scientific evidence supports the positive effect of these new RA treatments on productivity losses. At the same time, the studies by Neovius and Kalkan et al cited above highlight the challenges associated with investigating causal relationships for specific outcomes such as reducing of sickness absenteeism due to RA.

The cost effectiveness of these new medicines remains unclear which is an unacceptable situation given the vast amounts spent on these products. For example, more than 12 billion SEK in total was spent by the Swedish health care system on TNF inhibitors during 2005–2012 according to the Swedish National Board of Health and Welfare's annual compilation of statistics on the use of medicines (National Board of Health and Welfare, 2013a).

In Chapter 5, we revisit the challenges associated with conducting effectiveness studies based on real-life observational data on the use of new medicines in clinical practice. In this context we will also be reviewing, from a wider perspective, studies that use aggregate national and regional longitudinal data to analyse the link between the introduction of new medicines and health trends in the population.

The distribution of costs and benefits – examples from four success stories

Four of the studies in Table 3.1 also included estimations of the real cost of using the medicines and correlated these with estimated value:

- HIV/AIDS (Philipson and Jena, 2005)
- Hyperlipidaemia (Lindgren and Jönsson, 2012)
- Chronic myeloid leukaemia (Lundqvist et al, 2013a)
- Breast cancer (Lundqvist et al, 2013b).

Comparisons of costs to value/revenue are intended to suggest whether investments in research, development and production of a new medicine have been worthwhile from a societal point of view. A further objective is to determine the relationships between incentives of the various stakeholders and the value generated by examining distribution of profits and burden of costs.

The accumulated survival gain from the development and use of antiretroviral drugs for the treatment of HIV/AIDS in the US by 2000

was estimated at 398 billion USD by Philipson and Jena (2005). Assuming a fixed annual number of new cases of HIV/AIDS (incidence) beyond 2000 and no changes in the efficacy of antiretroviral drugs, the anticipated value of the survival gain for future generations of HIV/AIDS patients was estimated at around 1,000 billion USD. Thus, the total anticipated value of the last 30 years of investments and breakthroughs in the treatment of HIV/AIDS was estimated at around 1,400 billion USD. This value was then divided into three categories: consumer surplus, producer surplus, and costs, in accordance with standard classification in economics. For these estimations, the authors assumed that the manufacturing costs of antiretroviral drugs accounted for 15% of expenditures on branded medicines overall. Under the assumption that future sales of antiretroviral drugs would remain at the same level as in 2000, the authors concluded that production costs would be 11 billion USD and producer surplus 63 billion USD. The greatest share of the value of antiretroviral drugs (1,330 billion USD) thus consisted of consumer surplus. Manufacturers/developers realised 5% of the total surplus and 95% accrued to consumers/patients according to these estimates.

Similarly, Lindgren and Jönsson (2012) estimated consumer and producer surplus of lipid-lowering treatment using simvastatin in Sweden from launch in 1987 to the year 2028. The total consumer surplus derived from simvastatin use was estimated at 1,083 EUR per capita. Savings from reduced health care costs and diminished loss of productivity were estimated at 59 EUR per capita. Total sales per capita were 113 million EUR). The producer surplus – the profit – was estimated at a total of 52 EUR per capita, corresponding to 5% of the total economic surplus, that is, consumer and producer surpluses together. Similar results on the distribution of surplus of statins were found in a recent publication on data from England and Wales covering 1990-2012 (Refoios Camejo et al, 2014).

Lindgren and Jönsson (2012) reported results for statins in Sweden similar to those that Philipson and Jena (2005) reported for antiretroviral drugs in the US. From a longer-term perspective, evaluation of innovative medicines such as antiretroviral drugs for the treatment of HIV/AIDS or the lipid-lowering drug simvastatin shows that the most of the value gained will accrue to consumers/patients. Successful new medicines will continue to generate health benefits for several decades, far beyond the expiry of their patents.

Lundqvist et al (2013a) adopted a somewhat different approach to demonstrating the added social value of new medicines in an SNS study that examined treatment for chronic myeloid leukaemia (CML) with imatinib. This new drug quickly and dramatically changed treatment for CML. During the initial period, 2002–2008, an estimated 75% of CML patients under the age of 70 received imatinib.

Lundqvist et al (2013a) estimated the potential health benefits, productivity gains, treatment costs and costs of consumption associated with life-years gained in a Swedish setting for a cohort of newly diagnosed CML patients who would receive imatinib at the same rate as those in 2000–2008. CML has an incidence of about 1 per 100,000 inhabitants in Sweden which corresponds to about 90 people per year. Findings were compared with two earlier treatment 'eras'. Era I, the 1970s, offered only symptomatic treatment. Era II, the 1990s, offered stem cell transplants for younger patients, interferon alpha therapy, and symptomatic treatment. Era III is the period during which imatinib has been first-line treatment CML.

The authors found that each new treatment technology introduced for CML increased life-years, but also produced higher health care and consumption costs. The benefits in terms of health and productivity gains, however, outweighed the increased costs. Figure 3.2 shows the difference between costs and benefits over time. Era III generated additional value equivalent to 168 million SEK over Era II for an annual cohort of 90 patients with new-onset CML. Compared to Era I, during which only symptomatic treatment was available, the additional value was 396 million SEK. Stated differently, if substantial expenditure in R&D had not occurred, treatment for CML patients would not have progressed beyond what was available in the 1970s and significant value would have been lost to society, even for this relatively small patient population.

R&D for CML has not been restricted to the development of new medicines. As early as in the 1990s, stem cell transplantation was available, mostly to patients under the age of 50 for whom a suitable donor was available. This intervention has the potential to eliminate the cause of CML and, if successful, is associated with significant survival gains. Risks are serious, however, with reported transplant-related mortality rates at 7% to 14% during the first three years following treatment

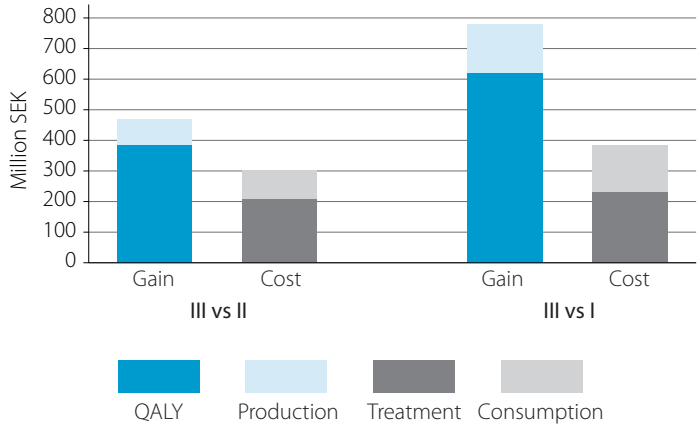


Figure 3.2 Increased value and cost of the treatment of chronic myeloid leukaemia (CML). Era III, during which imatinib has been first-line treatment compared with previous technologies during Era II and Era I. Million SEK. Source: Lundqvist et al (2013a).

(Oyekunle et al, 2011). Nonetheless, the development of new technology might have stalled given the significant progress made in this patient segment during the 1990s. As shown in Figure 3.2, the incremental value from adopting imatinib as first-line therapy was lower compared to the Era II technology than compared to the Era I technology. Over the remaining lifetime of an annual cohort of 90 incident patients, however, the discounted economic gain was estimated at 168 million SEK, or around 1.9 million SEK per patient.

In another SNS study, Lundqvist et al (2013b) contrasted the short-term to the long-term added value of two medicines used for the treatment of breast cancer. The first, tamoxifen, was introduced in Sweden in the late 1970s; and the second, trastuzumab, was introduced in 2000 for the treatment of metastatic HER2-positive breast cancer. Since 2005, trastuzumab has also been used as adjuvant therapy following surgery for HER2-positive breast cancer. The study estimated the value of the realised economic gain from the use of tamoxifen during 1979–2004 (patented and off-patent) and trastuzumab during 2000–2011 (patented only). Figure 3.3 illustrates economic gain of each medicine over available treatment options available before their introduction.

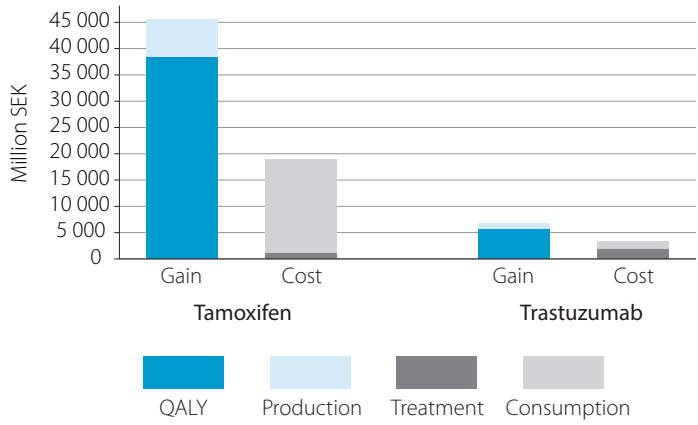


Figure 3.3 Increased value and cost of the treatment of hormone-responsive and HER2-positive breast cancer following the introduction of tamoxifen and trastuzumab: million SEK. Source: Lundqvist et al (2013b).

In the previous section, we noted the number of patients treated and the estimated value of tamoxifen (Table 3.2) and trastuzumab (Table 3.3). At present, tamoxifen is a standard option for the treatment of breast cancer following surgery in women with hormone-sensitive cancer. In Sweden, this is corresponding to 120 per 100,000 women in the population, or approximately 5,700 new patients annually. Lundqvist et al (2013b) estimated that a total of 75,000 women had received tamoxifen during 1979–2004 in accordance with treatment recommendations at the time (i.e. treatment for 1, 2 or 5 years). Considerable economic value has been created, which the longer time perspective used in the analysis makes clear. Figure 3.3 shows that treatment costs have been low (1 billion SEK compared to the total gain of 45 billion SEK). From a societal point of view, consumption costs are the highest component of costs – 17.9 billion SEK out of a total cost of 18.9 billion SEK (96%). Consumption costs are based on age-related average private and public consumption.

A somewhat different picture emerges from the analysis of the more recent drug trastuzumab. Estimates are based on the early implementation phase while the drug was still on patent. The far right bars in figure 3.3 show gains and costs for trastuzumab.

1. Productivity gains accounted for a smaller share of overall gains compared with tamoxifen. This can be explained largely by the fact that for nearly half of the observation period trastuzumab was only used for patients whose disease had metastasized. Treatment during this advanced stage is less likely to have an impact on productivity than is adjuvant treatment for patients in earlier stages of the disease.
2. Consumption costs accounted for 42% of total costs. There are two explanations for this. Firstly, during the early implementation phase trastuzumab was still patent-protected and the manufacturer was able to recover more of the costs of R&D. Secondly, during this early period, patients whose illness was more severe accounted for a relatively large proportion of the total number of patients treated. This group will gain comparatively few life years and thus increase consumption costs less.

These findings, based on medicines introduced for treatment 30 years and 10 years ago, agree with the results discussed above for antiretroviral drugs for the treatment of HIV/AIDS and for simvastatin as a lipid-lowering therapy. Analyses that consider societal gain and costs from a long-term perspective, and also take into account price changes after patent expiration, clearly demonstrate the value of new technologies increasingly accrues to patients/consumers over time. In the shorter term, treatment costs account for a greater share of the total costs. Because the treatment is more likely to still be patent protected, this is also the time when some of the costs of R&D may be recouped.

At what stage may success or failure be determined?

Above, we discuss four instances where values and costs accrue to society over the longer term. In the early 2010s, with data from randomised clinical trials and observational studies with several decades of follow-up, we may account for the costs of new medicines and calculate both health gains and net gains to society. But what was it like when these now well-established medicines were first introduced? At what point was it obvious that these treatments would be successes, not failures?

Firstly, in our opinion, the health care system is very good at identifying fairly early on those new medicines whose value does not justify their costs. The vast majority of new medicines that achieve relatively low sales do so not just because of their price, but because of doubt about whether their value justifies the cost. One example of a medicine that failed at a relatively early stage of marketing is inhaled insulin for people with diabetes. This product was approved in January 2006 and was deregistered in September 2008. According to the Swedish National Board of Health and Welfare medicines registry, it was used by 44 patients in 2007 and 21 patients in 2008 (Socialstyrelsen 2013b). A number of factors led to the withdrawal of the product: low sales, difficulty of use, and reports of a suspected link to lung cancer.

Orlistat is another example of a medicine that did not meet expectations. Approved by the EMA in 1998 for the treatment of obesity, the drug was dispensed to 12,600 patients in Sweden during 2012. This is 60% fewer than in the 20,900 patients 2006, the first year for which data are available in the National Board of Health and Welfare medicines registry.

New medicines may also disappear from the market as a consequence of new knowledge from clinical practice about adverse events. Rosiglitazone was approved by the Swedish Medical Products Agency in 2000 for the treatment of type 2 diabetes, a condition for which several other treatment options exist. As time progressed, studies emerged that showed a link between rosiglitazone and cardiovascular events. Since cardiovascular disease is common amongst people with type 2 diabetes, the risk was considered too high. Market authorisation for medicines containing rosiglitazone was withdrawn by the EMA in 2010, two years before the patent expired in 2012. Scientists have argued that risk signals for cardiovascular events could have been detected earlier if registry studies had been used in a systematic way.

The COX-2 inhibitor class of drugs provide another example of relatively long time lapse between initial marketing and the identification of clearly unfavourable risk-benefit ratio. These drugs were approved in 1999 and withdrawn from the market in 2004 following reports of an increased risk of myocardial infarction and stroke with prolonged use. However, no systematic studies have been done of the losses associated with the use of these medicines.

Both rosiglitazone and the COX-2 inhibitors were withdrawn because of risks identified in clinical practice in patients whose use was likely to be chronic and long-term. Cancer drugs, in comparison, are often used in severely ill patients with short life expectancies and are less likely to be withdrawn because of adverse events; cost or lack of efficacy is more likely to be the reason.

It often takes time to gather sufficient knowledge on the advantages and disadvantages of new medicines. This applies to preventive treatment of chronic conditions. The box shows the perceived value of two medicines for the treatment of type 2 diabetes from the 1950s to today.

THE VALUE OF TWO DIABETES MEDICINES

Sulphonylureas and biguanides were introduced in Sweden to treat type 2 diabetes in the 1950s (Östman, 2004). No modern comprehensive regulatory framework for conducting clinical trials prior to the approval of a new medicine then existed. In 1961, an American multi-centre study (the University Group Diabetes Program [UGDP]) was formed following the launch of these medicines. The UGDP study was terminated around 1970 as the active treatment arm appeared to show no positive treatment effect, but instead showed an increased risk of cardiovascular disease. The study design and choice of analytical methods have been criticised on a number of points by, amongst others, Kilo et al (1980).

Partly because of these flaws, the UK Prospective Diabetes Study (UKPDS) was initiated in the late 1970s. Its seminal results, based on ten years of follow-up data, were published in the late 1990s. The study found that lowering blood glucose levels reduced the risk of complications from diabetes such as kidney disease and eye diseases (American Diabetes Association 2002). The UKPDS study eliminated any lingering doubt about the value of intensive treatment of type 2 diabetes, including glucose-lowering therapy.

Regulation at the time when sulphonylureas and biguanides was introduced was very different from today and medicines entered the market much earlier, and with less evidence. Had these medicines instead been developed today, the clinical research studies would have been much better designed and the concerns raised during the 1960s, 1970s and 1980s, prior to the publication of the UKPDS results in 1998, could have been addressed much sooner. The story of the sulphonylureas and biguanides serves as an example of how society may lose out on considerable value by dismissing new technologies too soon. See also the SNS study by Steen Carlsson et al (2013).

The story of tamoxifen and trastuzumab, the two breast cancer medicines, may be viewed from a similar angle. By the time trastuzumab was introduced, evidence-based medicine had become an important part of clinical practice, cancer care was centralized and national guidelines were available from the Swedish National Board of Health and Welfare. In 2005, results were published that substantiated the value of trastuzumab as an adjuvant therapy in early HER2-positive breast cancer. In the same year, the Swedish Breast Cancer Group published guidelines recommending trastuzumab as adjuvant therapy in early HER2-positive breast cancer. Within two years, trastuzumab was used routinely in Sweden as adjuvant therapy.

Adoption of tamoxifen was slower. In the early 1980s, reports were published that demonstrated the benefit of tamoxifen as adjuvant therapy in early hormone-sensitive breast cancer. In 1985, the National Institutes of Health and the National Cancer Institute published recommendations for tamoxifen use as adjuvant therapy (Kemetli et al, 2009). It was not until five years later that tamoxifen began to be used routinely in Sweden as an adjuvant therapy.

Had the Swedish treatment guidelines been updated as swiftly for tamoxifen as they were 20 years later for trastuzumab, Lundqvist et al (2013b) estimated that an additional 10,900 women could have been treated with tamoxifen. The health benefit for these women would have been approximately 5,400 QALYs at a value of 4.6 billion SEK, a significant addition to the health gain of 39 billion SEK (+12%) that was realized.

The story of tamoxifen and trastuzumab underscore the importance of having established infrastructure in place for supporting and expediting local decision-making. This includes, for example, research programmes that analyse comparative effectiveness, including implications for both improving health and productivity, and efficiency gains from improved treatments that free up resources elsewhere; decision-making processes in health care system and at the national level provide support to individual prescribers by synthesising knowledge to guide clinical decisions.

As our examples have shown, determining whether a therapy is a success can be done much more quickly today than was possible 30 years ago. Careful assessments, however, are still crucial and this is especially

true for interventions whose full impact cannot be verified without decades of observation and analysis – preventive care is one example.

This chapter has highlighted the costs and gains associated with successful new medicines, including significant health gains and improvements in productivity. The research on rheumatoid arthritis in particular points to the importance of adopting multiple study approaches and conducting multiple subgroup analyses to more fully understand the value of new medicines.

Final comments

In this chapter, we have used examples from the SNS research programme on new medicines and other published sources to illustrate how innovations that change the way diseases are treated will continue to generate value for patients and society over the long-term. We have reviewed studies that demonstrate not only the substantial contribution of medicines to the welfare of society, but also their tremendous potential to both lengthen and improve individual lives. Lipid-lowering and antihypertensive treatments have helped reduce cardiovascular mortality over the last 30 years; ten years ago the cancer drug imatinib dramatically changed the prospects for people diagnosed with CML, as did insulin 100 years ago for people with diabetes. Antiretroviral drug therapy has turned HIV/AIDS, once a death sentence, into a treatable chronic illness.

In addition to health gains expressed as life years, the studies also captured health gains from improved quality from, for example, reduced pain and anxiety or increased ability to perform daily activities at work and in leisure time. Improved quality of life has been a key component in determining health gain from treating CML with imatinib and breast cancer with tamoxifen or trastuzumab. Studies on cardiovascular disease also assessed improvement in quality of life.

Five of the studies discussed estimated productivity gains. Four of these – new medicines for breast cancer, CML and cardiovascular disease, and one for RA – indicated productivity gains from working-age patients being able to return to work. Although productivity gains contributed to the gains in social welfare, health gains were the core component of the calculated value.

The study designs, data sets, and methodology varied across the studies. The studies all used registry data and data from published studies. Registry data were used primarily for determining disease prevalence and the number of individuals using a new medicine. Patient-level registry data on mortality were also a crucial aspect of the studies on antiretroviral drugs for HIV/AIDS, CML, and cardiovascular disease.

METHODOLOGICAL CHALLENGES

Six of the studies employed modelling for determining the value of new medicines. Modelling allows data from several sources to be merged with an aim of estimating the expected added value new treatments compared to present standard of care by exploring the patient values and costs given available data and making a prognosis for long term values. Modelling is an important tool for capturing all dimensions of value in an analysis.

A core methodological challenge in the analysis of the value of new technologies is accurately measuring the relationship between interventions and outcomes. For example, if several new treatment technologies for the same purpose are introduced in parallel, gains may be double counted. One way of managing this risk is used in a study of the value of new technologies in ischaemic heart disease (Lundqvist et al, 2012). This study looked at several new medicines and other health care technologies introduced 1980–2010. To avoid overestimating the value from the use of several new technologies at the same time, the employed a top-down design and measured outcome in terms of total decline in mortality from ischaemic heart disease and used published epidemiological data to determine how much of this decline was the result of new treatments. The authors thus identified the maximum possible health gain and prevented the sum of parts from exceeding the total.

The other modelling studies have based their analyses on the number of patients treated with a particular condition or treatment and summed up the anticipated gain per patient. This analytical strategy is useful for determining the value in defined patient groups and when utilisation data are available.

In summary, the choice of methodology for estimating the value of new medicines, or any other technology, is determined by two principal factors: the research question and access to data. The research question determines which patient population, the medicine, and other treatment components to be considered. Access to data and the quality of the data collected are crucially important for making accurate estimations.

Nevertheless, although the debate continues about the pros and cons of various methods, this is not an argument against estimations per se.

Our conclusion is that there is a large unmet need for increased knowledge regarding the value of new medicines, both in terms of actual use and outcomes. We need more knowledge regarding the relative effectiveness of new drugs when used in clinical practice and in comparison with other relevant treatment options. Perhaps the most important challenge is how to make data sets available for analysis.

Many medicines that are now regarded as standard treatment were initially met with guarded enthusiasm or even scepticism. At the early stages of introduction, particularly during the time when patents allowed higher prices to be charged, the use of lipid-lowering statins and the breast cancer drug tamoxifen were limited by relatively high prices and lack of evidence to support more widespread use.

Two important lessons from the success stories highlighted in this chapter are that:

1. It may take time to realise a new medicine's full potential for generating value
2. The allocation of value to society and the developer will shift over a medicine's lifecycle.

The first lesson emphasises the importance of continuing efforts to generate knowledge after a medicine reaches the market and starts to be used in clinical practice. In the coming chapters we will be revisiting the need for monitoring new medicines in clinical practice in more depth.

The second lesson is a reminder of the importance of having an effective patent system that rewards innovation with a monopoly on sales for a limited period of time. The costs of R&D for new drug are most likely to be recouped while it is still under patent protection.

Finally, the gains achieved in these success stories may not represent the maximum total benefit of any of the medicines. Had they been introduced sooner and more efficiently, the gains could have been greater. Chapter 4 discusses regional differences in the use of new medicines and what can be learned from this. Chapter 5 discusses the role of the patient and how compliance analyses can contribute to the value of new medicines in clinical practice.

References

American Diabetes Association (2002). 'Implications of the United Kingdom Prospective Diabetes Study', Diabetes Care 25 (suppl 1), pp 28–32.

Björck L., Rosengren A., Bennett K., Lappas G., Capewell S. (2009). 'Modelling the decreasing coronary heart disease mortality in Sweden between 1986 and 2002', European Heart Journal 30 (9), pp 1046–1056.

Björkholm M., Ohm L., Eloranta S., Derolf A., Hultcrantz M., Sjöberg J., Andersson T., Höglund M., Richter J., Landgren O., Kristinsson S.Y., Dickman P.W. (2011). 'Success story of targeted therapy in chronic myeloid leukaemia: a population-based study of patients diagnosed in Sweden from 1973 to 2008', Journal of Clinical Oncology 29 (18), pp 2514–2520.

Davies C., Pan H., Godwin J., Gray R., Arriagada R., Raina V., Abraham M., Medeiros Alencar V.H., Badran A., Bonfill X., Bradbury J., Clarke M., Collins R., Davis S.R., Delmestri A., Forbes J.F., Haddad P., Hou M.F., Inbar M., Khaled H., Kielanowska J., Kwan W.H., Mathew B.S., Mittra I., Muller B., Nicolucci A., Peralta O., Pernas F., Petruzelka L., Pienkowski T., Radhika R., Rajan B., Rubach M.T., Tort S., Urrutia G., Valentini M., Wang Y., Peto R. (2013). 'Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial', Lancet 381 (9869), pp 805–816.

Gulfe A., Kristensen L.E., Saxne T., Jacobsson L.T., Petersson I.F., Geborek P. (2010). 'Rapid and sustained health utility gain in anti-tumour necrosis factor-treated inflammatory arthritis: observational data during 7 years in southern Sweden', Annals of the Rheumatic Diseases 69 (2), pp 352–357.

Kalkan A., Hallert E., Bernfort L., Husberg M., Carlsson P. (2013). 'Costs of rheumatoid arthritis during the period 1990–2010: a register based cost-of-illness study in Sweden'. Rheumatology, Early access, doi:10.1093/rheumatology/ket290.

Karlsson J.A., Nilsson J.A., Neovius M., Kristensen L.E., Gulfe A., Saxne T., Geborek P. (2011). 'National EQ–5D tariffs and quality-adjusted life-year estimation: comparison of UK, US and Danish utilities in south Swedish rheumatoid arthritis patients', Annals of the Rheumatic Diseases 70 (12), pp 2163–2166.

Kemetli L., Rutqvist L.E., Jonsson H., Nystrom L., Lenner P., Tornberg S. (2009). 'Temporal trends in the use of adjuvant systemic therapy in breast cancer: a population based study in Sweden 1976–2005', Acta Oncologica 48 (1), pp 59–66.

Kilo C., Miller J.P., Williamson J.R. (1980). 'The crux of the UGDP. Spurious results and biologically inappropriate data analysis', Diabetologia 18 (3), pp 179–185.

Lindgren P., Geborek P., Kobelt G. (2009). 'Modeling the cost-effectiveness of treatment of rheumatoid arthritis with rituximab using registry data from Southern Sweden', International Journal of Technology Assessment in Health Care 25 (2), pp 181–189.

Lindgren P., Jönsson B. (2012). 'Cost-effectiveness of statins revisited: lessons learned about the value of innovation', The European Journal of Health Economics 13 (4), pp 445–450.

Lundqvist A., Levin L.-Å., Persson U., Steen Carlsson K. (2012). 'Värdet av forskning och ny medicinsk teknologi för hjärt-kärlsjukdom – en studie utifrån exemplet ischemisk hjärtsjukdom', IHE report 2012:3. Lund: Swedish Institute for Health Economics (IHE).

Lundqvist A., Norlenius Ohm A.-C., Dickman P., Höglund M., Stenke L., Gerdtham U.-G., Persson U., Björkholm M., Steen Carlsson K. (2013a). 'Medicinska framsteg i behandling av kronisk myeloisk leukemi', Stockholm: SNS.

Lundqvist A., Wilking N., Gerdtham U.-G., Persson U., Steen Carlsson K. (2013b). 'Målriktad behandling av bröstcancer', Stockholm: SNS.

Neovius M. (2013). 'Reumatoid artrit, biologisk behandling och förlorade arbetsdagar – exempel på användning av svenska hälsodataregister', Stockholm: SNS.

Ohm L., Lundqvist A., Dickman P., Höglund M., Persson U., Stenke L., Steen Carlsson K., Björkholm M. Real-world cost-effectiveness in chronic myeloid leukaemia: The price of success during four decades of development from non-targeted treatment to imatinib. Leuk Lymphoma. 2014 Aug 20: 1–16. Epub ahead of print. MMID: 25139694.

Oyekunle A., Klyuchnikov E., Ocheni S., Kroger N., Zander A.R., Baccarani M., Bacher U. (2011). 'Challenges for allogeneic hematopoietic stem cell transplantation in chronic myeloid leukaemia in the era of tyrosine kinase inhibitors', Acta haematologica 126 (1), pp 30–39.

Philipson T., Jena A. (2005). Who benefits from new medical technologies? Estimates of consumer and producer surpluses for HIV/AIDS drugs. NBER working papers. Cambridge, USA: National Bureau of Economic Research.

Refoios Camejo R.R., McGrath C., Miraldo M., Rutten F. (2014). Distribution of health-related social surplus in pharmaceuticals: an estimation of consumer and producer surplus in the management of high blood lipids and COPD. Eur J Health Econ. 2014 May;15(4):439-45. doi: 10.1007/s10198-013-0484-1.

Regional Cancer Centre Stockholm-Gotland (2011). Bröstcancer: Nationell rapport diagnosår 2010.

Swedish National Board of Health and Welfare (2013a). Läkemedel – statistik. Sveriges officiella statistik. Stockholm: Swedish National Board of Health and Welfare. Publications covering 2006–2012.

Swedish National Board of Health and Welfare (2013b). Statistics database of the Swedish National Board of Health and Welfare. Drug registry.

Steen Carlsson K., Berne C., Johansen P., Lanne G., Gerdtham U.-G. (2013). 'Behandling av diabetes i ett 100-årigt perspektiv', Stockholm: SNS.

Weiderpass E., Gridley G., Nyren O., Pennello G., Landstrom A.S., Ekbom A. (2001). 'Cause-specific mortality in a cohort of patients with diabetes mellitus:

a population–based study in Sweden', Journal of Clinical Epidemiology 54 (8), pp 802–809.

Wilking U., Jönsson B., Wilking N., Bergh J. (2010). 'Trastuzumab use in breast cancer patients in the six Health Care Regions in Sweden', Acta Oncologica 49 (6), pp 844–850.

Östman J. (2004). 'Från svältkurer till pankreastransplantationer. Diabetesbehandlingen i ett 100-årigt perspektiv"[From starvation cures to pancreas transplantations. Treatment of diabetes seen in a perspective of 100 years], Läkartidningen 101 (51–52), pp 4229–4231, 4233–4227.

4. Utilisation determines value – what can we learn from regional variation?

One interpretation of the results of the SNS research programme on the value of new medicines is that focus should be on the outcome, expressed as health and productivity gains. However, this outcome cannot be measured or evaluated without knowing how drugs and other treatments are actually used. In this publication we take the view that the value of innovative medicines is created as the medicines are being used, although this does not mean that all forms of use generate value. By systematically measuring and monitoring health care interventions in clinical practice and understanding their impact on people's health and well-being, new knowledge can be acquired.

This chapter discusses variations in the use of new medicines, in particular how regional differences may create opportunities for analysing the impact on patient health status and other outcome measures. Studies of regional variation are important tools in expanding our knowledge about the value of new technologies such as new medicines, especially during the early phases of use. We are interested not in the geographical region itself, but the fact that it allows us to study the use of medicines in unselected and broad populations and to compare patterns of use across regions. The Swedish health care system, in which county councils are responsible for their respective populations, is particularly well suited for such studies.

The American epidemiologist John Wennberg has been conducting research on geographic variations in the use of health care interventions for four decades. He published the first study on this topic in 1973 in

the journal Science where he explored variations in the prevalence of a range of surgical interventions in the state of Vermont (Wennberg and Gittelsohn, 1973). The authors concluded that the variation could not be explained by differences in population characteristics or health care insurance coverage, that is, demand factors. They identified supply-side factors, i.e. intervention choices made by hospitals and individuals, as being primarily responsible for the patterns observed.

The results published by Wennberg and colleagues over the last four decades sometimes have been regarded as controversial, since they have questioned prevailing views on equitable care and raised concerns about quality of care. Wennberg's approach broke new ground in using population data to identify patterns of use that were inconsistent with the assumption that all patients with a given conditions received the same health care interventions. Differences in outcomes also became evident.

American economists recently published a study that analysed whether regional variation in health US care expenditure could be explained by patients' demand for care and physicians' views on appropriate treatment (Cutler et al, 2013). To minimise the impact of financial incentives on supply and demand, the authors used data from Medicare, the government-funded health insurance programme for people aged 65 and older. Patients' own requests for treatment and treatment intensity affected regional variation only marginally, but a strong link was found between physicians' views on appropriate treatment and the level of health care expenditure. The authors concluded that physicians' own perceptions of treatment effectiveness determine which treatments they regard as appropriate. The influence of the physician's personal experience and peer network are high; the effect of practice guidelines is less clear. The next question, then, will be whether the differences in physicians' choice of treatment are reflected in health outcomes. We return to this question later in this chapter as we discuss one of the SNS studies on regional variation Sweden.

In the mid-1990s, the Swedish National Board of Health and Welfare created media headlines with the publication of statistics showing differences between hospitals in mortality from myocardial infarction (see, for example, reports and commentaries in the 1996 journal of the Swedish Medical Association, Läkartidningen, issues 44–46). Since then, the National Board of Health and Welfare has broadened its

efforts to collect statistics on patient outcomes and health care interventions by region in the Swedish health care system. As part of a collaboration between the National Board of Health and Welfare and the Swedish Association of Local Authorities and Regions (Sveriges Kommuner och Landsting [SKL]), statistics on the use of medicines and other health care interventions are published regularly to provide regional comparisons (SALAR and SNBHW, 2013). The results are based on statistics on predefined indicators that capture different aspects of health care such as medical outcomes, patient experiences, access to care, and costs.

Figure 4.1 is an example of a 2013 Regional Comparisons report that shows the variation across county councils in the number of patients per 100,000 inhabitants being treated for rheumatoid arthritis with biological agents. An almost two-fold difference can be identified in the number of patients being treated with biologicals in Jönköping compared with region Skåne. The report points out that although there is no definition of need that can reliably estimate how many patients should receive biological treatment, there are also no signs of overuse.

The differences in the utilisation of health care interventions highlighted in Regional Comparisons reports provide insights into the nature of the variation and how they are changing over time. A number of important questions however still need to be addressed. These include in particular how variations in the use of a medicine are affected by:

- The number of patients who can (potentially) benefit from the medicine
- The health and productivity gains that can be achieved both by the medicine and any relevant treatment alternatives.

The Regional Comparisons report from 2013 also examines medical therapy 6–12 months after an osteoporotic fracture and shows variation not only between counties, but also differences between men and women within each county. Figure 4.2 shows that the number of patients receiving medical treatment varies from just below 10% to just over 20% for women, and from around 2% to 6% for men in different county councils.

Regional differences may be desirable – for example, when the prevalence of a disease varies across regions, the use of medicine should also

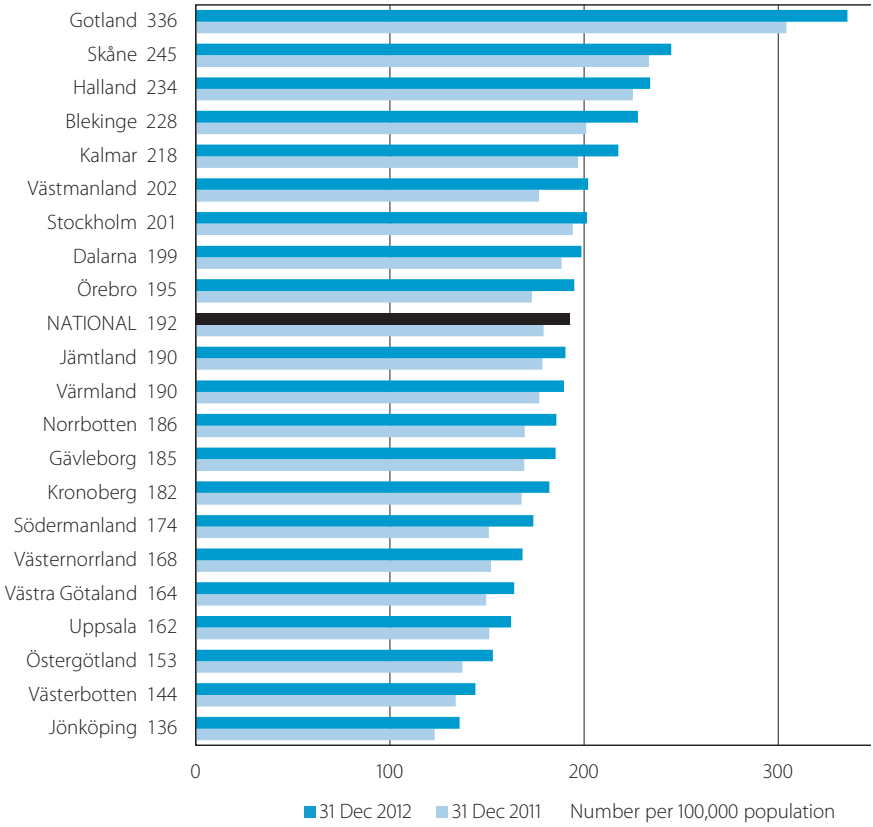


Figure 4.1 Regional variation, measured as the number of rheumatoid arthritis patients receiving biological treatment per 100,000 county population. Source: National Board of Health and Welfare (2013b) Figure 24A p 48.

vary. The Regional Comparisons reports lack sufficient data to track such differences.

Whatever the cause of variation, understanding the value of medicines can benefit from research into variations in the use. Moreover, such research may suggest whether and to what extent these variations are also reflected in population outcomes.

The effect of analyses and comparisons of regional variations in the use of health interventions can be to produce research-driven policy

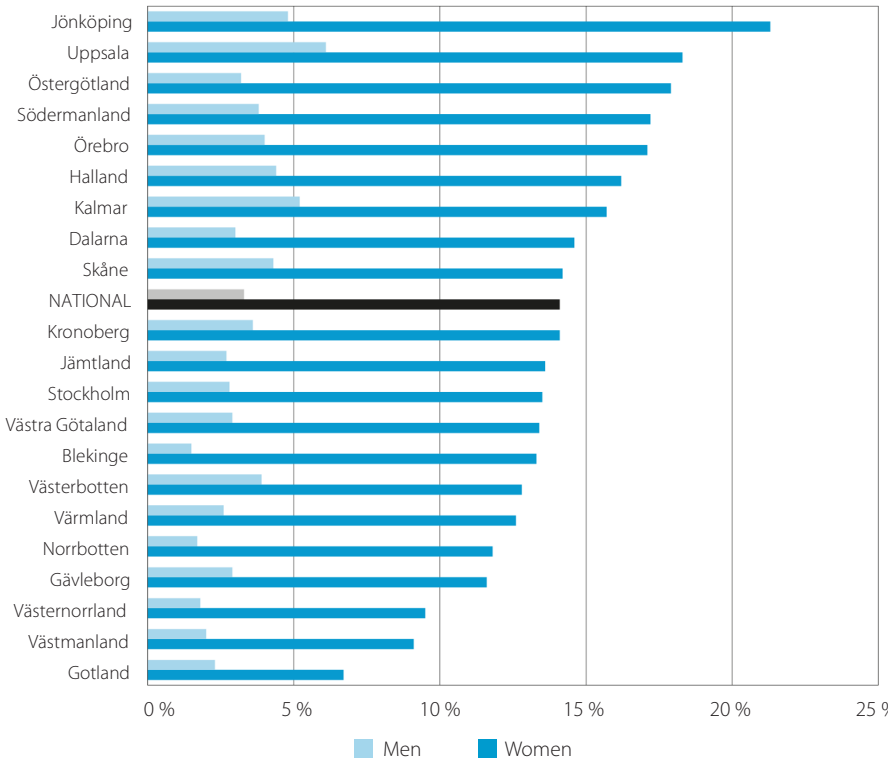


Figure 4.2 Regional variation, showing the number of patients with osteoporotic fractures who remained on medical therapy after 6–12 months per 100,000 county population. Source: National Board of Health and Welfare (2013b), Figure 23A p 46.

(Luft, 2012). Scientists are interested in identifying factors explaining variation and in developing statistical measures of effect. These studies can alter how society and decision-makers perceive reality. This ultimately may result in new health care policies intended to affect the situation. Wennberg's research unquestionably has altered views on the use of health care interventions and the use of observational studies to increase understanding about health care use and value of treatment technologies. These studies, however, described differences, but do not suggest what measures, if any, should be taken. Additional research is necessary to determine that.

Policy-driven research, according to Luft (2012), occurs when decision-makers specify the research objectives. The annual reports on quality and efficiency from the Swedish Association of Local Authorities and Regions and the Swedish National Board of Health and Welfare could be regarded as policy-driven research intended to provide information and data for public debate. Data that detail the variation in the use of new medicines, or other health care technologies, reveal little about value. However, if the same data is linked to both mortality and health outcomes, important results on of value of new medicines may be achieved.

Data sets like the ones used for Regional Comparisons reports are important to efforts to define the value of new medicines. Variations in both use and outcomes are essential. However, valid conclusions about the cause of variation also require careful analysis of other possible explanations for the patterns observed. We revisit this in Chapter 5 in a discussion of analysing clinical practice data to evaluate the efficacy and safety of medicines.

Regional variation and the value of tamoxifen

Let us go back to an example used in Chapter 3: tamoxifen, used since the late 1970s for the treatment of breast cancer. In an SNS study Lundqvist et al (2013b) determined that the total realised health gain from tamoxifen during 1979–2004 was around 45,000 quality-adjusted life years (QALYs). This estimate was based on national and regional sales figures. These figures also suggested significant variation across regions in the use of tamoxifen, with higher sales per 100,000 population higher than the national average in the Stockholm-Gotland region. There are at least two explanations for this variation:

- A larger proportion of breast cancer patients in the Stockholm-Gotland region received tamoxifen
- Treatment duration was extended from one to two years, and later to five years, earlier in the Stockholm-Gotland region than in the rest of the nation.

The authors calculated the health benefits foregone in regions that were slower than Stockholm-Gotland in adopting tamoxifen. Had the na-

tion as a whole adopted tamoxifen at the same rate as the region where uptake was fastest, a further 10,700 women with early breast cancer could have been treated at a total of 7,600 QALY, which would have increased total QALYs gained from 45,000 to 52,600.

Regional variation is unavoidable during the early implementation phase of a new technology such as a new medicine. Nevertheless, it is important to monitor trends and learn from them. As in the example of tamoxifen, variation may both affect a significant number of patients and fail to realise substantial overall health benefit.

Regional differences in the use of cancer drugs

As part of the SNS project, Jönsson and Wilking (2013) presented a review of the introduction and use of new medicines in oncology. Between 1998 and 2008, sales of cancer drugs increased dramatically, and then reached a plateau (Figure 4.3). Sales increased in all regional health care authorities, although at varying rates, which led to significant variation across regions. The differences were particularly evident during the final five years of the period when sales plateaued at different levels.

While this variation in the use of cancer drugs has been well known to Swedish oncology specialists, it has not led to major debate. No analysis has been done to identify which factors may explain the differences in sales. One possible explanation for the lack of studies, according to Jönsson and Wilking (2013), is an absence of the patient-level statistical data needed to identify variations in indications and treatment patterns. Aggregated figures for the entire region alone are not helpful in determining overuse or underuse.

Another unanswered question relating to this variation in total cost of cancer care is due to the use of medicines alone or if it may also be related to differences in the rate of use of other aspects of cancer care. It may be important to know, then, whether regions with high use of medicines purposely have chosen medicines over other treatment options such as surgery or radiation. Sufficient data are not available to answer this question because health care costs are not systematically reported by input factor at regional level. In principle, the information exists in

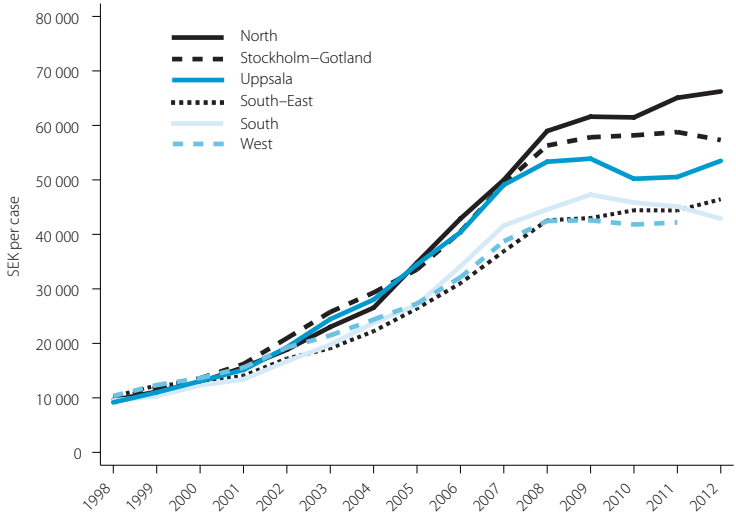


Figure 4.3 Population-based sales of all cancer medicines in Sweden's six regional health care authorities during 1998–2012. SEK per case. Source: Jönsson and Wilking (2013), Figure 2 p 10.

patient records. However, data in this format requires extensive effort to process and adapt for research purposes. Individual county councils have carried out studies in specific conditions, but more comprehensive efforts are lacking.

Still unknown is whether utilisation of different types of interventions such as medicines, surgery, radiation – or no treatment – will yield different results in terms of health outcomes and welfare gains. Jönsson and Wilking (2013) point out that regional variations such as those shown in Figure 4.3 may be the result of both overuse and underuse of medicines.

The example of bevacizumab

Bevacizumab was introduced in Sweden in 2005 and is currently available for the treatment of metastatic colorectal, lung, breast, renal and ovarian cancer. Amongst other indications, it is approved for first-line treatment of advanced colorectal cancer. Studies are underway to determine whether there is a benefit in adding bevacizumab as an adjuvant

to chemotherapy and surgery for the treatment of lung cancer and breast cancer.

In 2011 bevacizumab accounted for 5.3% of total sales of cancer drugs in Sweden. Sales grew by 21% during 2009–2010 and by a further 13% during 2010–2011 (Jönsson and Wilking, 2013, Table 1, p13). Sales subsequently dropped by 24% from 2011 to 2012 according to the latest statistics from the Swedish National Board of Health and Welfare (National Board of Health and Welfare, 2013a, Table 21, p41).

The differences across regional health care authorities at an aggregate level for all cancer drugs was even more prominent for individual medicines such as bevacizumab (Figure 4.4). The overall costs per cancer patient were four times higher in the region with the highest use of bevacizumab than in the region with the lowest use. Attributing this variation to demographics alone or to different interpretations of existing medical evidence is unrealistic. The most likely reason is variation in the use of bevacizumab in specific cancer diagnoses in the different regions.

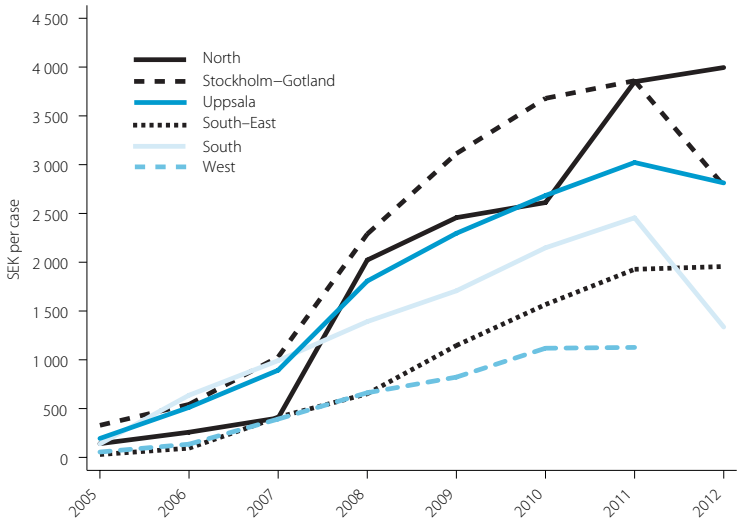


Figure 4.4 Use of bevacizumab in Sweden's six regional health care authorities during 2005–2012. SEK per case. Source: Jönsson and Wilking (2013), Figure 10, p 25.

The large variation in use is noteworthy given that lack of evidence to support the cost-effectiveness of bevacizumab. For example, the UK National Institute for Health and Care Excellence (NICE) found no evidence of cost-effectiveness in using bevacizumab for the treatment of ovarian cancer (NICE draft guidance, 2013). The results echoed those of previous assessments of use in colorectal cancer and breast cancer. New national cancer guidelines was recently issued by the Swedish National Board of Health and Welfare and these gave bevacizumab very low priority for the treatment of colorectal cancer, where use is not the greatest. Although it is reasonable to be generous in an early assessment, it is difficult to justify any use at all of a medicine that is not cost-effective, particularly eight years after market entry, unless use is in a clinical study setting intended to gather evidence or study potential uses.

It is noteworthy that the use of bevacizumab declined dramatically in two regional health care authorities (Stockholm–Gotland and the Southern regional county councils) during 2012. Even though it has been eight years since bevacizumab was introduced and new indications have been added over time, continuing regional variation suggests that bevacizumab use still follows a pattern normally seen during the early phase of medicine use. This suggests a continuing need for systematic clinical practice assessment and the analysis of available data. Since the costs of bevacizumab amounted to 111 million SEK in 2012 (National Board of Health and Welfare, 2013a) and the total cost since introduction amounts to over 600 million SEK, there are strong reasons for systematic analysis of the value of actual use in different indications. With up to eight years' follow-up data available on the use of bevacizumab, it is vital to supplement the results of previous clinical trials with descriptive analyses of outcomes as these have been observed during use in wider patient populations and without the strict selection criteria applied in clinical trials. At the time of its introduction, bevacizumab was an important drug with considerable potential value. However, unless a medicine is systematically assessed after market entry, and used in accordance with clinical studies, there is a significant risk of achieving no discernible value despite considerable cost to the health care system.

Bevacizumab is used by a number of county councils for the treatment of macular degeneration although the drug has no license for this

indication in Sweden. Clinical reports indicate that bevacizumab may be as effective as ranibizumab, developed specifically for this indication. Bevacizumab is used at lower doses for macular degeneration and so is unlikely to influence conclusions on its use in cancer. Of greater interest is that this off-label use is an example of how a new medicine may gradually be tried out in new patient populations. In the UK, NICE published a recommendation in February 2013 that comparative studies should be done to determine the cost effectiveness of these two drugs for macular degeneration. In such cases, where new treatment options are identified in clinical practice, it is important that the value of the medicine in the new indication is monitored and analysed within a framework of scientific studies. Several stakeholders have an interest in generating new knowledge; access to the data necessary to support such analyses makes the health care system itself a key stakeholder.

Regional differences, national guidelines and the role of the prescriber

In their SNS study, Brommels et al (2013) showed results from a qualitative survey carried out in regional health care authorities with comparatively high and low levels of prescribing of the breast cancer drug trastuzumab and TNF inhibitors for the treatment of rheumatoid arthritis. These two medicines have also been studied in other reports in the SNS research programme as described in Chapter 3. The aim of the Brommels et al study was to provide more detail on how the introduction and use of these medicines differ, and why. The study was based on structured interviews with clinical and administrative staff who were familiar with decision-making processes on medicines in their respective regions. A total of 18 interviews were conducted in 2012. The authors also analysed supplementary documentation such as annual reports and published statistics. This study thus examines one new medicine and one new class of medicines in the Swedish health care system that offer more than ten years of experience with effectiveness.

The authors' conclusions noted the central role of the medical profession in decisions about the use of new treatment technologies, including new medicines. The observed differences in the prescribing patterns for trastuzumab and TNF inhibitors, they suggested, could be explained

primarily by the attitude of peer networks towards a new technology. The study also identified the key role played by heads of department and other leading regional stakeholders in, for example, evaluating scientific evidence from clinical studies.

Prescribing clinicians were the most important stakeholder group in the introduction of new medicines. Clinicians that participate in clinical trials and generate evidence themselves emphasize the importance of this approach to gathering information about new medicines at an early stage – and using this information to enhance value for patients. Leading regional stakeholders, however, including health care planners, with more demanding and tighter evidence requirements, emphasize the need to set priorities and maintain equity across patient groups. A number of respondents from low-prescribing regions also used budget-related arguments to explain their region's attitude towards using new medicines. The authors pointed out that the general results of the study indicated that respondents' were cost concious. The interviews overall, however, did not suggest that this cost-conciousness had a societal perspective including regional or national health care costs affected clinical decision-making, but rather focused on local costs – the clinicians own budget and/or the financial burden for the patient.

Finally, Brommels and colleagues (2013) noted that the principal instruments for evidence based decision making, such as national and regional practice guidelines, were more likely to justify than to influence local treatment approaches. Our conclusion is that the study emphasizes the need for relevant data on which to base objective evaluations of prescribing patterns.

Unwarranted regional variation

It is a well known that the utilisation of new medicines varies across countries and regions. What is that not know is the extent to which this variation is acceptable given the objectives of good health and care on equal terms for the entire population as stated in the Swedish Health and Medical Services Act. In 2001 Wennberg wrote in the British Medical Journal about what he described as 'unwarranted' variation (Wennberg 2002). He identified three types:

1. Where an intervention is effective and safe, but does not get offered to all patients despite clear scientific evidence (underuse)
2. When patients may have different preferences for clinically equivalent options (preference-sensitive care)
3. When the relative capacity in the area, for example the number of physicians with certain specialist qualifications, determines the number of patients receiving care (supply-sensitive care).

Wennberg's classification of the three types of unwarranted variation in health care utilisation can be used as a reference case in the design of follow-up and evaluation studies of new medicines in Sweden. Below, we use the reports from the SNS research programme on the value of new medicines to illustrate each of the three types of unwarranted variation.

The first type highlights the problem of variation in the presence of clear scientific evidence. Such variation may be present early on or develop gradually. Lundqvist et al (2013b) have described regional differences over time in the sales of the breast cancer drug tamoxifen. The Stockholm-Gotland region consistently used more tamoxifen per 100,000 inhabitants than the national average.

The difference continued after expiry of the tamoxifen patent in the early 1990s when total sales dropped due to price cuts. The regional variation in sales shown in Figure 4.5 is not likely to be explained by regional differences in the number of women eligible for tamoxifen treatment, as measured by the number of breast cancer surgeries. Even though treatment recommendations for tamoxifen have evolved towards longer treatment durations over the 25 years shown in the figure, it is remarkable that sales in the Stockholm-Gotland region differed from the national average for so long. Variations in sales in Sweden cannot be explained by differences in the price per dose because prices for reimbursed medicines such as tamoxifen are set nationally.

In the case of new medicines with clear scientific evidence to show that the benefits outweigh any potential risks, Swedish regulators should be systematically monitoring market entry to spot underuse at an early stage. Any regional differences during the early adoption phase of a medicine should be transient, but is important to watch for unwarranted variation at later stages of the product lifecycle of the medicine.

The second type of unwarranted variation arises from preference-

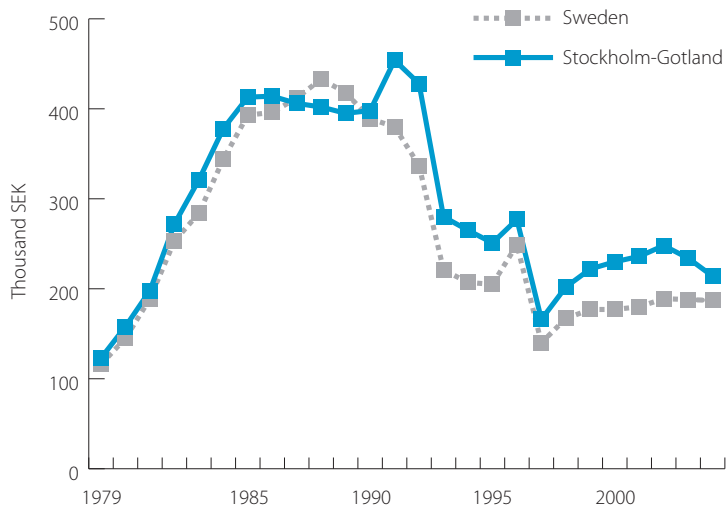


Figure 4.5 Total nominal sales for tamoxifen per 100,000 population in the Stockholm–Gotland region and in Sweden overall during 1979–2004. Thousand SEK. Source: Lundqvist et al (2013b), Figure 2 p 10.

sensitive care. Under the SNS research programme, Lundqvist et al (2013a) determined the value of alternative treatment strategies for chronic myeloid leukaemia (CML) described in Chapter 3. Imatinib is the current first-line treatment and works by inhibiting uncontrolled cell proliferation in CML. Successful treatment can transform an illness that would limit life expectancy into a chronic illness. However, treatment is life-long and involves a certain risk of adverse events such as weight gain, sudden haemorrhage, susceptibility to infection, and loss of white blood cells, according to the Swedish national drug formulary FASS (Swedish Association of the Pharmaceutical Industry Service AB, 2013). Stem cell transplantation may be an option for younger patients with access to a suitable donor; if successful, this will remove the underlying cause of the disease. This operation is not without risk, however, and may fail entirely. Although imatinib is considered first-line treatment for CML, according to Wennberg's argument, it would be wrong to deny stem cell transplantation to a patient provided it is clinically feasible and the

patient prefers this intervention over life-long medical treatment. This assumes, of course, that the patient is given adequate information on all available treatment options.

The third type of unwarranted variation arises from the supply side and the structure of the health care system. The study by Brommels et al (2013) offers one example of this in describing the uptake of the TNF-inhibitor medicines. A second example is the recently published American study mentioned earlier in this chapter (Cutler et al, 2013). The use of TNF inhibitors for the treatment of rheumatoid arthritis has varied greatly in Sweden. Several research studies and registry-based follow-up surveys have indicated that utilisation in the Västra Götaland region has been below both the national average and other urban areas. Brommels et al (2013) reported that the presence of fewer rheumatology specialists was considered a contributing factor to the lower prescribing rate for TNF inhibitors in the Västra Götaland region. The number of specialists in this region was 2.2 per 100,000 inhabitants, compared with other urban areas, with 3.3–3.5 specialists per 100,000 inhabitants. Registry studies, national guidelines, and monitoring of drug utilisation have all contributed to a targeted effort to strengthen rheumatology in the Västra Götaland region as part of a regional mandate for 2013 that allocates resources for additional staff and increases investment in TNF inhibitor therapy.

Summary

The existence of regional variation in the utilisation of health care technologies has been regarded as primarily an issue of equal access to care. This is based on the assumption that the variation concerns important interventions that may improve treatment outcomes. If the variation is related to interventions of dubious value, the assessment would be quite different. It is important, therefore, to clarify both the causes and consequences of observed regional variations.

Regional differences have been noted for a long time, but have received little attention in health care policy. A likely explanation is that variations may be acceptable if uncertainty is high about indications and treatment outcomes. Cancer treatment is one example of substantial regional variations that has been obvious for a long period

of time. However, better evidence about indications and outcomes has changed this. Trastuzumab is indicated in breast cancer patients who express a particular marker, HER-2, which can be measured objectively. This makes it possible to determine whether all female patients have been tested, what the test results showed, and whether or not the patient was appropriately treated in each case. This allows regional variation to be measured and analysed, and any variability explained. Differences also may exist for trastuzumab in the duration of treatment or, more commonly, before switching to other treatments. Such variations should also be documented and analysed.

A major change in Sweden, as elsewhere, is that the cost per treated patient has increased dramatically – for example, both for biological treatment of rheumatoid arthritis and multiple sclerosis and for new cancer drugs. As a result, large variations are more difficult to accept for medicines whose appropriate use is not entirely clear unless use helps resolve the question of the value of the intervention. The cancer drug bevacizumab provides an example. The issue is not that the health care system has spent over 600 million SEK on this medicine since 2005, but instead that there is no analysable documentation of how it has been utilised or what results have been achieved.

The example of bevacizumab emphasises that much closer collaboration between the manufacturer and the health care system should begin on market entry and include agreements that ensure a cost-effective utilisation. Large regional variations in the use of newer cancer drugs for the treatment of malignant melanoma, prostate cancer, and myeloma and/or myelodysplastic syndrome suggest that the health care system is on the verge of repeating past mistakes, despite the fact that we now know so much more and are much better prepared.

The use of biological treatments has been monitored more closely, but large regional variations also are observable for these medicines. This raises the question as to whether these variations reflect failure to realise the full value of these medicines. Further analysis is required to determine this.

Prescriber interviews have revealed that local standards of therapy exist, but have been unable to explain how these developed or whether they are justifiable, and have provided no guidance on how to change them. Assessment of whether or not observed regional variation is

compatible with the criteria for a cost effective and equitable health care system, as stated in the Swedish Health and Medical Services Act, requires individual patient-level data for analysis. Such data allow indications to be studied in the context of individual patient characteristics, considering both dosage and duration. Since an increasing amount of health care resource expenditure is accounted for by elderly patients with multiple co-morbidities and treatments, a comprehensive approach to data collection is required.

Once relevant patient-level data become available, it will be possible to investigate whether observed regional variations produce different outcomes. Such studies, however, will not be sufficient for providing information on the value of new medicines and other medical interventions in clinical practice. To this end, additional studies will be required that can describe and analyse the outcomes of intervention over time at the individual patient level.

Since chronic illnesses are becoming increasingly prevalent, comparisons of the implications of different treatment strategies for resource use and outcomes over the longer term are increasingly important. Diabetes, rheumatoid arthritis and multiple sclerosis, and most diseases of the brain, are examples of diseases where overall treatment outcome can be assessed only over a very long time. Cancer also is increasingly becoming a chronic illness that is treated over a long time with a combination of interventions; the effects of each intervention may be known, but the combined outcome remains to be assessed.

References

Brommels M., Hansson J., Granström E., Wåhlin E. (2013). Professionen, pennan och pengarna – regionala skillnader i användning av läkemedel. Stockholm: SNS.

Cutler D., Skinner J., Dora Stern A., Wennberg D. (2013). 'Physcian beliefs and patient preferences: a new look at regional variation in health care spending', NBER working paper series, Cambridge, MA: National Bureau of Economic Research.

Jönsson B., Wilking N. (2013). Värdering och implementering av nya läkemedel – med exempel från cancerområdet. Stockholm: SNS.

Luft H.S. (2012). 'From small area variations to accountable care organizations: how health services research can inform policy', Annual Review of Public Health 33, pp 377–392.

Lundqvist A., Norlenius Ohm A.-C., Dickman P., Höglund M., Stenke L., Gerdtham U.-G., Persson U., Björkholm M., Steen Carlsson K. (2013a). Medicinska framsteg i behandling av kronisk myeloisk leukemi. Stockholm: SNS.

Lundqvist A., Wilking N., Gerdtham U.-G., Persson U., Steen Carlsson K. (2013b). Målriktad behandling av bröstcancer. Stockholm: SNS.

LIF Service AB (2013). FASS. Downloaded on 29 August 2013 from http://www.fass.se/.

NICE draft guidance (2013). 'Ovarian cancer (metastatic) – bevacizumab (with paclitaxel and carboplatin): final appraisal determination document' (dated 25 March 2013). Downloaded on 15 October 2013 from http://guidance.nice.org.uk/TAG/279/FAD/FinalAppraisalDetermination/pdf/English.

Quality and Efficiency in Swedish Health Care, Regional Comparisons, Swedish Association of Local Authorities and Regions and Swedish National Board of Health and Welfare, 2013.

Swedish National Board of Health and Welfare (2013a). Läkemedel – statistik för år 2012. Sveriges officiella statistik. Stockholm.

Swedish National Board of Health and Welfare (2013b). Öppna jämförelser 2013. Jämförelser mellan landsting. Stockholm.

Wennberg J., Gittelsohn A. (1973). 'Small area variations in health care delivery', Science 182 (4117), pp 1102–1108.

Wennberg J.E. (2002). 'Unwarranted variations in health care delivery: implications for academic medical centres', British Medical Journal 325 (7370), pp 961–964.

5. From clinical trials to clinical practice – evaluating the efficacy and safety of medicines

Approval and use of new medicines today is based on a set of national and international statutory regulations. In the early phases of development, the roles and responsibilities are divided between the pharmaceutical industry and international and national regulatory authorities, as described in the introductory chapter of this book. However, once the new medicine has been approved and introduced into clinical practice, clear requirements for data reporting and the monitoring of effects no longer apply. In Europe, reimbursement decisions are governed by a single, general rule that decisions must be based on objective and verifiable criteria: the EU's Transparency Directive.

Both in Sweden and internationally we see a trend towards increasing demand for comparative effectiveness studies based on real-life data on new medicines. For payers of health care services, it is not enough to know that the efficacy and safety of a medicine has been proven in an experimental setting. Payers also want to know whether health and welfare gains of the medicine are great enough to justify its costs or if spending the same amount of money elsewhere in the health care system would generate more benefits for patients. Additionally, payers need to know whether the treatment will result in outcomes in a wider patient population that are essentially the same as those in strictly controlled clinical trial settings. The current allocation of responsibilities, incentives and resources means that central evidence is not created. No stakeholder has clear responsibility for undertaking systematic analyses of new data based on the use of new medicines in clinical practice. This

applies equally to other new health care technologies.

In this chapter, we discuss strategies for generating evidence about the efficacy, safety and value of new medicines by conducting real-life clinical effectiveness studies. We review the research objectives of studies included under the SNS research programme on new pharmaceuticals, with supplementary citations from international published studies. The focus of this chapter is on follow-up studies and analyses carried out to date, as well as opportunities for developing and improving evidence generation. We begin with an area of activity with a long tradition of continuously monitoring medicines after approval: pharmacovigilance, that is, the identification, assessment, understanding and prevention of drug-related injuries and disorders.

Increasing regulatory demands for data supporting risk-benefit assessments

Safety is the one aspect of new medicine that is routinely monitored even after the product has been approved and entered the market. Requirements for adverse event reporting exist in most countries. In Sweden, suspected adverse drug reactions can be reported to the Medical Products Agency by both health care professionals and private people under the spontaneous reporting process. Moreover, the Medical Products Agency also may require pharmaceutical companies to carry out specific safety studies after marketing authorization if considered necessary. Requirements for such safety studies are becoming more common. An EU-level database, Eudravigilance, has been created to collect adverse events reports from throughout the EU. The European regulatory authority, the European Medicines Agency (EMA) has developed recommendations to guide this reporting. Research shows adverse event reporting has been relatively effective in detecting new and serious adverse drug reactions (Harmark and van Grootheest, 2008).

In an SNS study, Gyllensten and Steen Carlsson (2013) reviewed the feasibility of using systematic follow-up based on Swedish registry data to analyse the prevalence and implications of drug-related morbidity during the early implementation phase of new medicines. The term 'drug-related morbidity' covers both lack of therapeutic efficacy and unwanted side effects. The objectives of these analyses thus include

negative consequences from both appropriate use of a medicine and from inappropriate use or failure to prescribe a medicine. The authors conclude that studies published to date largely focus on adverse effects – injuries and other events – that occurred during hospitalisation and that the most common method of detecting drug-related morbidity was review of hospital records.

Gyllensten and Steen Carlsson (2013) suggest that Swedish health care providers and regulatory authorities have a unique opportunity to combine data from national patient and drug registries to support analyses of drug-related morbidity. The authors note, however, that supplementary information would be required in most cases to identify causal relationships. An important beginning would be to develop a list of diagnostic codes and trigger signals that would flag the need for analysis to verify possible adverse reactions and other drug-related morbidity in Sweden. Such analyses would help to increase awareness of which adverse events may require medical attention. The authors suggested that valuable evidence could be collected from carrying out systematic registry analyses during initial use of new medicines.

Regulatory demands for data also are increasing for studies that monitor clinical effectiveness after marketing commences. A recent European Commission discussion paper points out that data can be generated in clinical practice in two ways: through observational studies and pragmatic trials (European Commission, 2012). Both rely on systematic approaches to collecting information from clinical practice.

Monitoring the effectiveness of a new medicine is necessary in a number of situations. One example is when a medicine has been approved based on data using surrogate measures, for instance biomarkers, that indicate that disease progression has been halted. Several approved cancer drugs have been able to show positive effects on surrogate markers in clinical trials; however, clinical study duration of up to two years still may be insufficient to quantify patient-related hard endpoints, such as survival. In such situations, it may make sense to grant conditional approval subject to the submission of follow-up data. Follow up studies may also be required to determine whether results obtained in the clinical development programme can be achieved in routine clinical care. Other follow-up aspects related to comparative effectiveness include: the possible outcome of using the new medicine in combination with other

treatments or in sub-populations with specific patient characteristics, and any impact of the health care system or local health care services on outcome, and so on.

Increasing regulatory demands for follow-up data also reflect the reality that approval decisions for new medicines are necessarily based on limited information. A balance always must be struck between demanding more data prior to the approval decision, which would delay patient access to the medicine, and applying less stringent decision criteria that may risk introducing treatments with incomplete adverse event profiles. Continuing efforts after approval to reduce uncertainty, for example with respect to potential rare adverse effects, is therefore warranted.

Increasing demands from reimbursement bodies for data supporting cost-effectiveness assessments

Bodies that make decisions on whether or not new medicines should be reimbursed, fully or in part, are now demanding data in addition to that from randomised clinical trials (RCTs). Assessments of the type carried out by Swedish Council on Health Technology Assessment (SBU) or the Cochrane collaboration and other national or regional health technology assessments (HTA) organizations, initially only covered medicines and other treatments that had been in use for a prolonged period of time. This meant data would be available from both clinical trials and real-life clinical practice. However, increasing demand for HTA analyses at an earlier stage in a drug's lifecycle means that systematic collection of data on both resource use and effectiveness increasingly is required for all new technologies. Such effectiveness data must include both disease-specific endpoints and patient-reported outcomes in changes in health status and quality of life.

Registry studies constitute an important tool for developing information about what value can be realised from the real-life use of medicines. Access to national registries that contain data on millions of patients provides data important to conducting accurate research. Luce et al (2012) have listed 13 key principles for comparative effectiveness research (CER), which is the study of the relative effectiveness of interventions. Briefly stated, these principles are as follows.

1. The study objective should be valid, clearly stated, and focused on providing relevant decision support
2. All relevant stakeholders (patients, advocacy groups, health care providers, payers, employers, manufacturers, politicians) should be as much as possible be actively involved and/or kept informed during the planning and conduct of the study
3. The study should address the perspectives of the decision-makers affected
4. Before the study begins and during the course of the study, its relevance should be reviewed to ensure that it meets the needs of decision-makers
5. Bias should be minimised and transparency maximised
6. The study should adopt a broad approach to include the full range of treatment options
7. The study should evaluate clinical, health-related and system outcomes most relevant to decision-makers
8. All relevant evidence should be included, including new evidence that becomes available during the course of the study
9. The study should incorporate appropriate methods for assessing the relevant outcomes of alternative interventions and intervention strategies
10. The study should aim to assess outcomes, interventions and prevention overall and in subgroups in health care settings
11. The study should explicitly take into account any uncertainty in the study variables
12. The study should consider the applicability of the study results to other relevant patient groups, health care settings and systems of care
13. A plan should be developed when the study is first considered and designed to communicate, disseminate, implement and evaluate the results.

These 13 principles incorporate best practice in all scientific research, including clear objectives, choice of adequate methodology, and transparency. A key aspect emphasised in several of the principles is the importance of adopting the decision-maker's perspective and describing how the study results can provide evidence capable of improving patient's lives.

New health care technologies are of interest to multiple stakeholders, including patients and patient advocacy groups, health care providers, private and public insurance providers, employers, manufacturers and politicians. However, not all stakeholders have decision-making roles that require relative effectiveness studies. The decision-makers in the use of a new medicine, for example, include payers, prescribers, and the patients using the medicine. It should be in the interest of all parties concerned, however, to be aware of and understand the evidence acquired through real-life use. The authors urge that relative effectiveness studies be carried out using a broad approach to ensure they meet the requirements of more than a single group of decision-makers. This requires involving stakeholders other than those immediately concerned and by adopting a broad perspective.

We noted earlier that mechanisms are in place for capturing adverse drug events. However, there is a lack of established structures for carrying out systematic analyses of other outcome aspects of medicines as used in real-life clinical practice. This is not due to knowledge gaps or any notion that all uncertainty can be regarded as negligible. Scientific input from both RCTs and follow-up observational studies, such as cohort analyses and registry-based studies, has certainly increased substantially in the last decade. Despite this, as Neovius and Ramsberg (2013) pointed out in their SNS study, conspicuously large knowledge gaps remain about the value of several health care interventions and measures, including medicines currently in routine use. What is missing in particular is:

- Regular follow-up and accumulation of evidence from use in real-life clinical practice
- Evidence about the magnitude of real-life clinical effectiveness compared with the most relevant alternative treatment, that is, relative effectiveness.

Relative effectiveness studies are very important for regulatory bodies that decide whether new medicines should be reimbursed. Optimal decisions cannot be based solely on data from experimental studies and RCTs regardless of whether these are well-conducted and of high internal validity. There is no substitute for additional evidence acquired from the medicine's use in real-life clinical practice in patient populations

larger and more varied than those in the clinical trials. HTA analyses, then, must take into account the entire target patient population and not just patients identical to those included in the clinical trials.

The demand for relative effectiveness studies is growing not just in Sweden and Europe, but also in the US where large insurance companies can access data on both treatments and outcomes. A fundamental aspect of relative effectiveness studies is the interest of payers in determining whether new medicines, and other technologies, provide value for money.

One attempt is to link the level of reimbursement for new medicines to actual outcomes. This provides an incentive for the health care system to try new medicines, since the payer pays the full amount only if the treatment is successful. It also provides pharmaceutical companies with incentives for developing new medicines and other treatments that can potentially create significant added value. Only medicines that are effective and have few adverse events will succeed under this approach.

Increasing demands from the health care system for data on treatment outcomes

Health care providers and particularly third-party payers in Sweden, Europe, the US and other developed nations are facing increasing pressure from demographic and structural economic changes. An important challenge lies in ageing populations and increased demand for health care services that will have to match budgets sizes determined by taxpayers' and buyers' of health insurance ability and willingness to pay.

Health care systems that explicitly require evidence about positive outcomes – healthier patients – require the right data. With this in mind, approaches need to be developed for systematic, population-level monitoring of the outcomes of new treatments, including new medicines. Patient-level outcomes are traditionally monitored by the health care system through patient records; yet to be exploited is the greater opportunity, which is regular collection and analysis of population-level data that allows comparing the value of new medicines to alternative treatments. Improving data collection in clinical practice is particularly important when multiple treatments are available that are expected to be roughly equal in efficacy.

The decision-maker's perspective is a recurrent theme in the 13 principles for relative effectiveness studies summarised above (Luce et al, 2012). The individual or patient is critical to the appropriate use of any medicine. Analyses of the actual outcomes of the use of new medicines, then, must consider not only prescribing and dispensing, but also treatment compliance.

In their SNS study, Anveden Berglind et al (2013) presented results from Swedish registry data on dispensed prescriptions of statins, a class of lipid-lowering medicines used for prevention of conditions such as cardiovascular disease and diabetes. Statins were introduced in Sweden during the late 1980s and thus could not be regarded as 'new' medicines during the 2010s. Patent protection for the first statin, simvastatin, expired in 2003 and generic statins have been available since then. In 2013, the annual cost per patient of statin treatment varied between 200 and 500 SEK.

The registry analysis included information from patient, cause-of-death, and medicines registries maintained by the Swedish National Board of Health and Welfare and the total population registry maintained by Statistics Sweden. Anveden Berglind et al (2013) noted that 25% of the adult Swedish population had at least one marker for cardiovascular disease, diabetes, or hypertension alone with no other marker for cardiovascular disease. National treatment guidelines state that these populations should be offered statin treatment; however, only between 30% and 60% of these received statin prescriptions during the year-long study period, which is only around 10% of the adult population. One measure of poor compliance was that patients who began statin treatment between July 2006 and June 2007 subsequently stopped filling their statin prescriptions. During the first year of treatment, compliance was 60%, and after three years just over half of patients remained on the treatment.

In Chapter 3, we described a study by Lindgren and Jönsson (2012) that estimated the value realised to date, and projected the future value and costs, for the lipid-lowering agent simvastatin. This study calculated a high value for simvastatin based on sales data derived from prescriptions records. The study by Anveden Berglind et al (2013) indicated that the dispensing rate may be considerably lower than would be expected from treatment recommendations and guidelines. Thus, behaviours

evidently exist that make it difficult to fully realise the potential value of new medicines.

Although the study by Anveden Berglind et al (2013) offered no explanation for why half of the patients had stopped statin treatment after three years, this analysis of registry data identified potential problems that may affect the likelihood of realising value and emphasized the need to understanding why patients discontinue treatment. One explanation, at least for preventive medicines, is that people tend to rate the value of future gains relatively low, which reduces incentives for compliance. Registry data also may help identify potential underuse of drugs.

Study design and methodological challenges

Analysis and interpretation of registry data present methodological challenges. Case studies of the value of specific new medicines or new medicines for specific diseases, such as several of the examples discussed in Chapters 3 and 4, cannot be extrapolated to other medicines or disease areas. It also is not possible to combine the results from studies that use different methodologies. One solution may be to use national-level data and analyse the link between aggregate measures of the use of medicines and population health outcomes. In one SNS study, Pettersson and Lichtenberg (2013) used aggregate Swedish longitudinal data on mortality, the introduction of new medicines, and pharmaceutical sales data from the period 1997–2010 to analyse whether innovations such as new medicines had any impact on life expectancy.

One of the authors of this report, Lichtenberg, has published a series of studies that use econometric analysis to try to isolate the impact of new medicines on mortality and health care costs. Previous results have indicated that survival gains reduced health care costs as the number of innovative medicines used increased (see for example Lichtenberg, 2001, 2005, 2013). Lichtenberg has based his analyses on aggregate data at disease level or regional level. To isolate the impact of new medicines, any general trend that might improve health – for example, improved living conditions – was assumed to affect trends in the same way for all diseases or regions analysed. Any additional variation between diseases or therapeutic areas then could be attributed to the new medicine.

The regression analyses performed by Pettersson and Lichtenberg (2013) indicate that approximately one third of the increased life expectancy during the study period could be attributed to the introduction of new medicines. However, the authors caution against the risk of overestimating the relative importance of new medicines as the cause of significant decreases in mortality rates for particular diseases could be related to changes in other complementary and non-pharmacological interventions for those diseases that have occurred at the same time.

Analyses of aggregate national and regional data provide group-level reports on the use of medicines and outcomes. By identifying patterns of co-variation, this type of analysis may help generate hypotheses about potential links. Pettersson and Lichtenberg conclude that their findings support policies that promote innovation and the early introduction of new medicines.

Aggregate studies, however, lack sufficient information for conclusions about direct causal relationships. These require access to information about which individuals in the population actually received the treatment and what the outcomes were. To demonstrate a biological effect thus requires determining that patients using the new technology also were the ones who derived the health benefits. This requires analyses based on patient-level data, and if possible, in an experimental setting.

AGGREGATE DATA AND CAUSAL RELATIONSHIPS

Debate continues within the scientific community whether and what conclusions can be drawn from the type of aggregate-level co-variation analysis developed by Lichtenberg. The primary challenge is to determine what proportion of the overall variation can be attributed to new drugs and what most likely is explained by other factors. Studies that have criticised Lichtenberg's work claim that the choice of econometric specifications and empirical model may substantially influence the results and that aggregate data may mask considerable variation at patient level (see for example Zhang and Soumerai, 2007; and Schnittker and Karandinos, 2010).

Access to patient-level data has obvious analytical advantages, especially if the dataset includes several years of follow-up. In principle, the same methods used by Pettersson and Lichtenberg (2013) for analysing aggregate data could be applied to patient-level datasets such as those

used by Anveden Berglind et al (2013) for analysing compliance with statin therapy. Swedish registry data are available at patient level and offer great potential for statistical analysis as a basis for generating hypotheses for future research as well as investigating causal relationships, particularly during early clinical use of new medicines.

Patient populations in clinical practice are rarely, if ever, as homogenous as those included in RCTs. To build a broader base for decision-making, additional information is required to supplement traditional trials that are designed for experimental settings, as noted in the 13 principles of relative effectiveness studies (Luce et al, 2012).

THE CHOICE OF METHOD SHOULD BE DETERMINED BY THE OBJECTIVE

Schwartz and Lellouch (2009) differentiate between studies that intend to understand relationships (Is there an effect?) and studies that inform decisions (What effects can be seen in the entire patient population concerned?).

The ultimate aim of the former is to show that the medicine works as intended and the balance between efficacy and safety is acceptable. In the latter case, minimising the risk of choosing an inferior treatment option for an individual patient is an equally important objective. Unless all patients respond to treatment in exactly the same way, the two studies do not necessarily need to provide identical results about which treatment is superior.

Experimental studies, such as randomised controlled trials (RCTs), are considered by many to be the methodological 'gold standard' for identifying and analysing statistically significant differences in efficacy between treatments (Lauer and D'Agostino 2013). Using an experimental study, an investigator attempts to eliminate as far as possible any other factors that may be responsible for systematic variation between the study groups. One approach is to ensure the patient base is large enough to minimise the risk of introducing systematic variation in any of the of the study groups' characteristics despite randomisation. However, larger patient populations also mean higher research costs.

Another approach is to apply inclusion and exclusion criteria strategically to ensure that any difference in efficacy between the treatment options is highly likely to show up in the study patient population. For example, in pivotal studies that are part of the regulatory approval decision, it is common to include patients of specific age groups and

with well-defined disease criteria; patients with co-morbidities are typically excluded.

The aim of RCTs is to ensure that causes of differences that appear in a specific selection of patients are attributed correctly. However, Lauer and D'Agostino (2013) claim that the current method – creating experimental settings using large, multinational, expensive RCTs – is no longer viable. They argue that registry-based RCTs instead could create the evidence about which treatment methods and medicines provide the greatest benefit to patients and best value. They regarded registry-based RCTs as a technological revolution in that they have produced changes in standards, guidelines and the conduct of research and, importantly, led to substantial cost savings.

Although valid, robust studies provide important evidence for decisions, they rarely provide enough of the right kind of evidence for decisions in routine clinical practice. Patients treated in real-life clinical practice often are very different from those included in RCTs. Acquiring evidence of the effectiveness in real-world patient populations is critical to good clinical decision-making. Questions that need to be asked in whether effectiveness is the same as in the clinical trials; and whether it is lower, or even higher, in a particular sub-population.

Monitoring use of the treatment in the real world can help answer these questions. Such studies should provide information about, amongst other things, how the treatment affects patient populations that were excluded from the original clinical trials – because of age or co-morbidities, for example.

The next step after approval and introduction of a new medicine, then, should be to collect and analyse data for the purpose of developing more and better information on outcomes. This can be done most efficiently by aggregating data and analysing it at the population level. The 'silo' approach that focuses on each patient record separately rarely can provide useful comparisons of treatment options.

Randomisation of observational studies – the best of two worlds?

In their SNS study, Neovius and Ramsberg (2013) discuss the gaps in knowledge that exist after a medicine is approved and enters the mar-

ket. They authors list the following examples of outcomes that are not usually captured in clinical trials.

1. Events that take time to develop will not be observed in studies of short duration. This applies to both health benefits and adverse events.
2. The use of the treatment as a third-line option usually is not studied. Published trials focus on first-line or second-line use of medicines.
3. If more than one company or research group is developing medicines for the same indication, it is not possible to undertake comparative studies prior to marketing. It is sometimes considered unethical to compare treatments even after launch and, companies may be less interested in conducting further studies with active treatment comparators.

It would be unrealistic to require long-term studies for drug approval for a number of reasons. Firstly, patients may be harmed as they forego health improvements when market entry is delayed. Depending on type of disease and treatment this may imply that the patient do not receive the treatment at all, or, for treatment of chronic diseases, will receive the treatment much later than could have been the case. Secondly, the price of the product likely will be higher because longer studies increase clinical development costs and shorten effective patent protection. From a societal perspective, then, it may be best to the health care system at least partly responsible for collecting evidence on the long-term effectiveness of new medicines used in clinical practice, rather than relying solely on producer-initiated follow-up studies for such data.

Neovius and Ramsberg (2013) note that, from a societal perspective, it is important to remember that although observational studies for monitoring long-term effectiveness may be cheaper to run, evidence from such non-experimental studies will be regarded as weaker since non-random errors will not be controlled to the same extent. At the same time, however, the population of patients is larger and extensive amounts of information are routinely recorded that are relevant for analysing long-term effects and outcomes.

According to Neovius and Ramsberg (2013), 'pragmatic', registry-based RCTs carried out in clinical practice in Sweden and elsewhere have the potential to revolutionise evidence generation – for the same

reasons as are noted by Lauer and D'Agostino (2013). Such research randomises patients in a 'regular' health care setting to different treatment options for the purpose of comparison. Treatment outcomes then are monitored in existing patient-data registries. This has at least two important advantages: patients can be monitored in a normal clinical setting, which avoids any effects from the artificial setting of a standard experimental RCT, and cost for the research will be relatively low because the treatment would have been administered, and data gathered, even without the study. Evidence generated from pragmatic studies in clinical practice, then, could supplement current RCTs and observational studies carried out post-launch.

As illustrated in Figure 5.1, one way of looking at pragmatic registry-based studies is to consider them along a continuum from between being purely descriptive to being completely experimental.

The strength of the experimental study is that, assuming the study has sufficient statistical power, it allows conclusions to be drawn about causal relationships that demonstrate outcomes, such as effectiveness of treatment. The experimental design allows the investigator to select which patients are included in the study and control variability. Experimental studies are not intended to collect data on use in real-life clinical settings; even the clinics involved in RCTs may be unlike those an everyday patient would visit. In RCTs, moreover, patients are selected to include those in whom the medicine is expected to have maximum effect. If the trial's purpose is to show only that the investigational drug has the intended effect, the drug under study will be compared to placebo. Such studies are an important first step in understanding efficacy, but they are only an incomplete guide for clinical decisions in

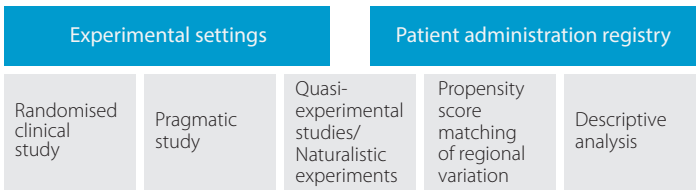


Figure 5.1 Study design and data sources: from randomised clinical trials to descriptive analysis.

real-life settings where other active treatments are the typical alternatives, not the no treatment (placebo) alternative used in many efficacy trials. What is needed for decisions about the choice of treatment are the results of research that compares the drug to alternative treatments as provided in clinical practice.

The advantages and disadvantages of descriptive analyses from patient registry data are in principle the opposite of those for RCTs. Their primary strength is that all patients are included and that registry data capture large amounts of longitudinal information on actual health care consumption, including diagnostic and surgical procedure codes, medicines use, mortality, and disease relapses. The primary disadvantage is that conclusions about causation rarely are possible.

Experiments and clinical practice in one

Between the two extremes represented by RCTs and descriptive analyses lie three other approaches: pragmatic studies, naturalistic experiments, and 'propensity-score matched' analyses (Figure 5.1). Each may be based on registry data and so offer an opportunity to include at a reasonable cost all patients who would be eligible for using a new health care technology in clinical practice.

In Chapter 4, we discussed the lessons that can be learned from regional variation. Patients who are similar in essential characteristics, including diagnosis, may receive different treatments in different parts of the country. Careful analysis of registry-based observational data allows observable systematic variation between study populations to be disregarded, such as age, gender, previous medical history, or socio-economic status. Although not all sources of error can be eliminated, any impact on the study's finding can be minimised by the study's design – for example, in the choice of statistical methods or skilful analysis of available registry data. Any weaknesses in the use of such approaches is at least in part balanced by the fact that observational data allow extensive patient populations to be studied at comparatively low cost.

Studies using naturalistic experiments, quasi-experimental settings, or propensity score matching based on regional variation do not in themselves trigger any changes in the health care options offered to

patients included in the study. In this sense, they encroach less on the patient's everyday life than does an RCT. An experimental study design predetermines what treatments will be offered a patient and, as a result can require the patient to forgo the use of an alternative, potentially more effective treatment. This may prove to be a barrier to patient recruitment for such studies.

Neovius and Ramsberg (2013) note that choice of treatment is an important challenge in the experimental design of pragmatic studies. In today's health care system, without evidence on the relative effectiveness of alternative treatments, it is considered good medical practice for the physician to make a more or less arbitrary choice of treatment for the patient. Clinicians are constrained, however, from assigning treatment truly randomly to eligible patients with the aim of generating new knowledge from analyses of these data without first informing the patient about the uncertainty and obtaining informed consent. Current research protocol and ethics also preclude a physician from randomising treatment without the patient's informed consent.

The authors conclude that patients may be at risk of suboptimal treatment both in RCTs and in pragmatic studies. If pragmatic studies are randomized, new evidence may be generated over time that will broaden the knowledge base that informs decisions, benefiting the patients of the future. When the focus of the study is an intervention that treats a chronic disease, even today's patients may benefit if the study reduces uncertainty about treatment options. Arbitrary decision-making may endure, however, if the new evidence is not generated from clinical practice experiences.

Who is responsible for closing knowledge gaps?

The most important point of this chapter is the trend towards the increasing use of studies based on actual use to determine the value of drugs, rather than only RCTs.

Clinical trials conducted as a condition of market authorisation are carried out by the pharmaceutical company; the results are provided to regulatory authorities and, after licensing, to physicians and other health care decision-makers. These studies are designed to show that

the medicine works as intended and that the balance between efficacy and safety is acceptable.

Decision-makers within the health care system are interested not only in ensuring that medicines are used appropriately for individual patients, but also that new medicines should be more efficacious than existing treatment options. Such data are available in most health care systems; collaboration with the pharmaceutical industry in using these data could provide important new evidence that benefit all those concerned. Relationships with clinical practitioners also will change. Traditionally, the pharmaceutical industry has collaborated with health care professionals in their capacity as clinical trial investigators. As new approaches to gathering data from actual clinical practice become more important, there is a continued need for collaborations with the aim of generating additional real-world evidence on efficacy, safety, and value.

A challenge inherent in such collaboration is that the industry and health care systems have different incentives and goals. Whilst the interest of a pharmaceutical company is in marketing its own products, the interest of the health care system is in comparing alternative interventions to identify those that offer greatest value. The difference in objective, however, is less of an obstacle than the current lack of evidence from use in clinical practice.

The health care system and pharmaceutical industry are not the only stakeholders with an interest in increasing the evidence based on the use of new medicines in clinical practice. Patients and the general public also are increasingly interested.

Adequate resources for collecting, maintaining and providing the data from actual clinical practice are essential if generating evidence from this source is to continue. The health care system has a key role for improving accessibility to data for the purposes of generating new knowledge.

Conclusions

In this chapter, we identified large gaps in knowledge about the value of several health care interventions and approaches currently in use, including medicines. These gaps exist because no mechanisms exists for

regular systematic follow-up and evidence development that capture the actual effects of new technologies in clinical practice.

Evidence that supports assessment of the value of new medicines increasingly will come from studies of effectiveness in actual clinical practice. Regulatory risk–benefit decisions long have included reports of real-life adverse events as well as data from RCTs. Since effectiveness is dependent on how a medicine is used in different health care settings, the collection and analysis of data from different countries will be necessary to create a complete picture. Data on effectiveness of new medicines in clinical practice increasingly will be required by national authorities for making decisions about pricing and reimbursement. Such decisions traditionally have been based primarily on data gathered during RCTs. For the reasons noted above, however, RCT data are limited and decision-making bodies now are requesting supplemental studies conducted in actual clinical practice after marketing begins.

Because it is the health care system that collects and maintains information on use and effectiveness of interventions in actual clinical practice, increasing demands for such data also will increase costs to the health care system. It is important, then, that regulatory bodies coordinate demands as much as possible and that data collection be carried out as efficiently as possible.

A number of other trends also demonstrate the importance of data from actual clinical practice. The health care system, for example, will gain because it increasingly will need such data to manage its operations to meet efficiency and equity targets. Patients are increasingly insistent on having evidence that can help determine whether they have access to the best possible care. Greater attention is focused on decisions about the allocation of health care resources and evidence of appropriate use is important in supporting those. Similarly, studies that better define appropriate use are important in satisfying increasing demands for rationality and transparency in decision-making. New requirements for additional information on real-life clinical use and effectiveness, then, are not just a technical detail, but are essential to good decision-making in all aspects of health care.

The growing focus on evidence gathered from actual clinical practice is a major change for a pharmaceutical industry used to generating, analysing, evaluating and communicating data based on controlled

clinical trials. Clinical experimental studies are specifically designed to ensure high internal validity by controlling factors that could influence the results. Data from real-life clinical use has high external validity since they are gathered in the setting where the medicine is actually used. This is achieved, however, at the expense of diminished control over other factors that may influence the results, making conclusions based on cause and effect tenuous at best. This is a dilemma that the pharmaceutical industry must learn to address.

The criteria for data quality and analytical methods that apply to clinical practice studies are no less stringent that those for RCTs. The demands for scientific rigour will become increasingly strong as the results become more significant. It will not be possible to argue against demands for such data on the grounds that clinical practice research does not provide an experimental laboratory-like setting. The demands for transparency in study conduct and results may present challenges, but are unavoidable. This will be particularly true for results used in decisions about pricing and reimbursement.

References

Anveden Berglind I., Kieler H., Linder M., Sundström A., Wettermark B., Citarella A., Andersen M. (2013). Värdet av statiner – användningsmönster och följsamhet till behandling. Stockholm: SNS.

European Commission (2012). Delegated act on post-authorisation efficacy studies (Article 10B of Regulation (EC) No 726/2004 and Article 22B of Directive 2001/83/EC). Brussels: Directorate General for Health and Consumers.

Gyllensten H., Steen Carlsson K. (2013). Nya läkemedel och läkemedelsrelaterad sjuklighet. Analysmöjligheter i svenska registerdata. Stockholm: SNS.

Harmark L., van Grootheest A.C. (2008). 'Pharmacovigilance: methods, recent developments and future perspectives', European Journal of Clinical Pharmacology 64 (8), pp 743–752.

Lauer M.S., D'Agostino R.B., Sr. (2013). 'The randomized registry trial – the next disruptive technology in clinical research?', The New England Journal of Medicine 369 (17), pp 1579–1581.

Lichtenberg F.R. (2001). 'Are the benefits of newer drugs worth their cost? Evidence from the 1996 MEPS', Health Affairs 20 (5), pp 241–251.

Lichtenberg F.R. (2005). 'The impact of new drug launches on longevity: evidence from longitudinal, disease-level data from 52 countries, 1982–2001', International Journal of Health Care Finance and Economics 5 (1), pp 47–73.

Lichtenberg F.R. (2013). 'The impact of pharmaceutical innovation on longevity and medical expenditure in France, 2000–2009', Economics & Human Biology (0).

Lindgren P., Jönsson B. (2012). 'Cost-effectiveness of statins revisited: lessons learned about the value of innovation', European Journal of Health Economics 13 (4), pp 445–450.

Luce B.R., Drummond M.F., Dubois R.W., Neumann P.J., Jönsson B., Siebert U., Schwartz J.S. (2012). 'Principles for planning and conducting comparative effectiveness research', Journal of Comparative Effectiveness Research 1 (5), pp 431–440.

Neovius M., Ramsberg J. (2013). Räkna med register och randomisera mera! Stockholm: SNS.

Pettersson B., Lichtenberg F.R. (2013). The value of pharmaceutical innovation – within the context of policies that impact use of new medicines in Sweden. Stockholm: SNS.

Schnittker J., Karandinos G. (2010). 'Methuselah's medicine: pharmaceutical innovation and mortality in the United States, 1960–2000', Social Science & Medicine 70 (7), pp 961–968.

Schwartz D., Lellouch J. (2009). 'Explanatory and pragmatic attitudes in therapeutical trials', Journal of Clinical Epidemiology 62 (5), pp 499–505.

Zhang Y., Soumerai S.B. (2007). 'Do newer prescription drugs pay for themselves? A reassessment of the evidence', Health Affairs 26 (3), pp 880–886.

6. How should new medicines be paid for?

This chapter discusses how society pays for innovative medicines, individually or collectively. How we pay influences the R&D choices for which new medicines are developed, how soon they reach the market, how they are used in practice, and how their value is distributed throughout the population.

Direct payments by patients account for a diminishing part of the overall expenditure for medicines, and thus the funding of new drug development. Out-of-pocket payments, for all or part of the cost of a medicine, still are important, however. In Sweden, they account for around one quarter of total expenditures on medicines, ranging from 22% to 27% in the period 2000 to 2012 (Apotekens Service AB 2013, Table 1:2). Co-payment schemes that require patients to pay a portion of the cost prescription also can be designed to achieve efficiency and equity.

Co-payment criteria

In the SNS study Medicines – When Is Self-Pay Acceptable? [Läkemedel – när är det rimligt att betala själv?], Carlsson and Tinghög (2013) analysed the boundaries between collective and individual responsibility in health care. The specific question asked was when it would be appropriate for individual patients to pay for medicines themselves. In times of increasing strain on public finances, the question that arises with increasing regularity is whether some medicines should be paid

for entirely, or partly, by the patient and, if so, which ones. Paying out of pocket makes the patient responsible for both valuing and funding the medicine. However, only patients with the ability to pay the price the market has set will have access to that medicine. Therefore, as stated in the report, it is important that criteria be clear about when a new medicine will not be covered by public funding.

The analysis in the report adopted an equity perspective and did not address the question of out-of-pocket payment from an efficiency perspective. The co-payment element of the Swedish national pharmaceutical benefits scheme has been designed to balance economic, efficiency and equity objectives (Swedish Government Official Reports, 2000). Equity targets are met by capping the out-of-pocket expenditures for reimbursed medicines at 2,200 SEK per year, which means those with the greatest need will receive the most support. In addition, this scheme is designed on a sliding scale: the patient pays 100% of the cost of medicines up to a maximum of 1,100 SEK; above this amount the co-payment share gradually drops to 10% as total expenditure rises from 3,901 to 5,400 SEK during the coverage period. If the out-of-pocket payments for medicines exceed 5,400 SEK during a twelve-month period, the patient then pays no co-payment.

Efficiency is encouraged by the relatively higher out-of-pocket cost for patients who spend comparatively little on medicines annually, thus increasing sensitivity to price and cost. This allows the patient's own valuation of the cost and benefit of the medicine to contribute to a more efficient market.

The financial objective of the national pharmaceutical benefits scheme requires balancing the out-of-pocket share against total expenditures. An out-of-pocket portion of more than 25% could affect equity. A report on a new pharmaceutical benefits scheme (Swedish Government Official Reports, 2000, p15) proposed an out-of-pocket level in the range of 28–32%; however, this has not been implemented. The lion's share of total medicines expenditure occurs in a very small group of patients whose serious illnesses require multiple or particularly expensive medicines.

Carlsson and Tinghög (2013) base their analysis of individual responsibility for the cost of medicines on five characteristics of health care: 1) health care services are not a goal in themselves, but exist to

improve health, 2) patients and health care providers have different levels of knowledge regarding health status and health care options, 3) the benefit of any medicine to the individual patient is often uncertain, 4) the intervention may produce highly desirable external effects, such as vaccinations that lessen the risk of disease not only for the individual patient, but also for society, and 5) the demand for health care services involves a degree of unpredictability and inconsistency.

Based on these characteristics, the authors devise six criteria that in their opinion should be met for co-payment schemes to be regarded as 'fair'. The health care intervention or product should be:

1. One that most people understand well enough to decide whether the treatment is appropriate and of acceptable quality, both before and after use
2. One for which decisions are likely to be made primarily by people capable of making informed decisions based on careful consideration
3. One that does not have important external effects
4. Affordable for virtually all patients who need it
5. In enough demand to sustain a private market
6. Intended to improve performance, function or appearance beyond what can be considered 'normal' or medically justified.

The authors apply these six criteria to four medicines and two specialist food products. The appropriateness of out-of-pocket payment is judged based on human dignity, need and solidarity, and cost effectiveness. These are the three ethical principles governing reimbursement decisions made by TLV.

In their concluding remarks, the authors state that self-pay for medicines lends itself to analysis based on these criteria. In their opinion, this tool should not be used to control drug expenditure, but rather for identifying products and services that may be considered as appropriate for the private market, given efficiency and equity. They maintain that 100% self-pay would not be appropriate for very expensive medicines, even if they are not sufficiently cost-effective to qualify for state funding. Instead, a scheme for shared payment could be considered under which society covers the cost up to an agreed limit of cost-effectiveness, and the patient has the option of paying the rest. The authors emphasised

that such a solution would be associated with a number of complications that must be addressed before deciding on this option.

Carlsson and Tinghög conclude that there is no perfect way to define the boundaries between public and private areas of responsibility in paying for treatments. Each case requires finding an appropriate balance through a process this is both transparent and based on clear principles.

It is important, then, to have clear criteria in place for determining which medicines should be paid for by public funds. However, with clinical research focusing increasingly on serious conditions in well-defined and often small patient populations, and given the high price of these medicines, high co-payment rarely is an option for such innovative medicines. For example, most health care systems now specify that new cancer drugs should be fully reimbursed if included in the reimbursement system.

The report on the national pharmaceutical benefit scheme published in 2000 showed that several new medicines used for the treatment of chronic illness had annual treatment costs of 100,000 SEK. As shown in Chapter 1, an annual cost of one million SEK per patient for new medicines is not uncommon. Seen from this perspective, the contribution made by co-payments to medicines expenditure is negligible and accounts for a very small share of the cost of innovative medicines in Sweden. Co-payments do fund a large portion of the cost of cheaper generic medicines and so contribute to the efficiency of this market. However, generic substitution is what ultimately generates pressure to reduce prices in this market.

Potentially, higher co-payments could increase revenue, reduce public expenditure, and enhance efficiency by reducing overuse. However, these advantage must be balanced against the disadvantage that higher co-payments will mean that some patients will not have access to needed medicines.

Sweden has no laws against patients paying privately for treatments that are not publicly funded. This does raise issues about whether the health care system should pay for any additional resources required for the administration and monitoring of the treatment. After some debate in the UK, it was agreed that the NHS will do so (Jackson, 2010).

Co-payment in other countries

As shown in Table 6.1, many countries have a system where the amount of co-payment varies by medicine. This system has been used in Sweden and included a list of medicines that were exempt from co-payment. The only remnants of this system are insulin, which is exempt from co-payment, and medicines for communicable diseases that threaten the public health.

Co-payment schemes differ across countries; The Netherlands and Malta have no co-payment at all. The most common approach is co-payment based on a percentage of the total cost, occasionally with a cap on total co-payment, or some other variation on how co-payment percentages are applied.

The Swedish model balances objectives without creating incentives for choosing medicines based on reimbursement status. Exempting insulin from the co-payment scheme has put a certain amount of pressure on physicians to prescribe insulin rather than other antidiabetic drugs that are subject to co-payment. Increasing the cap on Swedish co-payment fees from 1,800 SEK to 2,200 SEK in January 2012 (the first change since the mid-1990s) was an unpopular move; however, no major controversies about the co-payment scheme have occurred over the last decade.

Table 6.1 Design of co-payment schemes in different countries.

1	No co-pays: The Netherlands and Malta
2	Flat rate: Austria, Italy, UK (with implicit ceiling: prescription pre-payment certificate)
3	Percentage rates: Belgium, France, Greece, Estonia, Finland (with annual ceiling), Latvia, Lithuania, Poland, Portugal, Slovakia, Slovenia and Spain
4	Uniform %: Cyprus, Germany, Norway
5	Co-insurance, with % decreasing with accumulated expenditure over a given period and with a ceiling: Denmark and Sweden
6	Deductible: Ireland, Sweden
7	In many countries there are specific exemptions for certain products as well as for some patient and socio-economic groups

Source: Espin and Rovira (2007). Authors' translation.

The role of co-payments

The issue of co-payments was the subject of an intense international debate during the 1990s. Many health economists objected to the system, arguing that it was an inefficient and unfair way of controlling drug costs (see, for example, Barer et al, 1994). This criticism was supported by several empirical studies, and for a long time little support existed for using co-payments as either a means of controlling spending or to achieve goals for efficiency and equity . What later became known as 'value-based pricing' emerged as an alternative policy instrument for controlling costs and managing the use of new medicines.

Renewed debate has emerged recently about the role of co-payment in today's health care systems where value-based pricing and reimbursement of medicines based on cost efficiency dominate approaches to managing and controlling the cost of innovative medicines (Drummond and Towse, 2012).

Drummond and Towse argue in favour of out-of-pocket payment for any portion of the cost of a medicine that the public system does not cover. This system is in use to some extent in the US where certain medicines are covered in full by insurance for some conditions, but the patient must pay an additional cost. The reasoning behind this option is that it may both improve access to new medicines and capture patients' preferences for different therapies. If patients are willing to pay a substantial portion of the cost of a particular medicine, this signals that its perceived value is high compared to cheaper alternatives – suggesting that coverage policy decisions may need to be reconsidered. Open to question, however, is how much importance public payers should attribute to patients' subjective and possibly poorly-informed opinions. Moreover, this would present many design challenges for co-payment systems and the cost of administering them might outweigh the relatively small contribution to financing new medicines.

The objections to a proposed increase in out-of-pocket payments in Sweden are easy to understand. The principle of equity is deeply rooted in Swedish health care, that is, no one should be able receive better care than someone else by paying for it privately. Those who can afford it however, are not prohibited from seeking care outside the public system, in or outside Sweden.

The role of private insurance and funding health care has been

discussed. A very limited proportion of health care delivered in Sweden is funded by private insurance. According to the World Health Organization Health Expenditures series, private insurance coverage in Sweden accounted for only 1.4% of total private health care expenditure and 0.3% of overall health care expenditure in 2011 (World Health Organization, 2013).

To control costs, private insurance also may impose co-payments and/or caps on the total amount covered. In the US, a hotly-debated consequence of this has been the substantial number of personal bankruptcies caused by very large health care bills (Himmelstein et al, 2009 and Ramsey et al, 2013). The pharmaceutical industry has developed and funded a voucher scheme to help patients gain access to drugs that are expensive and subject to high co-payments.

Co-payment applied to innovative medicines for serious diseases poses a number of challenges. For this reason, third-party payers, whether private or public, will continue to be the dominant funding source. The design of any such system, then, is more important that co-payment percentages themselves.

How should public payment systems for innovative medicines be designed?

The way health care providers are remunerated has changed away from payment per day, or per visit, or by specifying a global budget. The driving forces have been the division of the health care system into purchasers and providers and an increase in the share of private health care providers who contract with public payers. Today's sophisticated contracts both specify service volumes and set quality parameters. One example is using diagnosis-related groups (DRGs) to pay hospitals, an approach that both has increased productivity and improved cost control.

An increasing amount of health care is provided outside the hospital setting, or through collaboration involving several health care institutions and settings. This has created the need for new reimbursement structures that are based on the value of a combination of services provided during a health care episode ('bundled payments'). In Sweden, such reimbursement systems are often referred to, somewhat inaccu-

rately, as 'value-based payments' following a publication by Porter and Teisberg (2006) that received widespread attention. Bundled payments also have been part of a strategy to reform the US health care system (see Newcomer, 2012, for an example in cancer treatment in the United States). This is an interesting approach to reducing costs; a systematic assessment of the US experience shows a modest effect on costs without any negative impact on quality (Agency for Health care Research and Quality, 2012).

There is good reason to explore whether and how well new health care payment systems tried in other countries might work in the Swedish health care system. One recent development, for example, is the 'pay for performance' model (known as P4P). An extensive literature is available about P4P, including recommendations on how it should be designed. The approach has been debated and attempted for a long time in health care. The intent is to help improve efficiency; however, whether this is an achievable goal, and under what circumstances, is an open question (Emmert et al, 2012; Anell, 2010). A single answer to the question is unlikely because the success or failure of P4P depends on the setting and the detailed design of the payment system. See Eijkenaar (2013) for a summary and for guidance on the design of P4P agreements.

To date, the new methods developed for payments from public payers to private and public health care providers has included medicines only partially. However, agreements made between pharmaceutical companies and NICE regarding the terms for recommending the use of innovative medicines by the NHS in England and Wales have triggered additional efforts over the last ten years (Towse et al, 2012). This began in 2002 when, following NICE's initial refusal to recommend reimbursement for new drugs for multiple sclerosis (MS). Four pharmaceutical companies reached an agreement with the Department of Health (DH) to lower the price of new MS medicines unless specific effectiveness targets were met. The observational study that was initiated to evaluate this took years to complete and was inconclusive. No price adjustments were made. Debate was widespread about both the choice of methodology and the interpretation of results. We will return to this experience in a later discussion on methods for managing uncertainty in decisions about the value of medicines.

The NICE/DH agreement on MS medicines was based on the

principle of payment by results, more commonly referred to as coverage with evidence development (CED) because the medicine is covered under the reimbursement system whilst new data are collected and analysed. Carlson et al (2010) have published an international review of studies evaluating this approach, which shows that such evidence has been linked explicitly to payment in very few cases. The most common scenario is revision of the reimbursement decision, as in several cases in Sweden where the TLV has insisted on such follow-up studies. In a review of CER agreements by Puig-Peiró et al (2011), the authors identified 24 publications about CER in the literature, more than 40% of which were about MS medicines in the UK. The study suggested that considerable cost is involved to set up and administering these agreements. The benefits identified include better access to new medicines, pricing that is more in line with the value, encouraging innovation by rewarding it, and reducing uncertainty for the payer.

Not surprising, given their costs, new cancer drugs have been the subjects of a number of new payment methods. For example, in 2006, after initially deciding against a recommendation for including Velcade in the NHS, NICE reached an agreement with its manufacturer, Janssen-Cilag. This specified that Janssen would repay the NHS for expenditures on the drug unless the medicine met a specific effectiveness criterion: a reduction in the level of a certain biomarker (serum M-protein) of less than 50%.

Although similar agreements have been reached, the most common approach to reimbursement coverage for pharmaceuticals is to pay a certain price per unit – for example, tablet or vial – regardless of the level of efficacy achieved, which keeps the focus on the unit rather than its effect. This is a basis for prices set by TLV in decisions about reimbursement under the national pharmaceutical benefits scheme. Unit prices also are used for international price comparisons and differences between countries in such prices have given rise to parallel trade, that is, exporting from countries with a low price per unit to countries with a higher price per unit. This creates arbitrage for traders, but also reduces revenue for the innovative firms.

To price 'per pill',or per pack, was the obvious choice when pharmaceutical markets (countries) were privately funded. As long as pharmaceutical markets remained essentially national, prices could be varied

according to each countries ability to pay. In their position as monopolists, pharmaceutical companies could set prices that they judged would maximise revenue in each market. This also provided maximum income to fund R&D on new medicines.

As long as reimbursement remained limited and consumption levels could be controlled with co-payments, the situation remained largely stable. Pharmaceutical companies through marketing to prescribers could influence prescription volumes. However, the introduction of several expensive orphan drugs, and especially a number of important cancer drugs (trastuzumab and imatinib, see Chapters 3–5), led to a change. As the market for innovative medicines became increasingly characterised by negotiations with public payers, starting with fixed price was no longer optimal. Considerable flexibility is required when price and quantities are negotiated in parallel.

The development of a single European market with uniform pricing, as the result of the internal market in the EU, and an increasingly globalised pharmaceutical market, have made global pricing a core function in major pharmaceutical companies. The development of international reference pricing systems provided additional incentives for centralised price control to discourage price reductions from spreading from country to country (Stargardt and Schreyögg, 2006). This system has now reached the end of the road, and a return to pricing according to the value to each market (value-based pricing) is currently underway. This means a return to price discrimination as a model of generating maximum revenue and maximum contribution towards development costs.

The rise of value-based pricing is clear; however, designing value-based pricing, or reimbursement, approaches and, in particular, implementing these in health care systems with different decision-making structures and mechanisms will be a lengthy process. By way of comparison, the implementation of DRG-based remuneration for hospital care took approximately 20 years to complete.

Value-based pricing of medicines

Value-based pricing (VBP), in contrast to cost-based pricing, is not novel to the pharmaceutical market. The first example was Tagamet, a medicine for the treatment of gastric ulcers that was introduced in the

US in 1976 and in Sweden in 1978. Tagamet replaced antacids and was much more effective. It was launched at a price that was much higher than the antacids it replaced. The justification was improved efficacy, which also meant reduction in the number of ulcer patients that would require surgery. Just over ten years later, Astra launched Losec for the same indication and with even greater efficacy. The price of Losec was also based on analyses of added value.

The principle behind VBP is that the price is determined by evidence on the outcome of treatment. A value is assigned to this outcome. In the cases of Tagamet and Losec, no formal calculations of value were made, but data showing shorter treatment duration, earlier return to work, fewer patients receiving disability pensions, and improved surgical procedures were used as indicators that the value of the outcome justified the price. At that time cost-effectiveness was no more than an informal criteria for reimbursement – used, for example, in price negotiations between Apoteksbolaget (the National Corporation of Swedish Pharmacies) and the company marketing the medicine in Sweden. According to the legislation at that time on price control of pharmaceuticals, prices should be "reasonable".

In the early 1990s, Canada (province of Ontario) and Australia introduced cost-effectiveness as a formal criterion for decision-making on pricing and reimbursement. It was not until the creation of NICE in 1999, however, that cost-effectiveness became a key criterion for assessing a medicine in relation to its price. The creation of TLV in Sweden in 2002 formalised the existing informal approach to assessing new medicines based on cost-effectiveness.

The move towards a system where decision-making on utilisation and payment is based on systematic assessments of cost-effectiveness, that is, whether the drug provides sufficient value for money, thus has been underway for a long time. As a basis for making reimbursement decisions, however, it is just one of several principles regularly applied. In Germany and France, reimbursement and pricing decisions still are based primarily on clinical efficacy data (patient benefit), in combination with negotiations on pricing and volume (budget impact). However, a change is underway in France that will require more systematic cost-effectiveness studies after marketing commences. This is also being considered in Sweden, as discussed in Chapter 5 and elsewhere.

Value-based pricing is a form of price discrimination that allows prices to vary by indication and by country, according to each country's ability to pay. This principle can be illustrated as shown in Figure 6.1.

The factor K is the willingness to pay for a given improvement in health outcome, for example, 500,000 SEK per life-year or QALY gained. Whether a new medicine has a greater value that could justify a higher price will depend on any potential savings, health outcomes, and society's willingness to pay for better health.

Whilst it may be easy to agree on this in principle, the details of how to calculate savings, measure health outcomes, or assign values to health improvements are less straightforward. Despite these obstacles, most health care systems clearly are moving towards this approach because it is better than the alternatives. We already have explained why co-payment no longer works and why 'internal reference prices' only work for new medicines where the outcomes are identical to those already on the market. A third option, external reference pricing, has become increasingly common in an international and transparent market. As a result, pharmaceutical companies have been forced to attempt to

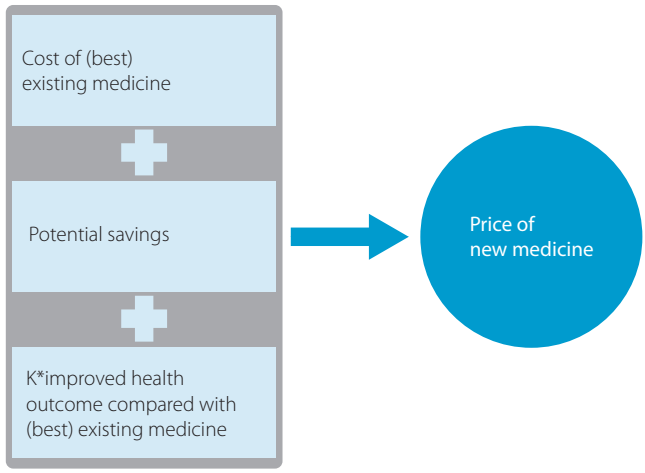


Figure 6.1 Value-based pricing.

control prices in different country markets to prevent unwanted price reductions.

The international reference pricing system has meant, amongst other things, that prices in countries with a relatively low ability to pay have become as high as those in rich countries. This, in turn, has resulted in very limited use of new medicines in lower-income countries. This is a problem for patients in these countries, clearly, but it also is a problem for companies: contributions to development costs would have been greater if more product had been sold at a lower price. Variable pricing, or price discrimination, is of interest to both the supplier and the payer in this case. Value-based pricing is a means of achieving appropriate prices in each market that are acceptable to both pharmaceutical companies and health care payers, although the specific details of how the systems work will differ.

In Sweden, TLV has been developing and administrating a value-based pricing and reimbursement system since 2002. Until now, this system has been accepted by the industry, the government and the parliament. However, there are indications that a reassessment may be underway with respect to how prices for innovative medicines develop from launch until patent expiry. International price comparisons have shown that Swedish prices are higher than in other comparable countries for certain high-volume medicines five to ten years after launch. Because an agreement was reached recently between the government and the industry on price reductions on older medicines, it is probably safe to assume that this issue now has been removed from the agenda (Swedish Ministry of Health and Social Affairs, 2013).

Suggested changes in the value-based pricing system have primarily involved proposals to extend it to cover all treatments – not just prescription drugs – and other health technologies. However, this will be very difficult to implement since not all such technologies can be objectively identified, classified and evaluated (Dental and Pharmaceutical Benefits Agency, 2013).

Value-based pricing in the UK

The pricing system for medicines is changing in the UK away from a system based on regulation of pharmaceutical industry profits to one

based on the principle of value-based pricing. Pharmaceutical companies still will be able to set their own prices. For new medicines funded by the UK National Health Service (NHS), however, the price set by the manufacturer will be assessed based on estimates of value, in the same way that has been done by NICE since 1999.

The details of this system are not yet finalised, despite the fact that it is due to come into effect in 2014. However, reports suggest an extension of the type of cost savings will be included in the assessment, reflecting the societal perspective adopted in the Swedish system. QALYs will still be used as a measure of health outcome, but this may be supplemented with information on disease severity. It is not yet clear whether this will mean that QALY calculations vary by diseases, or whether disease severity will be taken into account when determining the willingness to pay for one QALY as is currently done for end-of-life interventions in small patient populations. In the Swedish system, this aspect is incorporated into decision-making under the principles of equality and giving priority to the most severely ill patients.

Value-based pricing and design of payment systems

Value-based pricing is a way of pricing a medicine in relation to its value when administered to patients. This principle provides no clear guidance on the details of the actual payment, nor does it take into account the uncertainty associated with estimating value. In addition, it is not designed to suggest what proportion of the value of the medicine to society should accrue to the pharmaceutical company that has developed the medicine. In Chapter 3, we showed two examples of studies that have estimated and allocated the value of new medicines that accrues to users/society and to the manufactures in the longer term.

To illustrate the difference between value and payment, it may be appropriate to begin with comparing the development of a new medicine to building a bridge.

DUPUIT'S BRIDGE AND PRICING PUBLIC GOODS

French engineer and economist Jules Dupuit published an article in 1844 in which he used the construction and use of a bridge to illustrate the difference

between the value of a public utility and how to price its use. The value of the bridge consists of the willingness to pay for future crossings. The price placed on using the bridge should be equal to the cost associated with the crossing (the marginal cost). Since this will be close to zero, funding the bridge fully or partly by public means will be a rational approach. If the bridge has to be funded by fees, price discrimination, that is, variable fees according to the value to individual users and their willingness to pay, provides maximum public utility (Ekelund 1968).

Building the Öresund Bridge between Malmö and Copenhagen cost approximately 20 billion SEK, roughly equivalent to the cost of developing two new medicines. The bridge will have value for a long time to come. Most of the annual cost of the bridge, approximately 1 billion SEK, consists of interest payments and re-payments on the loans that financed the investment. Only around one quarter of the annual cost is accounted for by maintenance and administration.

The charges for using the bridge have a complex design and vary for by user. For those crossing the bridge by train, the charge is included in the ticket price for the train. Heavy goods vehicles pay a higher fee for crossing than cars. In addition, various discount schemes allow the fee to vary depending on how frequently a user crosses the bridge. Thus price discrimination is applied for financing the costs, possibly because the owners are in a monopoly position. This does not mean the bridge is the only way of crossing the Öresund Strait; all it means is that the owner of the bridge can decide the price of this crossing for different users. The price paid has nothing to do with the actual cost of allowing someone to cross the bridge; this cost is virtually zero for a single crossing. However, prospective travellers will only choose the bridge if the value exceeds the price they pay for crossing.

The issues associated with financing new drug development are in principle identical to those associated with financing the Öresund Bridge. The cost of treating one additional patient will be negligible once the medicine is already on the market; the marginal cost will be close to zero. This is true even when production cost for the compound are considerable because these are largely fixed and not dependent on the volume of drug produced. From the point of view of society as a whole, then, it is not rational to prevent anyone from accessing the medicine

just as it is not rational from a public finance point of view to prevent anyone from crossing the Öresund Bridge. However, the bridge must be paid for, and if no fees are charged for crossing the bridge, taxation would be the only means of funding it. Were this the case, the bridge would probably never have been built in the first place.

The rational payment mechanism for an innovative medicine would be for the patient to pay the marginal cost and the remainder to be funded through insurance and taxation (Garber et al, 2006). This is indeed the case in countries with publicly funded health care systems. However, the issue of how to pay for the public share remains. A rational approach would be to pay a lump sum that is equivalent to the value to all patients who use the medicine for the approved indication. In principle this seems simple, but it requires all potential users to be identified and the value calculated for each one. Because this is highly impractical, the prevailing model is for all users to pay the same price. As a consequence, however, the treatment of patients where the value is less than the price will not be cost-effective, even though the value exceeds the variable cost.

One solution to this dilemma could be to split the payment in two: a fixed share that is independent of the number of patients treated and a lower fee per patient treated. An article by Persson et al (2012) suggested that the contribution made by the central government in Sweden towards the funding of medicines should be a fixed amount, as outlined above, with the medicine then made available to county councils at a reduced price. There is a certain logic to this approach, although how it could be implemented in practice is not entirely clear. First of all, the variable cost must be determined, followed by the amount of fixed remuneration for each medicine. Although we have yet to see this approach applied in practice, a system of discounts for use above a certain volume could be as a step in this direction.

Applied consistently, value-based pricing suggests payments will be largely fixed. This could be viewed as a subscription, in the same way that we pay for phones or Internet access, which have a similar cost structure, that is, marginal costs are negligible within capacity limits. It is conceivable to have a system where prices differ depending on the indication or patient population, if the benefits vary. However, for reimbursement levels to be correct, this would require documentation

of the number of patients treated for each indication. This information is not routinely available at present. In Chapter 5, we discussed the opportunities and challenges associated with developing ways to monitor health outcomes and other benefits of new medicines using real-life clinical practice data.

Uncertainty and value-based pricing – the need for follow-up studies

Estimating the value and cost-effectiveness of a new medicine involves uncertainty, which can be quantified in different ways. One option is to calculate confidence intervals for the cost-benefit ratio. The question is how this uncertainty should be accounted for when making decisions on remuneration and utilisation.

An option in cases with a high degree of uncertainty may be to apply a lower price or a higher discount. There are signs to suggest that this is the most common approach to managing uncertainty. Drug companies tend to prefer fixed discounts to making reimbursement dependent on future uncertain outcomes. The advantage of this is that no follow-up data are required and that the company has certainty regarding revenues.

The most common approach to managing uncertainty in decision-making about reimbursement is to require that data be collected to inform reassessment at a predetermined time in the future. This method has been used in various countries since 1999. The most common approach is to collect data to substantiate assumptions about real-life clinical effectiveness, and to validate assumptions made in the cost-effectiveness estimate that was the basis for the decision.

REAL-LIFE STUDIES OF CLINICAL EFFECTIVENESS

An early example was the decision by NICE in 2002 to insist on data collection on the effectiveness of medicines for the treatment of MS to support a potential revision of the price. Despite the fact that extensive data were collected, the question regarding effectiveness remains unanswered because it still is not clear what the observed outcome should be compared to the alternatives (McCabe et al, 2010). This illustrates the importance of planning such studies in advance to ensure objectives can be met. Estimate the outcome of new MS medicines today is more straightforward because data on existing treatments are available for comparison.

Conditional approval has been applied by the TLV in several cases (see Ivergard et al, 2011). In around one quarter of the cases, this meant data had to be collected to show that the drug was actually used in the patient populations listed in the reimbursement decision. One quarter of cases involved follow-up for the purpose of verification of effectiveness data, and in half of the cases the objective of data collection was a combination of these two.

Requiring data collection for follow-up, then, already is established practice in Sweden. The Swedish national pharmaceutical benefits scheme is designed in principle as a product-based reimbursement scheme under which reimbursement is for the medicine, not the indication. However, this contradicts the cost-effectiveness criterion, which can only be met in defined patient populations in relation to defined treatment alternatives. In principle, a given medicine can be used for any indication under the scheme. The pharmaceutical company has an incentive to follow the restrictions on use imposed by TLV since there is obviously a risk that TLV may reassess the reimbursement decision.

The normal procedure for coverage with evidence development is for TLV to grant temporary reimbursement for a period of two years, followed by reassessment. To date, the initial decision has not specified any criteria about how data collection should be carried out. It has been up to the company to decide on this and to fund the research. In some cases, it has proved difficult to collect the required data within the stipulated time frame; in such cases TLV has tended to extend the deadline. In summary, it should be noted that in the majority of cases TLV has received the data requested and the reimbursement decision has been ratified (Ivergard et al, 2011).

Price control and co-payments

Price control and co-payments are no longer viable means for managing the use and controlling the costs of innovative medicines. In the case of some innovative medicines, there may be an argument for patients paying the full cost themselves, based on predetermined criteria. But even in these cases, there will often be groups of patients for whom this will have unwanted outcomes. It is only in exceptional cases, then, that no assessment of price and value is required for public funding.

The maximum payment level or cost ceiling under the Swedish national pharmaceutical benefits scheme protects high-needs patients from incurring high costs. The design of this 'high cost protection' also promotes efficiency, especially with respect to the use of older medicines that are sold at low prices after loss of patent protection, and amongst low-consumption users who pay a large portion of the cost themselves.

Medicines used in hospitals are paid for as part of the public hospital financing system, with no government price control. It is not uncommon for treatment decisions to involve a choice between orally administered medicines and those administered by injection or infusion. The funding of a medicine should not be dependent on where or how it is administered to the patient, but rather on the costs and outcomes associated with the available alternatives.

Reference pricing, discounts, and value-based payment and use

Reference pricing leads to international price conversion, which is often regarded as positive in terms of price control. In practice, however, pricing differences across countries have been reduced by charging a higher price in lower-income countries and a lower price in higher-income countries. Reference pricing thus has become a barrier to price discrimination across countries, which leads to curtailment of company revenues for reinvestment in new drug development. Additionally, reference pricing provides incentives for companies to develop launch and pricing strategies to forestall reference pricing that also may lead to significant delays in access to some products in some markets.

Value-based pricing, or rather value-based payment, has become the dominant principle for decision-making on the use of innovative medicines in a number of countries. Unless a medicine is innovative and provides improved treatment outcome compared to the available alternatives, the price will be the same as for existing alternative products on the market. The value-based price will differ across countries, and for indications within each country, because value depends on several factors: how the medicine is used, for which patients, and in the place of what the alternatives; and how much each country is willing and able to pay for the improvement in outcomes.

In situations where the pharmaceutical company and the payer are unable to agree on the price of a medicine, there will be strong incentives on both sides for reaching an agreement involving a non-disclosed discount.

DISCOUNTS ARE BECOMING INCREASINGLY COMMON

Negotiations on discounts are now a regular part of decisions made in the UK by NICE when deciding whether to recommend use of new medicines in the NHS.

The French system of non-disclosed agreements on pricing and volume is in principle a discount system, with the added benefit of promoting higher levels of use by offering quantities in excess of what has been agreed within the 'envelope', for free or at a lower price.

Germany has recently introduced a system of price negotiation that will occur after the reimbursement decision.

In Sweden, a limited number of agreements on price discounts have been reached at county council level.

Value-based payment paves the way for new principles for the design of payment systems for innovative medicines. Price per unit has become irrelevant. The critical consideration for pharmaceutical companies will be revenues; the key concern for payers will be the number of patients who can be treated and total cost. It will no longer be meaningful, or even possible, to compare prices per pack, tablet or vial in across countries.

Conclusions

Our main conclusion is that it is important, both from a health care point of view and in a wider societal perspective, that Sweden remain at the forefront in the development, assessment and use of new medicines – and that legislation, governing bodies and decision-making procedures ensure this is possible. A new system for paying for medicines is needed that will combine the health care system's need for effective and equitable resource utilisation with continuous incentives for innovation.

Value-based pricing is a commendable idea, but it focuses too heavily on price. Most important for companies developing new medicines and for health care providers is basing remuneration and use on value. Since

the value of different uses of the same medicine may vary, the value-based price will vary as a result. Reimbursement decisions, therefore, should be based on the number of patients treated for each indication, rather than only on a price.

Decisions about the utilisation and reimbursement of new medicines will necessarily involve uncertainty about the value of a medicine in real-life clinical practice. The key change will be that the heath care system will be collecting and making available more and different types of data with may uses, including the design of new payment systems. Payment by patient treated and by health care episode increasingly will be linked to the health outcome realised. To be successful and realize the full potential of changes in these data and processes, the relationship between the health care system and the innovative pharmaceutical industry must be one of partnership and trust.

References

Agency for Health care Research and Quality (2012). Bundled payment: effects on health care spending and quality. Closing the quality gap: revisiting the state of the science. Evidence Report/Technology Assessment. Publication No. 12–E007–EF.

Anell A. (2010). Värden i vården – en ESO-rapport om målbaserad ersättning i hälso- och sjukvården. Rapport till Expertgruppen för studier i offentlig ekonomi 2010:7. Swedish Prime Minister's Office.

Apotekens Service AB (2013). Läkemedelsförsäljningen i Sverige 2012 (version: januari–december). Stockholm: Apotekens Service AB.

Barer M., Bhatia V., Evans R., Stoddart G. (1994). User charges, snares and delusions: another look at the literature. The Premier's Council on Health, Well-being and Social Justice, Ontario.

Carlson J.J., Sullivan S.D., Garrison L.P., Neumann P.J., Veenstra D.L. (2010). 'Linking payment to health outcomes: a taxonomy and examination of performance-based reimbursement schemes between health care payers and manufacturers', Health Policy 96 (3), pp 179–190.

Carlsson P., Tinghög G. (2013). Läkemedel – när är det rimligt att betala själv? Stockholm: SNS Förlag.

Drummond M., Towse A. (2012). 'Is it time to reconsider the role of patient co-payments for pharmaceuticals in Europe?', European Journal of Health Economics 13, pp 1–5.

Eijkenaar F. (2013). 'Key issues in the design of pay for performance programs', European Journal of Health Economics 14 (1), pp 117–131.

Ekelund R. (1968). 'Jules Dupuit and the early theory of marginal cost pricing', Journal of Political Economy 76 (3), pp 462–471.

Emmert M., Eijkenaar F., Kemter H., Esslinger A.S., Schoffski O. (2012). "Economic evaluation of pay-for-performance in health care: a systematic review", The European Journal of Health Economics: HEPAC: health economics in prevention and care 13 (6), pp 755–767.

Espin J., Rovira J. (2007). Analysis of differences and commonalities in pricing and reimbursement systems in Europe. Final Report. European Commission.

Garber A.M., Jones C.I., Romer P. (2006). 'Insurance and incentives for medical innovation', Forum for Health Economics & Policy 9 (2) (Article 4).

Himmelstein D.U., Thorne D., Warren E., Woolhandler S. (2009). 'Medical bankruptcy in the United States, 2007: results of a national study', American Journal of Medicine 122 (8), pp 741–746.

Ivergard M., Jönsson B., Jönsson L. (2011). 'Drugs on probation – The Swedish experience with coverage by evidence development', unpublished manuscript.

Jackson E. (2010). 'Top-up payments for expensive cancer drugs: rationing, fairness and the NHS', Modern Law Review 73 (3), pp 399–427.

McCabe C., Chilcott J., Claxton K., Tappenden P., Cooper C., Roberts J., Cooper N., Abrams K. (2010). 'Continuing the multiple sclerosis risk sharing scheme is unjustified', British Medical Journal 340: c1786.

Newcomer L.N. (2012). 'Changing physician incentives for cancer care to reward better patient outcomes instead of use of more costly drugs', Health Affairs 31 (4), pp 780–785.

Persson U., Svensson J., Pettersson B. (2012). 'A new reimbursement system for innovative pharmaceuticals combining value-based and free market pricing', Applied Health Economics and Health Policy 10 (4), pp 217–225.

Porter M.E., Teisberg E.O. (2006). Redefining health care: creating value based competition on results. Boston, MA: Harvard Business School Press.

Puig-Peiró R., Mestre-Ferrandiz J., Sussex J., Towse A. (2011). 'Literature review on Patient access schemes, flexible pricing schemes and risk sharing agreements for medicines', poster presented at the ISPOR conference. Value in Health 14. Abstract 243.

Ramsey S., Blough D., Kirchhoff A., Kreizenbeck K., Fedorenko C., Snell K., Newcomb P., Hollingworth W., Overstreet K. (2013). 'Washington State cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis', Health Affairs 32 (6), pp 1143–1152.

Ministry of Health and Social Affairs (2013). 'Utvecklad takprismodell för vissa äldre läkemedel och krav på laga kraft av beslut om sanktionsavgifter'. S2013/6586/FS.

Stargardt T., Schreyögg J. (2006). 'Impact of cross-reference pricing on pharmaceutical prices: manufacturers' pricing strategies and price regulation', Applied Health Economics and Health Policy 5 (4), pp 235–247.

Swedish Government Official Reports (2000). Den nya läkemedelsförmånen. SOU 2000:86.

Swedish Dental and Pharmaceutical Benefits Agency (TLV) (2013). 'Delrapport – TLV:s regeringsuppdrag att göra hälsoekonomiska bedömningar av medicintekniska produkter'. S2012/2788/FS (partly).

Towse A., Garrison L., Puig-Peiró R. (2012). The use of pay-for-performance for drugs: can it improve incentives for innovation? Occasional Papers. London: Office of Health Economics, OHE. 12/1.

World Health Organization (WHO). 'Health expenditures series'. Downloaded on 19 September 2013 from http://apps.who.int/nha/database/DataExplorerRegime.aspx.

7. Summary, conclusions and recommendations

The new focus on the value of medicines in policy decisions about medicines and the pharmaceutical industry is rooted in a number of interdependent factors. In the background is the tremendous progress that has been made over the past 50 years in developing innovative medicines, many of which now are available as generics at low cost. Going forward, new medicines not only will need to provide benefits over existing therapies, but they also must be priced competitively. To continue to produce drugs that are true therapeutic advances, pharmaceutical companies are increasingly focusing on therapeutic areas with large unmet needs. Although the potential value of such new drugs is high, the costs of development and the risks also are higher. The average cost of developing a new medicine is now over 10 billion SEK (Chapter 1). As a consequence, new medicines reaching the market are increasingly expensive.

New drug development has generated unquestionable value for patients, health care providers and society as a whole. The health care system's ability to pay for new medicines, however, has not kept pace with development costs. The US, Europe and Japan, home to the three largest pharmaceutical markets, have funded previous innovation. The economic downturn, however, has made it difficult for these health care systems to continue to expand and finance new treatments. Economic growth in other parts of the world as yet has been able to compensate for this only to a limited extent. In countries such as the BRICs, health care costs remain low in absolute terms, but only a minor share of the

population is as yet able to afford innovative medicines (Chapter 1).

Whilst the health care system is finding itself under increasing financial strain, the pharmaceutical industry has become increasingly dependent on public health insurance and public health care systems for funding the development of new medicines. Direct payments from patients now account for a very small portion of the income from medicines (Chapter 6). As a result, the future of the pharmaceutical industry now depends on the ability and willingness of health care systems to pay. Because expenditures in major health care markets no longer are increasing significantly, public and private health care budgets are limited, making competition for what is available increasingly tough. For the same reason, decisions about the pricing and use of medicines are increasingly based on formal analyses where the value is weighed against the cost. Although the principles underlying value analyses are the same, practical implementation and decision-making vary across countries. In all countries, the requirements for market entry are becoming increasingly challenging for new medicines; greater amounts of time and resources are required to prove that the value of a new medicine warrants its use and reimbursement.

It is not only the demand side of the pharmaceutical market that is changing. The industry itself is changing as the increasing risk and cost of drug development lead to mergers, which have produced fewer and larger pharmaceutical firms. Leading Swedish pharmaceutical companies have merged with companies from other countries and operations in Sweden have subsequently been cut back. Although Swedish exports of medicines still exceed imports, the surplus has declined in recent years as has a number of people employed by the Swedish pharmaceutical industry. A crucial question is what actions can effectively break this trend and once again make Sweden an attractive location for innovative drug development and production. The answer to this question is far from simple; but analyses done to date agree that a critical factor is how the health care system uses and pays for new medicines.

Decisions about reimbursement and use of new medicines

Decision-making about the use innovative medicines is a complex process. It has been the focus of numerous analyses and discussions, and medicines remain one of the most common topics of official studies and reports (Chapter 2). This reflects both market dynamics and the importance of legislation, governing bodies and decision-making adapting to changing reality. The traditional separation of the market into a hospital market, where medicines constitute a very small part of the overall budget, and a primary care market, governed by price control and co-payments, no longer is compatible with the functioning and management of the pharmaceutical market and health care system (Chapter 6). Budgets now integrate secondary care, primary care and medicines and, for some health services, the budget for medicines may be as large as the budget for staff. The use of a new medicine is determined by its value in relation to cost, whether it is administered as an infusion in the clinic or as a tablet a patient takes at home.

The health care system, rather than physicians or patients, is the most important customer for new medicines. The health care system's decision to pay for and use a new medicine is crucial; the very small private market cannot provide the revenues needed for development costs. Criteria set by the health care system for the use of new medicine, then, and the decisions based on them are increasingly important for the innovative pharmaceutical industry. Today's health care system is focused on results, in the form of improved health and quality of care, and is willing to pay for new medicines that can help improve outcomes.

It is important that decisions about new drug development take into account what the health care system is willing and able to pay for. Formal processes for facilitating discussion by bringing together health care payers, regulatory authorities and pharmaceutical companies at an early stage of the R&D process are under development at the EU level and in individual countries. For example, pharmaceutical companies can receive joint guidance from the Swedish Dental and Pharmaceutical Benefits Agency (TLV) and the Medical Products Agency on the design of clinical studies. Informal contacts between health care payers, regulators and companies developing new medicines are also important. The establishment of a Foresight Institute at Medicon Village in Lund

in the south of Sweden to study trends in Swedish and international markets, will give companies of all size, including the smaller ones, access to information on evolving health care needs and requirements. More resources need to be invested in initiatives of this type in Sweden for companies to gain a competitive advantage.

Market access and reimbursement

The approach to assessing new medicines has changed over time. In the case of prescription medicines, which are most of the market, physicians and patients judge the value and make the decisions. Price control and co-payments are used to control costs. The creation of the Swedish Pharmaceutical Benefits Board in 2002, and the subsequent extension of its responsibilities and name change to TLV in 2008, introduced a formal process for evaluating the value of medicines to patients and for making decisions about reimbursement.

Most new medicines are developed for serious conditions and patients unquestionably benefit from improved treatments. It could be argued, then, that once an innovative medicine has been approved by the Medical Products Agency, it should be covered under the national pharmaceutical benefit scheme in accordance with two of TLV's guiding ethical principles – human dignity, and needs and solidarity. Cost-effectiveness, the TLV's third governing ethical principle, however, is in reality the primary criterion for determining value and driving decision-making on pricing and reimbursement. A medicine will be reimbursed under the pharmaceutical benefits scheme provided the asking price is set at a level where the cost per QALY gained, a measure of health gain and value, is considered reasonable. The decision on whether to include the medicine in the pharmaceutical benefits scheme also will stipulate the price. In principle, then, the decision balances price against value.

Although the system has worked well, three problems have emerged in recent years. Firstly, prescription medicines used in ambulatory setting are not the only innovative medicines on the market, and it would be counterintuitive not to extend the same approach to other settings of use. Progress towards this includes giving TLV the authority to assess hospital-administered medicines without making decisions on price. The option of extending TLV's remit further, to cover other health care

interventions, also has been discussed. The objective assessment of the value of new medicines has become an important health care policy instrument in Sweden, as in many other countries.

The second problem is that TLV assessments of cost-effectiveness and decisions on reimbursement also include official decisions on price. Because of the international reference pricing system applied in some countries, pharmaceutical companies understandably are concerned that reducing the price in one country may lead to price reductions in other countries. One possible response is to make the official price a starting point for negotiations on discounts or other conditions for reimbursement. This is becoming common in other countries, but has only recently been considered in Sweden. This change, however, renders both the existing Swedish price control approach and the international reference pricing system inoperative. The pharmaceutical market is characterized by large variations in national health care systems' ability to pay; it is not surprising that a system of differential pricing will develop that replaces uniform international prices. These trends present both opportunities and challenges for payers and pharmaceutical companies.

The third problem faced by the current approach to assessing medicines is that the value of a medicine will not be known when it first enters the market (Chapter 3). The available evidence on efficacy and safety is based on selected patient populations using the drug under experimental conditions. Additional evidence is needed on the effectiveness of medicines in wider patient populations in real-life clinical practice. Only by using the medicine and collecting additional data will it be possible to assess value with greater certainty.

Existing EU regulations for market authorisation require a decision by the European Commission based on scientific assessment by the EMA. The need for additional data after marketing authorization has been part of many such decisions; particularly data collection to allow detection of any rare adverse events that may occur once a product is used more widely (Chapters 3 and 5). Decisions can then be reassessed based on this data. Market authorisation has been revoked in some cases, but in others indications have been extended or restrictions lifted. Assessing the value of a medicine, of course, requires more than the safety and efficacy data gathered for regulatory approval. With this in

mind, EMA now also is requiring further data on use in real-life clinical practice to inform the decisions about risk-benefit (Chapter 5).

Data that can demonstrate the value of new medicines in real-life clinical practice is important to traditional health care regulatory authorities, the Medical Products Agency, bodies that assess the cost effectiveness of medicines, and the TLV. In several cases TLV has insisted on follow-up data documenting that the medicine is used for the approved indication and that the assumptions made in the cost-effectiveness assessment are consistent with real-life clinical practice.

Follow-up real-life clinical effectiveness studies have become important not only in assessing the value of existing medicines, but also in guiding decisions about future R&D. Only medicines that can provide enough evidence of value for money to payers will generate the revenue necessary for making continuing drug development profitable for the pharmaceutical industry (Chapter 1).

Objectively assessing the value of medicines

The most important aspect in assessing the value of a medicine is reliable assessment of relevant treatment outcomes. Medicines that affect survival can be assessed in terms of life-years gained. If the main outcome is improvement in quality of life, QALYs can describe health gain. QALYs take into account that not every additional life year gained will be the same in quality; they also capture improvements in quality of life from, for example, fewer side effects or improved functioning as a result of reduced pain or anxiety. The main advantage of this measure is that it allows comparison of different treatment options and diseases.

New medicines may also produce economic benefits by reducing sickness absenteeism or disability pensions. Similarly, reductions in mortality amongst the working-age population will lead to increased productivity, although this may be counterbalanced by greater costs to society for the years of survival beyond working age. Medicines also may reduce the cost of other health care interventions. For example, effective medicines for the treatment of gastric ulcers reduced hospitalisation and surgery expenditures, and medicines for the treatment of hypertension and hyperlipidaemia have reduced the incidence of stroke and myocardial infarction, and thus the associated treatment costs (Chapter 3).

Studies of the value of innovative medicines show that the most important aspects of value are improved quality of life and prolonged survival, as illustrated in the SNS study of medicines for the treatment of breast cancer (Chapter 3). The largest gain due to increased productivity occurs in conditions that affect younger people, such as type 1 diabetes and rheumatoid arthritis. Substantial gains due to reduced health care costs occur when a medicine or vaccine is capable of curing or preventing a condition that would otherwise require prolonged and expensive chronic treatment; an effective new treatment for Alzheimer's disease would be an example.

A significant part of the welfare gains associated with innovative medicines is generated after patent expiry, that is, when the medicine is no longer 'new'. Treatment for HIV/AIDS and cardiovascular disease are examples (Chapter 3). Pharmaceutical companies that develop new medicines receive a relatively small share of the overall value accruing to society. Most of the cost of R&D is funded by the sales of a handful of very successful and valuable medicines; the larger share of medicines that enter the market have modest sales that are not sufficient to cover development costs. Successful medicines also must fund the costs of R&D for medicines that never reach the market. Companies that are unable to produce 'blockbusters', then, will face serious financial difficulties, which has been an important stimulus for the mergers and acquisitions that are taking place within the pharmaceutical industry.

The studies of individual medicines that we have presented and discussed above show that innovative medicines can create value that far exceeds cost (Chapter 3). Our examples were selected from a number of well-known innovative successes to illustrate how value is calculated. The extent and nature of the challenge of capturing this value by ensuring optimal clinical use has become increasingly important as data on regional variations in the use of medicines have become more widely available (Chapter 4).

Observations about regional variations in use are not new; they exist not only for medicines, but also for most other health care interventions including, for example, surgical procedures. Attention to the issue has intensified with the increasingly urgent need to contain the growth in health care expenditure and improve health care outcomes without a substantial increase in resources. This has led to questions about whether

the variations observed across regions are justified or whether there is overuse in some regions and underuse in others.

Another reason for the renewed interest in causes of regional variation is that treatment indications are becoming increasingly specific – for example, trastuzumab is effective treatment for patients with HER2-positive breast cancer and genetic testing can reveal whether a patient is HER2-positive. Treatments such as this that allow effective targeting in a well-defined population increases the value per patient. For broader indications, the per patient value will be lower since not all patients will benefit, or benefit equally, from the treatment. Such variation may be more acceptable in cases where value is uncertain but the cost per patient is low than in cases where value is clear but costs are high.

Studies of regional variation

Many important treatments show regional variation in the extent of use, but the explanations for this are few and unclear. The most common explanation is that local clinical practice patterns vary (Chapter 4). Although this may be true, the origin and evolution of these local practices need to be analysed. This is especially important in cases where studies show a lack of scientific support for practice differences or when patient requests reveal serious treatment differences across regions. Such practice variations often are based on nothing more than individual clinical experience or the opinions of practitioners with substantial local influence.

Studies of regional variation in the use of medicines have been important in stimulating thought and research. Available data and analyses, however, rarely indicate the source of the problem and how it can be addressed. Patient-level data are needed that can compare use by indication, and assess treatment and outcomes for patients across regions.

Studies of regional variation provide a snapshot of clinical practice at a specific point in time. These may be an important starting point for analyses of how well the health care system operates and how it can be improved. But this is only a beginning. Also needed are longitudinal data for comparative evaluation of treatment options that can help determine 'relative effectiveness', that is, the extent to which a new intervention (such as a new medicine) is better than the alternative

treatments available in clinical practice. Studies of relative effectiveness indicate how much innovation the medicine offers, allowing decisions about at what price it will be cost-effective. In Chapter 5, we discussed SNS studies and internationally published work that demonstrate the need for studies based on data from real-life clinical practice, and the methodological challenges involved in determining the extent to which treatment outcomes differ.

As clinical practice varies both within and across countries, so too will the cost-effectiveness of interventions. Cost-effectiveness also may vary with the characteristics of the patients treated and how efficiently the health care system is able to produce results with the resources used. Although new treatment approaches and medicines now disperse across countries at ever-increasing speed, use and outcomes still may vary substantially. Understanding the full value of a medicine, then, requires evidence from observational studies of actual clinical practice; clinical trial results alone, the traditional source for evidence about value, no longer are enough.

The growing number of stakeholders

Assessments of the value of new medicines inform decisions made by payers and other important decision-makers, whose remits are to find a balance that achieves social objectives. This affects not only what data are relevant in assessing a new medicine, but also defines what groups should be allowed to provide input. Because results potentially affect all of society, the process of assessing new medicines should consider the needs and perspectives of all stakeholders. Whilst previously the monitoring and assessment of clinical studies was the sole responsibility of one stakeholder – the company performing the R&D – evolving interest in evidence on the value of medicines means that regulatory authorities (such as EMA) and payers also increasingly have a greater stake in this process. Other stakeholders that have become more influential are patient advocacy groups, under the new formalised reimbursement process, and the general public who are represented on various bodies responsible for assessing the value of medicines. These groups have an interest in data that is relevant to their perspectives. This includes scientific data on mechanisms of action and biomedical parameters,

but also extends more broadly to data about expected effects on daily functioning, quality of life, and costs.

The increase in the number and composition of stakeholder groups will help drive the development of new infrastructure that can use the evidence available from real-life studies more efficiently. The direct link is clear here between the desire for better medicines and more efficient use of health care resources to achieve better outcomes. Involving more stakeholders in decision-making also increases transparency and the application of distinct and verifiable criteria, an important change from the past when decisions often were made ad hoc by a few individuals.

Comparative effectiveness research

The process of producing relevant evidence for assessment and decisions about use is changing dramatically in countries with highly developed health care systems, both in Europe and the US. The US market has been vital as a funder of new drug development and at one time accounted for more than half of pharmaceutical industry revenues worldwide, despite the fact that medicines accounted for just over 10% of health care costs in the US, compared with twice or three times this amount in some European countries. However, the health care system is changing in the US as well and 'comparative effectiveness research' (CER) is becoming a core element of improving accessibility and cost-effectiveness in US health care (Chapter 5). Although the usefulness of such studies may be limited in other countries where patterns of clinical practice and resource use are different, advances in the methodological approach will be of interest everywhere. One thing is certain: the greater use of CER will change the way medicines are assessed in both the US and Europe.

Methods for analysing observational data are different from those for analysing data from traditional clinical trials that are intended to test a hypothesis about whether a health care intervention is effective. Comparative effectiveness studies focus on determining the degree of improvement in treatment outcome. Because clinical practice may vary, experimental studies may be necessary that randomly allocate patients to one treatment or another.

Quality registries

For a long time, Swedish quality registries have recorded data on patients treated with a variety of interventions, from surgical interventions such as orthopaedic hip arthroplasty to drug treatments such as TNF-inhibitor therapy for the treatment of rheumatoid arthritis. These registries often are referred to as 'gold mines' of information about how the health care system works and what outcomes are achieved. However, closer analysis of these registries shows that this gold mine is largely untapped and that the 'gold' has to be refined to be useful and valuable.

Particular weak spots in quality registries are the insufficient information to allow assessment of the value of medical interventions, such as data on the impact on patient function and quality of life, and the level of health care resource use associated with treatments. However, they do contain a large amount of important detailed information, such as the durability of different prosthetic materials or the incidence of rare adverse events.

The most important issue for the future for quality registries is not how to make them more useful for evaluating different methodologies; supplementing registries with additional data is a relatively straightforward task. Instead, the challenge will be ensuring that relevant data on resource use and outcomes are recorded for all treatments and all patients without exception.

EXAMPLE: DEVELOPMENT OF NEW CANCER REGISTRIES

The cancer therapeutic area lacks registries of specific treatments or cancer types. Cancer patients typically receive multiple treatments, with medical therapy being just one of many options; the treatment process often involves the use of several medicines, either concomitantly or sequentially. In addition, cancers can be classified in different ways, and the novel individualised medicine approach is largely based on tumour biology data so that treatment is targeted based on this information, rather than at the actual organ in which the cancer is located. Because treatment has become so complicated, cancer has become the first therapeutic area where systematic follow-up of all patients has begun in a number of countries, including Italy and the UK.

Swedish cancer registries are comprehensive in terms of data on incidence and mortality, but incomplete with respect to studies on what treatments have been administered and their outcomes. Cancer is also an area where treatment progress happens gradually and in small patient populations. To identify

important change, then, rapid access to data on outcomes and the value of these treatments requires international collaboration in collecting and analysing comparative data. Follow-up studies in real-life clinical practice are needed to supplement and corroborate the results of previous international collaborations on experimental clinical trials for efficacy and safety. The new studies should also be collaborative and intended to produce data for assessing the value of cancer medicines in actual use.

How should drugs be paid for?

Decisions about the use of health care resources should be based on objective studies and valid criteria. Moreover, decisions about access to many health care interventions, including medicines, increasingly balance value against cost. The public sector's willingness to pay for medicines, then, depends on reliable data about the value of medicines. The strength of this trend is a result of a gradual shift over the past 50 years in who pays for most of health care: direct payments for medicines by patients has declined as public sector payments have risen.

The introduction of new medicines with very high treatment costs has meant that patient co-payments no longer can help limit the cost of these medicines. In any case, patients rarely are capable of evaluating the efficacy of treatment that is intended primarily not to provide relief from symptoms, but to prevent disease progression and improved survival. However, decisions on pricing and reimbursement for a number of new medicines have not been linked clearly to the extent of use within the health care system. We have seen examples where individual county councils have elected not to use a medicine despite its inclusion by TLV in the Swedish national pharmaceutical benefits scheme. There are also examples where a medicine is paid for by the county councils, despite the fact that the TLV has ruled against its inclusion in the national benefits scheme.

Deciding how we should pay for innovative medicines is an important question. Currently, the government and county councils share responsibility for funding expenditures for medicines, with the government funding most of the cost under the national pharmaceutical benefits scheme. The government decides, via TLV, which medicines are covered by the pharmaceutical benefits scheme and at what price.

County councils have the option of using and paying for medicines not covered by the national benefits scheme; individual patients have the option of paying out of pocket for medicines not covered by the national or county schemes. This division of responsibilities has worked well enough so far, but is becoming increasingly impractical. If change is to come, on which principles should it be based?

The first decision is whether a new medicine should be funded by the public health care system at all. Clear criteria must inform decisions on inclusion and exclusion. In Chapter 6, we referred to an SNS study that formulated and tested criteria for when patients themselves should pay for the medicine, concluding that new medicines rarely should be paid for by patients alone. This is particularly true given the increasing number of specific treatments for well-defined patient populations with serious conditions; public funding will be essential both to ensure the access of patients to these treatments and to fund future R&D.

What does this mean for patient co-payment? Today, about one quarter of the total national expenditure for medicines in Sweden is funded by patient co-payments. The co-payment scheme protects patients from high costs by capping the maximum twelve-month co-pay at 2,200 SEK. Under that ceiling, the co-payment creates price and cost awareness amongst patients, the majority of whom either only occasionally fill prescriptions or use cheap generic drugs.

Public funds, therefore, will pay for most of the cost of new medicines, which makes the design of the public payment system particularly important. The principle of value-based pricing, or rather value-based payment, is compatible with a variety of payment modes. As discussed in Chapter 6, important similarities exist between funding the development of a new medicine and building and operating a new bridge. In both cases, investment costs are high, although the cost of an additional unit of the medicine or an additional bridge crossing is comparatively low. If the price is set with the objective of recouping the investment cost through user charges, it will be so high that the risk of underusing the asset will be great. On the other hand, if the price is set lower to optimize use, revenues will be insufficient – and maintaining the investment will require additional funding, for example, through taxation.

To achieve revenue sufficient for repaying the private financing and maintaining the operation of the Öresund Bridge, for example, a com-

plex system of rates are applied that differ by type of transport. Some users pay a fixed price, others pay a price that varies depending on type of vehicle, and some frequent users receive a discount.

As with the Öresund Bridge, it makes little sense to charge the same price to all users of a new medicine because the value will vary. Artificially keeping the price low, however, prevents anyone who wishes to do so to contribute fully towards the fixed costs of using the medicine. For this reason, price discrimination always has characterised pharmaceutical markets. For a brief period, pharmaceutical companies did attempt to achieve uniform international pricing in response to factors such as the emergence of the EU single market and national systems of international reference pricing. The result was prices in wealthy countries that were lower than those in low-income countries.

The uniform pricing system is on its way out. In France, negotiations on price and volume have long been part of the decisions about new medicines. In England, NICE recommendations increasingly include agreements on non-disclosed discounts off the list price. In Germany, decisions to include new medicines in the public reimbursement scheme now will be followed by price negotiations. Extensive discounting off list price is long-standing practice in the US, where pharmaceutical companies also may pay the patient's co-payment when it is a barrier to access to the medicine.

It is time for Sweden to become part of this trend, allowing the health care system to make more flexible agreements with pharmaceutical companies that will improve patient access to new medicines within available budgets. Flexible pricing, or reimbursement based on volume, are not enough to address the issue of uncertainty about value of medicines. Instead, agreements will need to link at least a portion of the payment to actual treatment outcomes. To some extent, payments schemes tied to results are already are in place in other areas of the health care system, such as county council remuneration of hospitals and other health care providers. Designing and monitoring such agreements is complex and requires both a sufficient degree of trust and collaboration between the parties, and expertise and creativity needed to conclude the agreements.

A defined government budget for innovative medicines?

There is logic in the idea that the body making decisions on resource utilisation should also be responsible for funding. At present, the cost of medicines is funded partly by the government, mainly for historical reasons. There is no link between funding and the value of new medicines, and presumably the government's interests will be mainly fiscal – to prevent expenditure from becoming too high. However, the government could conceivably use some of this money to fund innovative medicines for a limited time to both improve access and gather the information needed to assess value.

Funding of selected innovative medicines outside regular county council budgets could facilitate and promote their use. Use undoubtedly would increase considerably and expenditures would certainly exceed today's levels. At present, new medicines introduced during the last five years account for 8% of the total sales of 30 billion SEK (Chapter 1). Introducing important therapeutic advances sooner will lead to increased use, and probably a slight increase in the total expenditures for medicines, but these disadvantages must be weighed against gains that could be achieved; in particular earlier information about the value of new medicines (Chapter 3). An early access system also would require higher administrative costs involved in identifying which medicines are eligible, negotiating contracts with pharmaceutical companies on pricing and volume, and monitoring to ensure the contracts are being followed.

Responsibilities at the national and regional level

Swedish health care policy is characterised by tension between centralised and decentralised decision-making, that is, between the national government and the county councils. Policies will be at their most successful when the government and county councils are in tune with one another. The new issues related to the value of new medicines will affect both the government and county councils and we expect both levels of government to continue to have responsibilities for health care.

As the pricing of a medicine according to indication becomes more important, the current system that artificially segments the market

according to setting of use will become unworkable. Having different systems for pricing medicines for ambulatory use differently from those for hospital use is quickly becoming unreasonable.

The Medical Products Agency and TLV carry out assessments and issue recommendations that set the parameters for the pharmaceutical market. Since these decisions are based on the same evidence, it makes sense to coordinate the two. The Swedish Council on Health Technology Assessment (SBU) and the Swedish National Board of Health and Welfare set national guidelines one use, carry out assessments of evidence and value, and issue recommendations intended to influence actual use. One disadvantage of the guidelines is that they are of necessity based on data collected internationally, which may or may not reflect the value of treatments within Sweden. The effect of guidelines is questionable in any case: the use of many health care interventions varies across regions anyhow, suggesting that adherence to the guidelines often is poor, and data rarely are available for follow-up and analysis.

Although it is not necessary to change the co-payment system for prescribed medicines, abolishing price control will require changing the system for paying for pharmacy services. Currently, this is regulated by setting pharmacy margins, that is, the difference between the pharmacist's purchase and selling prices. One solution may be to allow pharmacies to charge both a dispensing fee and a fee based on other services provided.

Demands for information about the value of new medicines and requirements for transparent and evidence-based decisions will change the climate within which county councils operate. Change in both processes and capabilities will be needed, particularly to ensure the systematic collection of information on use, treatment and outcomes that are essential for objective, reliable assessments of value and to identify variation across subgroups of patients. Developing health care reimbursement approaches that reward high-value interventions also is an important element in more efficient resource allocation and improved outcomes.

Concerns have been raised that county councils may not be able to cope with this task, and that short-term cost-savings goals and resistance to changing processes and procedures may prevail over potential long-term gains from innovative medicines and other new technologies.

No evidence supports this view, however, other than general references to the traditional attitude amongst county councils that research and evaluation are the responsibility of the central government.

The health care system will have little choice in the near future about being more involved in the process of innovation itself, which until now in Sweden has primarily involved a small number of physicians involved in clinical research in collaboration with the pharmaceutical industry. Being part of efforts to determine the direction of future R&D, however, is an integral part of the new focus on health care outcomes and increasing demands for evidence to show that resources are being used cost-effectively.

The patient's perspective

There is some risk that increased payer influence over the availability and use of therapeutic treatment options will mean the patient's perspective is lost. This is very important, and the conclusions and proposals presented in this publication take this into account. We need to remember that it is not demands from patients that have created the variations in clinical practice discussed above (Chapter 5). Patients must be properly informed about treatment alternatives and outcomes in order to make rational decisions, whether they are paying part of the cost of not. Studies of the type carried out by SBU empower patients by providing them with the information they need about available treatments and possible outcomes.

Focusing on health care outcomes clearly is in the patient's interest. Using cost-effectiveness to allocate resources will help ensure that resources spent maximise health gains. Requiring that outcomes be measured and evaluated based on actual clinical use also is very much in the interest of patients.

Requiring decisions to be based on objective and valid evidence that is accessible to the public should help ensure that patients have equal access to new medicines. Patients' representatives are taking an increasingly active part in formal decision-making, a positive result of greater transparency in decision-making about new medicines and other health care technologies.

Innovation and the value-based use of medicines – key issues for Swedish health care providers and the pharmaceutical industry

Sweden historically has been an influential actor in the increasingly international process of developing and evaluating new medicines. During the last ten years, however, Swedish pharmaceutical exports have stagnated and Swedish involvement in clinical research studies on new medicines has been declining. At the same time, the health care system is struggling to remain an international leader in the use and evaluation of new medicines. There are a number of explanations for this and some may see it as unnecessary that Sweden continue to be a leader. But the issue remains important because Sweden's role is central to both the future development of the health care sector and to the Swedish economy. Other countries are noticing similar trends and asking themselves the same questions.

It is beyond the scope of this publication to propose a programme for re-engineering the Swedish innovative pharmaceutical industry. But our observations and analyses, as well as those in other countries, make it clear that the health care sector is a critical factor in any strategy for change. The role of the health care system in funding innovative medicines, and thus determining and paying for their value, is of strategic importance. The objective is not merely to generate revenues for pharmaceutical companies, but to reward the development and appropriate use of important new advances.

Data on the impact of new medicines on clinical practice are becoming an increasingly important part of the development process. Contributing to the development of this evidence creates a strategic advantage for Sweden. The same data are necessary to guide modifications in the health care system and make it more efficient. Investments in health care information technology thus may serve dual purposes.

Proposals

What can be done to create a better framework for the development, introduction and evaluation of new medicines?

THREE 'MEGA TRENDS'

Decision-making regarding the payment (price) and use of new medicines will increasingly have to be made on objective and verifiable evidence, despite uncertainty regarding the outcomes.

– This requires systematic collection of relevant data, well-defined decision criteria, and follow-up monitoring of both outcomes and costs.

Decision-making regarding payment for (price) and use of new medicines will increasingly be based on evidence of real-life clinical effectiveness.

– This requires systematic recording of relevant data and development of methods for evaluating the real-life clinical effectiveness of alternative treatment strategies.

The number of stakeholders involved in decision-making regarding the value of new drugs has increased.

– This requires both greater information transparency and more active payer involvement throughout the entire process of development, assessment and use of new medicines.

1. Health care providers should be increasingly responsible for recording and collating real-life clinical practice data to support decision-making regarding funding (price) and use of new medicines (and other health care technologies).
   - The health care system is the primary stakeholder in implementing decisions based on the value of medicines in real-life clinical practice. Basing decisions on objective and valid criteria means that relevant and reliable data on actual outcomes will be required. Such data increasingly must be collected by the health care system in a way that enables analyses to be made that are relevant to decisions about resource allocation.
   - Current structures and principles for recording patient data need reviewing with a view to simplifying and streamlining the process and ensuring that follow-up targets on clinical effectiveness and value-based use are met.
   - An important consequence of achieving this may be that the costs of developing new medicines can be moderated by reducing the cost of clinical trials and follow-up studies; at the same time, data will become more relevant for all stakeholders.

2. Analyses of regional variation should increasingly be based on patient-level data that are essential to understanding the causes and consequences of overuse of underuse.
   - Studies on regional variation have been important in stimulating discussion on how health care resources should be allocated to deliver efficient and equitable health care services. Several Swedish and international studies have indicated that regional variations are not related to differences in demand or need in the population. Instead, variation is due to what is described as 'local practice traditions' that may persist over time and for which there is no scientific support from systematic studies.
   - Patient-level data are necessary to generate evidence for policies aimed at reducing the appropriate regional variation. Data about regional differences in the use of medicines and other health care technologies can also be used for clinical effectiveness studies. Data based on monitoring the treatment outcomes for an individual patient over time, however, would be needed as well.

3. Decisions on the funding (price) and use of new medicines, based on estimations of cost-effectiveness, should apply to all medicines, whether they are used in the hospital setting and fall under hospital budgets, or are used in primary care and are paid for by the national pharmaceutical benefits scheme. In the longer term, such assessments should be extended to include diagnostics and other health care technologies that are frequently used with, or as an alternative to, innovative medicines.
   - The existing segmentation of decisions about funding new medicines based on setting of use – primary care or secondary care – is neither reasonable nor appropriate. Decision and payment should be based on the same evidences and follow the same principles regardless of the setting of use.
   - Medicines are often part of treatment regimens that also include specific diagnostic procedures, other medicines administered concomitantly or sequentially, and other types of medical interventions. The current system of assessing the cost-effectiveness of medicines used alone should be extended over time to consider all aspects of alternative treatment strategies.

4. Pharmaceutical price control should be abolished and governmental funding of the national pharmaceutical reimbursement scheme should be replaced by a budget that covers innovative medicines, diagnostics and other treatments in line with the cost-effectiveness assessments made by the Dental and Pharmaceutical Benefits Agency (TLV).
   - Under the current system, TLV makes decisions regarding pricing, but assumes no responsibility for quantities, costs, or what patients are treated. These limits to the TLV's remit make it more difficult to reach agreements with pharmaceutical companies on value-based payment and value-based utilisation.
   - Patients, the health care system, and the pharmaceutical industry would all benefit if agreements, assessments and decisions were based not on price, but on which patients could benefit from the treatment and at what cost. Total patient benefit and cost to society are what determine value.
   - By funding important new medicines for an initial period of time, the government could both help ensure earlier access for patients and collect evidence about value in use. County councils would recieve these drugs outside the budget, to be used within agreed indications, provided relevant data on their use are collected. This would stimulate uptake of new medicines, but also requires careful follow-up and management to prevent inappropriate use.

5. Resources for evaluating and improving the use of innovative medicines (and other health care technologies) should be coordinated at the national level; county councils should increase capacity to undertake assessments and monitor use.
   - Regulatory approval decisions and decisions about funding for new medicines increasingly are based on the same data from clinical trials; both need follow-up data about real-life clinical effectiveness. In addition, there is a clear trend towards coordinating decisions about reimbursement at a European level. Collaboration between countries on clinical and health-economic assessment and studies on the impact of medicines on health care systems can create benefits as well as reduce costs.

- It is important that all the evidence developed, including data on the value of medicines and the studies undertaken by TLV for assessment of cost-effectiveness, be available to all stakeholders. This is an essential requirement for transparency and decision-making based on objective and verifiable evidence.
- The health care system is responsible for implementing decisions on value-based use and payment, and for collecting relevant data for evaluation and follow up. County councils must play an active part, jointly or individually, throughout this process. It is essential that county councils develop capabilities for participating in the processes of assessing, implementing and following up the use of new medicines. Activities should be coordinated at a regional and national level.
- A division of labour between county councils and the central government could echo that at European level between EMA/EUnetHTA and national regulatory/HTA bodies. This would generate accountability and involvement in ensuring value-based use and payment for innovative medicines and other health care technologies.

Authors

Bengt Jönsson is Emeritus Professor at the Stockholm School of Economics. He is one of Europe's leading health economists and is past chairman of both the Swedish and the international Health Economics Association (iHEA). He is vice-chairman of the European Commission Expert Panel on Effective Ways of Investing in Health and a member of the European Academy of Cancer Sciences. During the 1990s, he served as scientific advisor in a major SNS project, Nya spelregler för hälso- och sjukvården [New rules for health care], and has subsequently been involved in the studies Hälsa, vård och tillväxt [Health, medical care and growth] (2004) and Medicin för Sverige! Nytt liv i en framtidsbransch [Medicine for Sweden! A new breath of life for a key industry for the future] (2007).

He is co-author of one of the sub-studies in this project.

E-mail: bengt.jonsson@hhs.se

Katarina Steen Carlsson is Research Director at the Swedish Institute for Health Economics (IHE) in Lund, and health economics researcher at Lund University.

She was responsible for the feasibility study in this project and co-authored four of the sub-studies.

E-mail: katarina.steen_carlsson@ihe.se

Thank you!

A finished book is the result of a team effort. This is especially true in this case, as this book marks the end of a comprehensive project that has been going on for several years. We have been involved in this project in various capacities and we wish to thank everyone else involved: project managers and others at SNS, members of the reference group, researchers and specialised study authors, and everyone who has provided comments and generously offered their views. We are particularly grateful to SNS Research Director Göran Arvidsson, whose contributions have been vital for bringing the project and this book to successful completion. As authors we take full responsibility for anything that could have been done better.

Reference group

The companies, organisations and authorities listed below were represented on the research programme reference group by the following named members of staff. Michael Sohlman was chairman.

Nadia Bracken and Therese Carlborg, AbbVie
Birgitta Karpesjö, Swedish Pharmaceutical Society [Apotekarsocieteten]
Eva Fernvall, Apoteket AB
Suzanne Håkansson and Martin Henriksson, AstraZeneca
Thomas Broberg, Swedish Ministry of Finance
Johan Christenson, HealthCap
Anna Käll, Janssen
Anders Blanck, Swedish Association of the Pharmaceutical Industry [LIF]
Susanne Baltzer and Lars Dagerholt, Medical Products Agency
Billie Pettersson and Jacob Tellgren, Merck Sharp & Dohme
Erik Fahlbeck, Swedish Ministry of Enterprise, Energy and Communications
Johan Brun and Kerstin Falck, Pfizer
Pontus Johansson, Swedish Ministry of Health and Social Affairs
Maarten Sengers, Swedish National Board of Health and Welfare
Magnus Thyberg, Stockholm County Council
Bo Claesson, Swedish Association of Local Authorities and Regions [Sveriges Kommuner och Landsting]
Stefan Odeberg, The Dental and Pharmaceutical Benefits Agency
Maria Landgren and Jenni Nordborg, Vinnova

Review

Valuable comments have been provided by members of the reference group and by the following specialist reviewers:
Professor Kristian Bolin, Centre for Health Economics and the School of Business, Economics and Law at the University of Gothenburg
Mikael Hoffmann MD, president of the NEPI Foundation (Swedish Network for Pharmacoepidemiology), former consultant in clinical pharmacology at Linköping University Hospital

Professor Lars-Åke Levin, Department of Medical and Health Sciences, Linköping University

The Value of New Pharmaceuticals SNS research programme

Purpose

The purpose of this research programme has been to contribute knowledge to support decision-making that affects access to new medicines and determines how medicines are used. The focus has been on highlighting the value of medicines – predominantly new ones – from a broad and long-term societal viewpoint. The programme was intended to result in policy conclusions based on both theoretical and empirical studies.

Studies

Work began in the spring of 2011 with a feasibility study. The feasibility study involved three health economists reviewing the international literature in the field and mapping ways of studying the value of medicines.

The research programme was then designed as a series of independent theoretical and empirical studies that would also provide data for a policy-driven final report. Reports of the specialised studies were published as they were completed and involved presentation and discussion of both results and policy conclusions.

The aim of the final report was to provide an overall outline and analysis of questions and answers raised during the research programme and in other relevant research; to outline the conclusions drawn; and to present policy conclusions to support further debate and transition.

The work was carried out in three phases with publication of the final report in November 2013:

Phase 1: Empirical studies in selected therapeutic areas

Breast cancer, chronic myeloid leukaemia, and diabetes
Rheumatoid arthritis
Cardiovascular disease

Phase 2: Supplementary empirical and theoretical studies on particular aspects of significance to policy-making

Relationships between new medicines, life expectancy, and health care expenditure in Sweden

Regional variation in the use of new medicines – survey and analysis

Evaluation, decision-making and implementation: introduction of new medicines, with examples from cancer care

New medicines in the early phases of use: can analyses of Swedish registry data generate new knowledge regarding the incidence and costs of drug-related morbidity?

When is self-pay acceptable? On societal and individual responsibilities in the funding of medicines and medicines-related products

Using registries and more randomisation – a smarter way of acquiring knowledge in the health care system

Phase 3: Final report comprising overall conclusions and tangible policy proposals

Seminars and conferences

Major conferences with presentations and discussions of the eleven specialised study results were held in May 2012 and in February, May and October 2013. In addition, all studies have been discussed in seminars; a series of roundtable talks was held with invited delegates.

Reference group

A reference group has supported the work and contributed factual information and comments on the issues discussed and on draft reports. The researchers have carried out their academic work independently and without bias.

Funding

The project has been funded by grants from the following companies, authorities and organisations: AbbVie, Swedish Pharmaceutical Society [Apotekarsocieteten], Apoteket AB, AstraZeneca, HealthCap, Janssen, Kronans Droghandel, Swedish Association of the Pharmaceutical

Industry [LIF], Medical Products Agency, Merck Sharp & Dohme, Pfizer, Swedish Association of Local Authorities and Regions [Sveriges Kommuner och Landsting], Stockholm County Council, and Vinnova.

Reports

The Value of New Pharmaceuticals – a feasibility study [Värdet av nya läkemedel – en förstudie] by Ulf-G. Gerdtham, Ulf Persson and Katarina Steen Carlsson, Swedish Institute for Health Economics (IHE), Lund. May 2011.

Targeted treatment of breast cancer [Målinriktad behandling av bröstcancer] by Adam Lundqvist, Nils Wilking, Ulf-G. Gerdtham, Ulf Persson and Katarina Steen Carlsson. Wilking Region Skåne and Karolinska Institute; others IHE. January 2013

Medical advances in the treatment of chronic myeloid leukaemia [Medicinska framsteg i behandling av kronisk myeloisk leukemi] by Adam Lundqvist, Anne-Charlotte Norlenius Ohm, Paul Dickman, Martin Höglund, Leif Stenke, Ulf-G. Gerdtham, Ulf Persson, Magnus Björkholm and Katarina Steen Carlsson. Norlenius Ohm, Dickman, Stenke, Björkholm Karolinska Institute; Höglund Uppsala University; others IHE. February 2013.

Rheumatoid arthritis, biological therapy and work days lost – an example of using Swedish health registry data [Reumatoid artrit, biologisk behandling och förlorade arbetsdagar – exempel på användning av svenska hälsodataregister] by Martin Neovius, Department of Medicine, Karolinska Institute. February 2013.

The value of statins – utilisation patterns and treatment adherence [Värdet av statiner – användningsmönster och följsamhet vid behandling] by Ingegärd Anveden Berglind, Helle Kieler, Marie Linder, Anders Sundström, Björn Wettermark, Anna Citarella and Morten Andersen, Department of Medicine, Karolinska Institute. February 2013.

A century of diabetes treatment – a perspective [Behandling av diabetes i ett hundraårigt perspektiv] by Katarina Steen Carlsson, Christian Berne, Pierre Johansen, Gustav Lanne, and Ulf-G. Gerdtham. Berne Uppsala University Hospital; others IHE. February 2013.

The Value of Pharmaceutical Innovation – within the context of policies that impact use of new medicines in Sweden by Billie Pettersson,

MSD (SNS visiting research fellow on this project) and Frank R. Lichtenberg, Columbia University, New York. May 2013.

Appraisal and implementation of new medicines – with examples from cancer care [Värdering och implementering av nya läkemedel – med exempel från cancerområdet] by Bengt Jönsson, Stockholm School of Economics, and Nils Wilking, Karolinska Institute. May 2013.

Professionals, payments and pens – regional variation in the utilisation of medicines [Professionen, pennan och pengarna – regionala skillnader i användning av läkemedel] by Mats Brommels, Johan Hansson, Emma Granström and Emma Wåhlin, Medical Management Centrum (MMC), Karolinska Institute. May 2013.

New medicines and drug-related morbidity – analytical opportunities in Swedish registry data [Nya läkemedel och läkemedelsrelaterad sjuklighet – analysmöjligheter i svenska registerdata] by Hanna Gyllensten, Nordic school of public health NHV, Gothenburg, Sweden, and Katarina Steen Carlsson, IHE. October 2013.

Count on registries and randomise more! Make pragmatic, registry-based, randomised trials part of Swedish routine clinical practice [Räkna med register och randomisera mera! Inför pragmatiska, registerbaserade, randomiserade prövningar i svensk rutinsjukvård] by Martin Neovius and Joakim Ramsberg, Karolinska Institute. October 2013.

Medicines – when is self-pay acceptable? [Läkemedel – när är det rimligt att betala själv?] by Per Carlsson and Gustav Tinghög, Department of Medical and Health Sciences, Linköping University. October 2013.

The value of medicines [Värdet av läkemedel]. Final report. By Bengt Jönsson, Stockholm School of Economics, and Katarina Steen Carlsson, IHE. November 2013.

All reports can be downloaded from www.sns.se.

Research Director

Johanna Lind, MD, until 31 January 2013

Göran Arvidsson, PhD Associate Professor, from 1 February 2013

The cost of a medicine can be calculated rather easily. But cost is not the same thing as value. For medicines to be used efficiently, knowing value is crucial. *The Value of New Medicines* explains and critiques the concept of value, which has become a central focus of both scientific studies and health care policy. This book presents a framework for answering questions about value in an objective and verifiable way that is useful for policy making, and describes how to ensure that the introduction and use of medicines is based on value. Whilst the focus is on Sweden, the analysis and policy recommendations also may be relevant for other countries that are developing new policies, institutions and mechanisms to encourage the efficient and equitable introduction and use of new medicines under stringent economic conditions.

The report highlights the need to:

- Collect and analyse data from actual clinical practice to improve understanding of the effects, benefits and cost of medicines as a basis for assessing value
- Adopt sound decision-making processes that are consistent across the health care system
- Abolish price controls and permit prices of medicines to differ based on their benefits
- Create payment mechanisms that recognise that the value of a medicine can vary depending on the disease it is used to treat
- Analyse regional variations in patterns of use and treatment costs as the basis for policies that optimise the use of medicines
- Create incentives for best use and continuous evaluation of new medicines.

BENGT JÖNSSON, PhD, Emeritus Professor at the Stockholm School of Economics, is an internationally respected health economist and currently Vice Chair of the European Commission Expert Panel on Effective Ways of Investing in Health.

KATARINA STEEN CARLSSON, PhD, is Research Director at the Swedish Institute for Health Economics (IHE) and a Researcher in health economics at Lund University.

The Value of New Medicines is a translation of the final report of a research programme entitled The Value of New Pharmaceuticals, a project of the Centre for Business and Policy Studies (SNS) in Sweden. The purpose of the research programme has been to contribute knowledge to support decision-making that affects access to new medicines and determines how medicines are used.

SNS FÖRLAG

VÄRDET AV NYA LÄKEMEDEL

ISBN 978-91-86949-60-0

9 789186 949600