AN AUDIT REPORT BY THE SWEDISH NATIONAL AUDIT OFFICE

Safe and effective medicines

– How does central government deal with the influence of the pharmaceutical industry?

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SWEDISH NATIONAL AUDIT OFFICE

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Summary and recommendations

The Swedish National Audit Office (NAO) has audited how central government manages the influence the pharmaceutical industry experts on central government medicines regulation and knowledge-based management. The audit encompasses the Swedish Government, the Medical Products Agency, the National Board of Health and Welfare and the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU).

Justification for the audit

The Government and government agencies have a difficult task that involves promoting several different positive values that sometimes conflict with one another. Rapid access to new effective medicines and reliable knowledge about their effects are values that sometimes contradict. The promotion of public health and the promotion of enterprise can, at times, also be objectives that are difficult to reconcile.

Major clinical trials are financed and designed primarily by pharmaceutical companies. Pharmaceutical companies thus have a great deal of influence over how these trials are conducted and over the results that are communicated externally through research articles and marketing. This gives the pharmaceutical industry an informational advantage in relation to other actors in the pharmaceutical sector. At the same time, pharmaceutical companies invest large amounts in developing medicines and therefore have strong incentives to optimise the return on their investments. Since the authorities audited make decisions or provide guidance that has an impact on companies' potential return, they need to be alert to the risk of strategic influence being exerted by the pharmaceutical industry. Consequently, information provided by pharmaceutical companies must be assessed critically by government agencies.

Aim

The aim of the audit is to investigate whether the Government and government agencies act effectively and with integrity in central government medicines regulation and knowledge-based management, and thus pursue the primary objective of pharmaceutical policy; the promotion of public health.

The audit is based on two questions:

1. Is central government medicines regulation implemented in a way that compensates for the pharmaceutical companies' informational advantage?
2. Is central government knowledge-based management conducted in a way that compensates for the pharmaceutical companies' informational advantage?

Implementation

The audit is based on a review and analysis of parliamentary publications, government agencies' handbooks, instructions and process descriptions, as well as meetings and interviews with about 160 assessors, experts and managers. We have also made some comparisons with the ways in which other European government agencies manage the influence of the pharmaceutical industry.

Audit findings

The fact that pharmaceutical companies have an informational advantage and many points of contact with government agencies is an institutional challenge that makes it more difficult for these agencies to strike the correct balance between various positive values. In order to maintain a focus on public health, which is the main purpose of pharmaceutical policy, the Government and government agencies need to both be aware of the nature of the institutional challenges and set priorities that reflect this awareness. The audit shows that there are certain shortcomings in both of these respects.

- The Medical Products Agency has reduced the priority of certain assessments of pharmaceutical safety.

The Medical Products Agency's assessment of the efficacy and safety of medicines is primarily based on the pharmaceutical companies' own summaries and reports. There is a risk that this material emphasises the positive effects of the medicines and tones down safety problems. When the Medical Products Agency assesses the material, it therefore needs to be particularly vigilant with respect to potential safety problems. The Swedish NAO has noted several examples where information that relates purely to safety being set aside when the Medical Products Agency has been faced with a need to prioritise. At times, the agency has decided not to assess companies' safety reporting at several stages of the assessment process, to only partially process reports concerning side effect from healthcare personnel and the general public and to reduce the number of inspections of clinical trials. In addition, the agency has long found it difficult to recruit and retain doctors to work as clinical assessors, which risks jeopardising its chances of maintaining pharmaceutical safety.

- The Medical Products Agency does not maintain sufficient separation between its promotional and regulatory functions

The Medical Products Agency is principally a regulatory and supervisory authority. Consequently, the agency must ensure that pharmaceutical safety does not suffer because of pharmaceutical companies' economic interests. Apart from regulation and supervision, the agency is tasked with making it easier for pharmaceutical companies to develop new medicines. This takes place primarily through the provision of scientific advice and innovation support to pharmaceutical companies. The fact that it is simultaneously assessing and promoting the activities of pharmaceutical companies means that conflicts of interest may arise within the agency. A common way for government agencies to deal with potential conflicts of interest is to maintain a separation between promotional and regulatory activities, so that they operate independently of one another. In the Medical Products Agency, however, there is a tendency towards less separation of these activities.

- The Government's management of the Medical Products Agency sends mixed messages

In recent years, the Government has pursued a pharmaceutical policy that actively promotes innovation and involves the Medical Products Agency. In this way, the Government has gradually changed the role of the Medical Products Agency, from one that principally involves regulation and supervision, to one that now also encompasses promoting the development of new medicines. In some respects, the Government's policy has made the Medical Products Agency's already difficult task of striking a balance between various ways of promoting public health even more difficult. The conflict of interests that exists in the area of pharmaceuticals has thus been more clearly incorporated into the agency's remit. The change involves a shift in roles that may impair the agency's capacity to maintain a sufficient degree of integrity in relation to the pharmaceutical industry.

- Funding the Medical Products Agency's through fees may lead to incorrect prioritisation

The Medical Products Agency's principal revenue stream comes from the fees paid by pharmaceutical companies for the agency's assessments. By taking action to ensure a large allocation of assessment commissions from the European Medicines Agency (EMA), the agency can increase its revenue. Even before Sweden joined the EU, the Medical Products Agency assessed that a large number of EMA commissions (rapporteurship) is a key measure for ensuring the agency's funding. The Swedish NAO's audit shows that the Medical Products Agency has reduced the priority of purely safety-oriented tasks for a period of time in favour of more revenue-generating EU assignments. The ability of a regulatory and supervisory agency to increase its revenue

by reducing the priority of work involving safety may justify a review of the agency's funding model.

- The Medical Products Agency, SBU and the National Board of Health and Welfare have insight into the general problem of bias in published material, but do not compensate for this in an effective manner

The central government evidence base on which the healthcare system's priorities are based consists largely of articles published in scientific journals. It is well-known that positive results of clinical trials are more likely to be published than negative results. This means that the evidence base used by central government agencies is at risk of being influenced by the bias found in published material. The agencies are aware of this bias but do not believe that it has any major impact on their knowledge-based management. They only partly utilise the opportunities that exist to control for bias and compensate for it.

- Closeness to pharmaceutical companies challenges the integrity of government agencies

The Swedish NAO's assessment is that the Medical Products Agency manages the risk of individual conflicts of interest correctly at a procedural level, for example through declarations of interests. Each year, all assessors have to submit a declaration of interests that is assessed by their line manager. Around half of the assessors have stated that they have current or previous interests in companies that are affected by the Medical Products Agency's work. Around half of the assessors who have left the authority have taken jobs with a pharmaceutical company. When a large proportion of investigators have links to the pharmaceutical industry, this may impair the agency's ability to safeguard its integrity and strike the correct balance between different positive values on an overall level.

SBU and the National Board of Health and Welfare take a serious view of the risk of confidence being harmed should these agencies be perceived from outside as engaging experts with strong links to the pharmaceutical industry. However, the risk of these conflicts of interest having material consequences appears to be regarded as a less significant problem. At the same time, these conflicts of interest are difficult to resolve as the foremost experts in the area of pharmaceuticals tend to have or to have had some involvement with pharmaceutical companies.

Recommendations

The Government should not involve the Medical Products Agency in its innovation policy.

Promoting innovation and regulating medicines are tasks that are not always compatible. The role of the Medical Products Agency as a licensing and regulatory authority should therefore be made more clear-cut.

The Government should give the Medical Products Agency clearer incentives not to reduce the priority of purely safety-oriented tasks.

One way is to include a requirement in the agency's appropriation directions that it reports how it deals with purely safety-oriented tasks. Another way is to review the agency's funding model. The existing model may be problematic as it gives the Medical Products Agency economic incentives to prioritise those tasks that generate the most revenue, which may have a detrimental impact on the assessment of pharmaceutical safety. The Medical Products Agency's independence could possibly be strengthened if the fees were accounted for by income heading and the Government gave the agency an appropriation.

The Government should task the agencies with cooperating in order to make knowledge-based management more independent of producers.

One platform could be the newly established Council for Knowledge-based Management, which is to be a forum for cooperation on strategic issues concerning knowledge development.

The Medical Products Agency should assign a higher priority to work involving pharmaceutical safety.

Raising the level of ambition for those tasks that are purely safety-oriented is one method. One prerequisite for a higher level of ambition is to ensure that the units responsible for clinical trials, pharmaceutical safety and inspections have the resources and expertise necessary.

The SBU and the National Board of Health and Welfare should take further action to reduce the bias in the evidence base they use.

The SBU and the National Board of Health and Welfare should actively test various solutions in order to reduce the bias in the evidence base. SBU's literature reviews form the basis of other agencies' knowledge-based management and SBU should therefore have a lead role in this work. The Swedish NAO deem that SBU and the National Board of Health and Welfare can test several measures that aim to broaden their evidence base, including requesting information from medicines agencies and pharmaceutical companies, as well as systematically searching for studies in public databases.

However, broadening the evidence base requires a new method of working. One way to begin such reorientation can be to share experiences with foreign agencies and organisations that have made further progress along this road, for example the agencies' counterparts in the United Kingdom and Germany.

1 Introduction

1.1 Justification for the audit

Pharmaceutical treatment is one of the most commonly used treatment methods in the Swedish healthcare system. Medicines are of great benefit to many patients and are an indispensable part of care. At the same time, medicines have side effects – sometimes mild and temporary, sometimes serious and life-threatening. New effective medicines contribute to improving public health, but at the same time there is limited information available during the approval process about uncommon side effects or side effects that only appear following long-term treatment.[1] In order for pharmaceutical treatment's positive effects to be obtained, while also limiting any potential harm, prescribers and patients need to have reliable knowledge about the effects of the medicines. A number of agencies have been tasked with collecting, processing and communicating such knowledge on the basis of their different roles and competencies.

Knowledge about the risks and benefits of a new medicine is based on controlled trials of the effects of the medicine. These are initially conducted on animals and then on increasingly large groups of human beings. The results of trials of medicines on human subjects – clinical trials – constitute important evidence when agencies are assessing whether the medicines are safe and effective, and when they are issuing guidance to the healthcare system. The Medical Products Agency decides which medicines can be sold in the Swedish market and, together with the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) and the National Board of Health and Welfare, issues guidance on how medicines should be prescribed.

Major clinical trials are mainly financed by the pharmaceutical companies that produce the medicines in question. Pharmaceutical companies thus have great deal of influence over how these trials are conducted and over how and which results are communicated externally through research articles and marketing. This gives the pharmaceutical industry an informational advantage in relation to other actors in the pharmaceutical sector.

Developing medicines demands significant resources. According to the Swedish Association of the Pharmaceutical Industry (LIF), the trade association for the research-based pharmaceutical industry, it takes at least 10–15 years to develop a new medicinal

[1] For a description of the benefits and risks of medicines at a societal level and of the difficulties in assessing these, please refer to Electronic Appendix 2.

product at an average cost of approximately SEK 10–15 billion.[2] The decisions that are made within the framework of medicines regulation, and the guidance and knowledge support provided by government agencies, have an impact on how medicines are used and thus also on the pharmaceutical industry's potential to achieve a return on its investments. As these government agencies are also dependent on information that has been produced and reported by a private actor with commercial interests, they need to be vigilant of the potential for this information to be strategically controlled.[3]

The closeness between the agencies concerned and the pharmaceutical industry may make is more difficult to undertake a critical assessment of the information provided by pharmaceutical companies. This closeness is particularly evident in the case of the Medical Products Agency, whose assessments are funded by the fees paid to the agency by pharmaceutical companies and where it is common for there to be contact between the agency's assessors and the industry. However, it is also the case for SBU and the National Board of Health and Welfare, whose external experts may have links to the pharmaceutical industry.

1.1.1 Risk of institutional corruption

Several analysts rank Sweden as one of Europe's least corrupt countries and this also applies to the Swedish healthcare system.[4] The risk of corruption still exists, but it is expected to be structured in a more sophisticated manner than is traditionally associated with corruption.[5]

A report from the Expert Group on Public Economics (ESO) from 2012 concludes that points of contact between government agencies and industry can, generally speaking, entail conflicts of interest and that the Swedish approach to this risk has been

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2 Please refer to www.lif.se/grundfakta/forskning/, accessed 20/11/2015. For a cost estimate, see also Jönsson, B. & Carlsson, K. S. (2013), *Värdet av läkemedel* (The value of medicines), SNS Förlag. For an evaluation of the pharmaceutical industry's cost estimates, refer to Light, D. & Lexchin, J. (2012), Pharmaceutical research and development: what do we get for all that money?, *British Medical Journal* 2012:345.

3 Barrington, R. (ed.) (2014), *Transparency and good governance in global health: Transparency International UK's pharmaceuticals and healthcare programme*. Transparency International UK; the European Commission (2013), *Study on Corruption in the Healthcare Sector;* World Health Organization (2014), *Good Governance for Medicines: Model Framework, Updated version 2014*.

4 The European Commission (2014), *Special Eurobarometer 397: Corruption*.

5 Bergh, A. *et al.,* (2013), *Allmän nytta eller egen vinning? En ESO-rapport om korruption på svenska* (Public benefit or personal gain? An ESO report on corruption in Swedish), Report to the Expert Group on Public Economics 2013:2; BRÅ (2007), *Korruptionens struktur i Sverige: "Den korrupte upphandlaren" och andra fall om mutor, bestickning och maktmissbruk* (The structure of corruption in Sweden: "the corrupt purchaser" and other cases of bribery, corruption and abuse of power). Report 2007:21.

"uncertain and a little naïve"[6]. The Swedish NAO has arrived at similar conclusions in earlier audits.[7]

Swedish medicines regulation is a tightly regulated activity in which individual public officials have limited influence over the final decision on whether or not a medicine is approved. The risk of influential people utilising their position to secure benefits for themselves or those close to them, known as 'individual corruption', is therefore relatively small. Instead, the risk of corruption is at an institutional level.

The term *institutional corruption* is used to describe how an institution such as a government agency drifts away from its principal purpose due to the influence of a special interest. This influence is systematic and strategic and takes place within the scope of the law. Institutional corruption involves the agency's actual mode of operation becoming weaker and jeopardises public confidence in the agency.[8]

In developed democracies, *individual corruption* typically consists of isolated acts and the damage they cause is limited in time and scope. *Institutional corruption* is more difficult to detect, but constitutes a threat to the mode of operation of the agency in question. The damage thus risks becoming more lasting and often requires action to be taken at a structural level.[9]

In order to manage the risk of institutional corruption in terms of regulation and knowledge-based management in the area of pharmaceuticals, the agencies responsible need to be given the right institutional prerequisites and need to undertake their duties with a high degree of integrity.

There are several potentially aggravating circumstances which are worth highlighting. Concerning the Medical Products Agency, the agency is dependent on pharmaceutical companies providing reliable and comprehensive information about the medicines they have themselves developed and tested. The agency also has many points of contact with the pharmaceutical industry[10] and funds its entire assessment operation using fees from pharmaceutical companies. It is also common for the agency's employees to either have a past within the industry or for them to move on to positions at pharmaceutical companies. External experts engaged by the agency may also have current or previous links to pharmaceutical companies.

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6 Lindström, L. & Bruun, N. (2012), *Svängdörr i staten – en ESO-rapport om när politiker och tjänstemän byter sida* (Revolving door in central government – an ESO report on when politicians and public officials change sides), report to the Expert Group on Public Economics 2012:1, p. 108.

7 The Swedish NAO 2006:8, *Protection against corruption in government activities,* and the Swedish NAO 2013:2, *Protecting central government agencies against corruption.*

8 Lessig, L. (2013), "Institutional Corruption" defined, *Journal of Law, Medicine and Ethics*, Vol. 14(3).

9 Thompson, D. F. (2013), Two Concepts of Corruption. *Edmond J. Safra Working Papers* (16), p. 17.

10 Lindström, L. & Bruun, N. (2012), *Svängdörr i staten – en ESO-rapport om när politiker och tjänstemän byter sida*, report to the Expert Group on Public Economics 2012:1, p. 107 ff.

The National Board of Health and Welfare and SBU have fewer direct points of contact with pharmaceutical companies than the Medical Products Agency. Nevertheless, it is often also the case that the external experts engaged by these agencies have or have had links to pharmaceutical companies. One further potentially aggravating circumstance for these agencies is that they primarily base their literature reviews and guidance on published studies and that pharmaceutical companies have influence over *which* research results are published and *how* these results are presented.

How the Government and the agencies concerned manage the risk of strategic influence from the pharmaceutical industry has not previously been audited. However, this issue is of current interest in the United Kingdom, for example. Over the past decade, British parliamentary committees and the National Audit Office (NAO) have published several reports that are critical of how public-sector actors manage the risk of strategic influence from the pharmaceutical industry. Among other things, these reports address the closeness between the Medicines and Healthcare Products Regulatory Agency (MHRA) and the pharmaceutical industry. They also address the inadequate compensation for the industry's selective publication of clinical trials by agencies involved.[11] The Swedish NAO therefore sees that there are grounds to perform an audit to evaluate the relevance of these issues in a Swedish context. The Medical Products Agency, the SBU and the National Board of Health and Welfare work, in principal, towards the same ends and use similar methods to their British counterparts.

1.1.2 Conflicting values and conflicting objectives in medicines regulation

The Medical Products Agency is one of the national agencies in Europe tasked with ensuring that medicines released onto the market have a positive balance between risk and benefit. The Medical Products Agency, as do its EU counterparts, makes this assessment on the basis of preclinical trials[12] and clinical trials of the effects of medicines on a select group of test subjects. However, the actual effects only appear gradually, following long-term use by a large number of patients.

Medicines agencies have a challenge in finding a balance between making new medicines available quickly and waiting for more information on their efficacy and safety.[13] If the Medical Products Agency is relatively well-disposed toward risk, this contributes to patients gaining access to new medicines earlier. If, on the other hand,

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[11] House of Commons Committee of Public Accounts (2014), *Access to clinical trial information and the stockpiling of Tamiflu*; House of Commons Science and Technology Committee (2014), *Clinical Trials, Third Report of Session 2013–14*; National Audit Office (2013), *Access to clinical trial information and the stockpiling of Tamiflu*; House of Commons Health Committee (2013), *National Institute for Health and Clinical Excellence*; House of Commons Health Committee (2005), *The Influence of the Pharmaceutical Industry*; National Audit Office (2003), *Safety, Quality, Efficacy: Regulating Medicines in the UK*.

[12] Preclinical trials are trails of pharmaceutical substances in laboratories or animal models.

[13] Eichler, H-G, *et al.,* (2013), The risks of risk aversion in drug regulation, Nature Reviews: Drug Discovery (12). See also EMA (2016), Why do we need pharmacovigilance?

the Medical Products Agency is more cautious and risk-averse, this can mean that access to new medicines is delayed because companies are required to produce more information by, for example, conducting more trials.

The Medical Products Agency therefore needs to take two public health policy values into account – early access to medicines and good knowledge of the effects of these medicines. These values can be regarded as conflicting in the sense that prioritisation of one may take place at the expense of the other. There are thus two fundamentally important questions that characterise medicines agencies' assessment of risk and benefit:

1. What level of uncertainty should be accepted for a product to get market authorisation?
2. What level of risk should be accepted for expected benefit?

Even though the assessments conducted by medicines agencies are characterised by extensive EU regulation, there are no fixed rules governing how to strike a balance between risk and benefit in each individual case. Consequently, there is no definitive answer to the question of how the balance between tolerating and avoiding risk should be structured in order to maximise the effect on public health. Medicines agencies need to assess each individual case on the basis of their knowledge, expertise and professional judgement. According to a study by the EMA, these assessments vary significantly not only between different medicines agencies within the EU, but also between different assessors within each agency.[14] Several senior managers at the EMA have highlighted the danger of being too risk-averse, as this may result in patients missing out on new medicines.[15]

Several international studies show that different external factors influence how medicines agencies assess the balance between the risk and benefit of medicines. This research has shown, for example, that a company's status can be a predictive factor for medicines authorisation,[16] that regulatory authorities' receptiveness to commercial interests has had an impact on how they define carcinogenic medicines[17] and that

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[14] European Medicines Agency (2011), Benefit-risk methodology project – Work package 1 report: description of the current practice of benefit-risk assessment for centralised procedure products in the EU regulatory network, EMA/227124/2011.

[15] Eichler, H-G, *et al.,* (2013), The risks of risk aversion in drug regulation, Nature Reviews: Drug Discovery (12).

[16] Kim, J.W. (2012), Arbiter of science: Institutionalization and status effects in FDA drug review 1990–2004, *Strategic Organization* 10(2).

[17] Abraham, J. and Ballinger R. (2011), The neoliberal regulatory state, industry interests, and the ideological penetration of scientific knowledge: Deconstructing the redefinition of carcinogens in pharmaceuticals, *Science, Technology & Human Values* 37(5).

powerful patient groups have contributed to shorter assessment processes.[18] The risk-benefit assessment is thus not a purely regulatory or scientific activity.

The pharmaceutical industry develops medicines for treatment of patients in the healthcare system, but it also contributes to economic growth and providing job opportunities in the locations it operates.[19] The Swedish Government works actively to stimulate what is referred to as the life sciences. The aim of these initiatives is, on the on hand, to contribute to improving health and, on the other, to promote Swedish exports and create jobs.[20] An important part of this policy is to attract companies to perform clinical trials in Sweden.[21]

The enterprise policy interest is clearly indicated in the Medicinal Products Act (2015:315) that came into force on 1 January 2016. According to its legislative history, the new Medicinal Products Act shall primarily contain linguistic and editorial revisions of the old Medicines Act. However, an introductory paragraph that describes the overall aim of the act has been added to the new act.[22] The aim is primarily "to protect the life, health and well-being of humans and animals and to safeguard public health and protect the environment *without this preventing, to a greater extent than is necessary, the development of medicines or trade in medicines* in Sweden and within the European Economic Area (EEA)" (the Swedish NAO's italics).

The old Medicines Act does not contain any corresponding wording or consideration for the development or trade of medicines. Instead, and according to the legislative history of the old act, it was emphasised that pharmaceutical issues should be seen as part of the overall objectives of the Health and Medical Services Act (1982:763).[23] It stated that "pharmaceutical legislation mainly aims to ensure that individuals have safe medicines of a good quality".[24] This aim was not written down in the text of the act but has been generally accepted and similar wordings have recurred up until recently in both government bills and government official reports.[25]

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18 Epstein, S. (1997), Activism, drug regulation and the politics of therapeutic evaluation in the AIDS era: A case study of ddC and the 'surrogate markers debate', *Social Studies of Science* 27(5).

19 Olshov, A. (2014), *Läkemedelsindustrin i Danmark och Sverige 2014: Dansk succé och svenskt ras fortsätter* (The pharmaceutical industry in Denmark and Sweden 2014; the Danish success and Swedish collapse continues), Øresundsinstituttet.

20 Govt. Bill 2015/16:1, expenditure area 24, *Förslag till statens budget för 2016* (Proposal to the State budget for 2016) , p. 62.

21 Govt. Bill 2012/13:30, *Forskning och innovation* (Research and innovation), p. 81.

22 Chapter 1, Section 1, the Medicinal Products Act (2015:315).

23 Govt. Bill 1991/92:107, *Om ny läkemedelslag m.m.*, (About a new Medicines Act, etc.), p. 17.

24 Ibid.

25 See, for example, Govt. Bill 2013/14:93 *Ökad tillgänglighet och mer ändamålsenlig prissättning av läkemedel* (Greater accessibility and more appropriate pricing of medicines), where the aim of the Act is expressed: "The aim of the Act is to safeguard the interests of individual consumers and ensure that medicines are safe, efficient and of a good quality."

The wording of the aim of the new Medicinal Products Act is a consequence of the Government's implementation of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Consequently, the potential conflict between public health policy and enterprise policy objectives in the area of pharmaceuticals has become articulated in the Swedish wording of the act. However, the conflict between these objectives is even more clearly formulated in the EU directive. It states that the public health objective must be attained by means which *will not* hinder the development of medicines and trade in medicines.[26]

The policy area under which issues related to medicines fall within the European Commission has varied over time. Medicines now fall within the remit of the Directorate General for Health and Food Safety (SANTE), but have previously been the responsibility of what was then the Directorate General for Enterprise and Industry. In 2014, the European Commission proposed that these issues be moved back there, but withdrew the proposal following criticism, among others, health and consumer organisations.[27] It is thus clear that the different values may sometimes conflict.

When a regulatory agency is tasked with both promoting and regulating an external actor, a conflict of roles may arise. In a policy statement from 2003, the WHO wrote that effective medicines regulation requires medicines agencies to work on the basis of a clear aim to safeguard public health through safe and effective medicines. The WHO was of the opinion that tasks aimed more at developing the pharmaceutical industry risks creating a conflict of interest that impairs the effectiveness of the work of medicines agencies.[28]

1.2 Basic premises

The basic premise of the Swedish NAO's audit is the pharmaceutical policy priorities, namely the promotion of public health and that prescribers should have objective and impartial information about medicines:

- *Promoting public health is the foremost aim of pharmaceutical policy.*

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[26] The aim of the applicable EU directive is worded: "The essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health. However, this objective must be attained by means which *will not* hinder the development of the pharmaceutical industry or trade in medicinal products within the Community" (the Swedish NAO's italics). Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Celex number: 02001L0083–20091005).

[27] See, for example, Sandstedt, J. (2014), *EU flyttar inte medicinansvaret*, (the EU will not move the responsibility for medicines), *Läkemedelsvärlden*, 23/10/2014.

[28] World Health Organization (2003), *Effective medicines regulation: ensuring safety, efficacy and quality*. WHO policy perspectives on medicines, November 2003.

The Swedish NAO's basic premise is that the primary aim of pharmaceutical policy is to promote public health. As a method of treatment, medicines are covered by the requirements of the Health and Medical Services Act (1982:763) that patients receive safe care of a high quality. It is also evident in Chapter 1, Section 1 of the Medicinal Products Act (2015:315) that the promotion of public health is the foremost aim of pharmaceutical policy.

Medicines regulation needs to strive to balance two positive values: good knowledge about medicines and rapid access to new effective medicines. Both of these values are in line with the objective of promoting public health in different ways. Considering the informational advantage that pharmaceutical companies have about their products and the closeness between the Medical Products Agency and the pharmaceutical industry, there is a risk that the balance will shift towards rapid development of medicines at the expense of good knowledge about the effects of these medicines. Our basic premise is that the balance which is struck within medicines regulation is not to be influenced by enterprise policy and commercial interests.

- *Central government has to provide objective and impartial information about medicines.*

The importance of prescribers having access to neutral and objective information about medicines is stated in Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. The national responsibility of member states to give prescribers access to objective information about medicines is also emphasised here.[29] The Swedish NAO's basic premise is that central government has to provide objective and impartial information about medicines.

The profit motive and informational advantage of the pharmaceutical industry constitutes an institutional challenge that can be amplified if there is closeness between the agencies audited and the pharmaceutical industry. The basic premise of the Swedish NAO is that these agencies should be aware of this institutional challenge and choose priorities that reflect this awareness.

1.3 Aim and delimitations

The aim of the audit is to investigate whether the Swedish Government and the government agencies in question act effectively and with integrity in central

[29] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Celex number: 02001L0083–20091005).

government medicines regulation and knowledge-based management in order to achieve the primary objectives of pharmaceutical policy.

The audit is based on two questions:

- Is central government medicines regulation implemented in a way that compensates for the pharmaceutical industry's informational advantage?
- Is central government knowledge-based management implemented in a way that compensates for the pharmaceutical industry's informational advantage?

Delimitations

The audit focuses on the assessment tasks of the Medical Products Agency that have a bearing on information about the efficacy and safety of medicines, namely the assessments on which marketing authorisation and related product information are based. The information disseminated about a medicine by the Medical Products Agency is based on the medicine's summary of product characteristics (SPC). The company updates the SPC continuously, after which it is approved by the Medical Products Agency/EMA. The SPC is based on, in part, an assessment of the efficacy and safety of a medicine *prior to* marketing authorisation being granted and, in part, monitoring of the medicine's safety *following* marketing authorisation.

Many decisions within medicines regulation are made at the EU level, which means that the Medical Products Agency cooperates with other national agencies in the evaluations that are conducted. This audit only focuses on the Medical Products Agency's role within the scope of these joint assessments. This means that we are not expressing an opinion about all assessments that are conducted within the EU prior to the authorisation of a medicine, only about how the Medical Products Agency conducts its evaluations.

The three agencies which are included in the audit produce a range of knowledge-based management documents. For practical reasons, we have restricted ourselves to one key knowledge-based management product per agency: the Medical Products Agency's treatment recommendations, SBU's literature reviews and the National Board of Health and Welfare's national guidelines for health and medical care.

Table 1.1, below, contains a general description of the audited agencies' main roles based on the audit's focus on medicines regulation and knowledge-based management.

Table 1.1 The audited agencies' main roles within medicines regulation and knowledge-based management based on the audit's focus

Agency	Main task	Focus	Information/knowledge base
The Medical Products Agency	Medicines regulation. Issues permits for clinical trials, authorises medicines and product information. Conducts supervision, monitors safety post-authorisation and issues treatment recommendations.	Assessment of medicines' benefit in relation to risk.	Results of preclinical and clinical trials that have been submitted by pharmaceutical companies, side effect reports from healthcare professionals and the general public.
The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)	Knowledge-based management. Publishes systematic literature reviews and evaluates methods used in the healthcare system.	Comparisons of treatment methods post-authorisation.	Results of clinical trials and observational studies that are published in scientific journals.
The National Board of Health and Welfare	Knowledge-based management. Issues national guidelines.	Recommendations to the healthcare system.	Results of clinical trials and observational studies that are published in scientific journals.

1.4 Method

In order to obtain a comprehensive illustration of the industry's informational advantage, the Swedish NAO has met with representatives of Swedish Association of the Pharmaceutical Industry (LIF), representatives of research-based pharmaceutical companies, the Swedish Network for Pharmacoepidemiology (NEPI), the Swedish Medical Association's council for pharmaceuticals, IT and medical technology (RLIM), medical and social sciences researchers and representatives of the drug and therapeutics committees of Stockholm County Council, Region Skåne and Kalmar County Council.

In order to build up a picture of how the Swedish central government has managed the industry's influence at the national level over time, we have reviewed inquiries and parliamentary publications going back to 1977. In order to find out the agencies' views

on how risks of institutional corruption are managed, we have met representatives of the three agencies concerned. We have also reviewed the agencies' internal instructions and process descriptions that have a direct bearing on the assessment processes encompassed by this audit. In order to build up a picture of how operations are conducted in practice, we have interviewed managers, assessors and external experts who have intimate knowledge of the work of these agencies. We have also participated as observers during an internal quality assurance meeting at the Medical Products Agency.

In most cases, the interviews have been recorded and transcribed. The interviews have been followed-up with specific questions posed via email or telephone when necessary. The Swedish NAO conducted a total of 94 meetings and interviews with approximately 160 people.

In order to find out how the pharmaceutical industry's influence is managed in a comparable EU country, we have met investigators at the Swedish NAO's British counterpart, the National Audit Office (NAO), who have audited British medicines regulation and knowledge-based management. We have also interviewed public officials at the Medicines and Healthcare Products Regulatory Agency (MHRA), the EMA, and researchers who are active in the public discourse at the EU level concerning the industry's influence on the area of pharmaceuticals.

The Government and the agencies concerned have read and provided their viewpoints on the draft report before publication.

Please refer to Appendix 1 for a more detailed description of the audit methodology.

During the audit process, the Swedish NAO has appointed three reference persons who read and commented on the draft report:

- *Staffan Andersson*, docent, senior lecturer at the Department of Political Science, Linnaeus University.
- *Paul Hjemdahl*, professor at the Department of Clinical Pharmacology, Karolinska Institutet.
- *Svenne Junker*, PhD in business administration, Stockholm Centre for Organizational Research (Score).

1.5 Terms and abbreviations used in the report

CHMP
Committee for Medicinal Products for Human Use. The EMA's scientific committee responsible for the EMA's assessment of a specific medicine prior to the European Commission's decision regarding marketing authorisation.

CSR
Clinical Study Report. Final report of a clinical trial. Has to be sent to the medicines agency by the company responsible within one year of the study's completion.

DSUR
Development Safety Update Report. Safety report that has to be submitted by companies annually during the period in which clinical trials are being conducted and prior to the medicine being authorised.

EMA
The European Medicines Agency.

EPITT
European Pharmacovigilance Issues Tracking Tool. A database developed by the EMA to enable safety and risk management issues to be communicated quickly between the EMA, the national medicines agencies, CHMP and PRAC.

Pharmacovigilance
The science and the activities which aim to detect, evaluate, understand and prevent side effects of medicines and manage other medicine-related problems.

IQWiG
Institute for Quality and Efficiency in Health Care. German agency that is an approximate equivalent of SBU and the National Board of Health and Welfare.

MHRA
Medicines and Healthcare Products Regulatory Agency. The British equivalent of the Medical Products Agency.

NICE
National Institute for Health and Care Excellence. A British approximate equivalent to the National Board of Health and Welfare.

PRAC
Pharmacovigilance Risk Assessment Committee. A scientific committee within the EMA that focuses on pharmaceutical safety.

PSUR

Periodic Safety Update Report. A safety report that companies send at certain intervals following marketing authorisation.

The Q group

The Medical Products Agency's highest quality assurance body. Addresses all fundamentally important issues pertaining to assessment within the agency.

Regulatory material
Generic name for data, information, literature reviews and assessment reports that are produced within the scope of the Medical Products Agency's regulatory remit. This includes CSRs and the Medical Products Agency's own assessment reports. Subject to confidentiality assessment prior to disclosure.

SBU
Swedish Agency for Health Technology Assessment and Assessment of Social Services

SPC

Summary of product characteristics. A description of the characteristics of a medicinal product.

SUSAR

Suspected Unexpected Serious Adverse Reaction. Serious unexpected side effect.

2 The influence of the pharmaceutical industry

In this chapter, we describe in more detail how the economic incentives and informational advantage of the pharmaceutical industry constitute an institutional challenge that can be amplified if there is great closeness between the audited agencies and pharmaceutical companies.

2.1 The industry's informational advantage

To a large extent, the National Board of Health and Welfare and SBU rely on published studies when producing national guidelines and literature reviews. The Medical Products Agency's assessments within the field of medicines regulation are based on the evidence submitted by companies, which may be the results of both published and unpublished studies. In the following section, we describe how pharmaceutical companies have an informational advantage in relation to the agencies.

2.1.1 Funding of medicines research

Clinical trials are normally funded by the pharmaceutical industry. Pharmaceutical companies' total annual research and development costs are estimated to be approximately EUR 30.5 billion within the EU, and approximately EUR 1 billion in Sweden, according to the European Federation of Pharmaceutical Industries and Associations (EFPIA).[30]

One problem that is often noted is the lack of funding for large non-commercial clinical trials.[31] Representatives of the county councils' drug and therapeutics committees contend that it is difficult to obtain public research resources. Public-sector research funding bodies are not inclined to provide research funding for pharmaceutical research as funding such research is seen as the industry's duty.[32]

Thus companies test their own products. Systematic reviews of research have revealed that industry-financed research shows more favourable results than studies that are

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30 EFPIA (2015), *The Pharmaceutical Industry in Figures. Key Figures 2015*.

31 See, for example, SOU 2008:7, *Världsklass! Åtgärdsplan för den kliniska forskningen (World class! An action plan for clinical research)*. Interim report of the Clinical Research Inquiry, pp. 218 ff.

32 Meetings with representatives of drug and therapeutics committees 08/10/2013, 05/11/2013, 18/11/2013, 04/11/2013 and 22/01/2014.

independent of the industry.[33] Companies can steer a course towards more favourable results in several ways: through the choice of study design, by choosing how publication and reporting take place and, in some cases, by manipulating data.

2.1.2 *Choice of study design*

Central government agencies need to consider two public health policy values – early access to medicines and good knowledge about the effects of these medicines. A pharmaceutical company needs to manage the same conflicting values, but also needs to consider the value of generating profit for the company's owners. If the company is driven by short-term economic incentives, this can affect the methodological decisions the company makes when designing clinical trials. For example, companies may choose to:

- compare the efficacy of a new medicine with the efficacy of a treatment known to be inferior
- compare the efficacy of a new medicine with a too low dosage of a competing medicinal product
- conduct trials which are too small to show negative differences in relation to competing medicines[34]

There are also examples of companies producing seemingly impressive results by strategically selecting inappropriate comparison measures, patient groups or results measures, by using an inadequate selection, a short follow-up period or ending studies prematurely when the results are favourable.[35] According to the Medical Products Agency, such methodological flaws are taken into account when the agency assesses the information submitted by companies.[36]

2.1.3 *Selective publication and selective reporting*

In spite of it breaching the ethical principles of research,[37] many companies and researchers fail to publish results that are unfavourable. This pattern is well-researched.

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33 See, for example, Lundh A., *et al.,* (2012), Industry sponsorship and research outcome, *Cochrane Database Syst Rev*. 2012, No. 12, and Sismondo, S. (2008), Pharmaceutical company funding and its consequences: A qualitative systematic review, *Contemporary Clinical Trials* 29 (2008), p. 109–113.

34 Smith, R. (2005), Medical journals are an extension of the marketing arm of pharmaceutical companies, *PLoS Med* 2(5). See also Liedholm, H. (2014), *Evidensbaserad läkemedelsvärdering* (Evidence-based evaluation of medicines) *Läkemedelsboken 2014*, the Medical Products Agency.

35 See, for example, Marin dos Santos, M. & Attalah A.N (2015): FDAAA Legislation is working, but methodological flaws undermine the reliability of clinical trials: a cross-sectional study, *PeerJ 3:e 1015*. Sameer, S.C. (2003): Industry Funding of Clinical Trials: Benefit or Bias?, *JAMA 290(1)*.

36 Information provided by the Medical Products Agency when the agency fact checked the report.

37 World Medical Association (2013), *WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects*, p. 7 f.; World Health Organization (2015), *WHO Statement on Public Disclosure of Clinical Trial Results*. http://www.who.int/ictrp/results/reporting, accessed 18/12/2015.

Research shows that roughly half of all trials have not been published and that a trial with positive results is roughly twice as likely to be published, compared with a trial that has unfavourable results.[38] There is also a tendency to publish more than one version of trials that show positive results, without it being made clear that these concern one single study.[39] This pattern, referred to as *selective publication*, is a problem since it implies that the publically available knowledge about the medicine becomes misleading.

These problems are amplified by what is known as selective *reporting*, i.e. the original trial results are adjusted through more or less subtle methods prior to the publication of a journal article. Such methods are described in detail in the research literature.[40]

Examples of selective reporting:

- The trial is conducted at several different trial centres, but only results from the centres that showed the best results are published.
- Sub-group analyses are conducted, but only the results of the groups with the best results are published.
- Several outcome measures are used, but only those measures with most impressive results are presented.[41]

Accordingly, both selective publication and selective reporting risk contributing to scientific articles that do not provide an accurate and full picture of the results of clinical trials. This risk can be expected to be amplified if a company has strong economic incentives.

2.1.4 Manipulation of data

Companies can also manipulate or withhold data. At some point over the course of the past decade, the majority of major global pharmaceutical companies have been

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38 See, for example, van den Bogert *et al.,* (2015), Occurrence and determinants of selective reporting of clinical drug trials: design of an inception cohort study, *BMJ Open* 5(7). See also Song, F. *et al.,* (2010), Dissemination and publication of research findings: An updated review of related biases, *Health Technology Assessment* 14(8), and Schmucker, C, *et al.,* (2014), Extent of Non-Publication in Cohorts of Studies Approved by Research Ethics Committees or Included in Trial Registries, *PLoS One* 9(12).

39 For a description of this tendency, see Eliasson, M. (2008), *Duplikatpublicering ett sätt att förskönа forskningsresultat: oetiskt missbruk som hotar trovärdiga systematiska översikter och metaanalyser* (Duplicate publication a way of embellishing research results: unethical abuse which threatens credible systematic reviews and meta-analyses), *Läkartidningen*, vol. 97, no. 32–33.

40 See, for example, Liedholm, H. (2014), *Evidensbaserad läkemedelsvärdering, Läkemedelsboken 2014*,the Medical Products Agency, p. 1198 ff. and Melander, H. *et al.,* (2003), Evidence b(i)ased medicine – selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications, *British Medical Journal* 31(326).

41 Smith, R. (2005), Medical journals are an extension of the marketing arm of pharmaceutical companies, *PLoS Med* 2(5). See also Liedholm, H. (2014), *Evidensbaserad läkemedelsvärdering, Läkemedelsboken 2014*, the Medical Products Agency.

convicted of distortion or withholding information.[42] For example, one global company has been fined USD 3 billion for withholding information about side effects from the American Food and Drug Administration (FDA).[43] By extension, there is a risk that withholding information results in the authorisation of medicines that do not function as intended.

2.1.5 *Grey zones between clinical trials and marketing*

The research literature contains many examples of how clinical trials are also used by companies as marketing tools. Companies engage editors, statisticians and medical writers to produce scientific articles that market the product.[44] It is therefore not always entirely clear where the boundary between clinical trials and marketing lies. There is now extensive research that describes these different approaches.[45]

2.1.6 *Tendencies towards increased transparency*

Medicines agencies are the only public-sector actors who have a right to access all the results of clinical trials. Due to commercial confidentiality, it is significantly more difficult for other agencies (e.g. the National Board of Health and Welfare and SBU), researchers, prescribers, journalists and members of the public to access companies' data.

There is a risk that pharmaceutical companies use their informational advantage to exert a strategic influence on the data to which pharmaceutical agencies are given access, and that this influence is beneficial to these companies but not to public health. One way improve the chances of detecting such strategic influence can be to make the results of clinical trials available for scrutiny by a wider audience. This is something that has been discussed at the EU level. Requirements for increased transparency are also being pursued in the form of an international campaign which is advocating for all the results of clinical trials to be made public, even retroactively. As of May 2016, 88,000

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42 See, for example, Götzsche, Peter C. (2013) *Deadly medicines and organised crime: How big pharma has corrupted health care*. London: Radcliffe Publishing.

43 United States Department of Justice (2012), www.justice.gov/opa/pr/glaxosmithkline-plead-guilty-and-pay-3-billion-resolve-fraud-allegations-and-failure-report, 02/06/2012, accessed 26/11/2015.

44 See, for example, Light, D. *et al*., (2013) Institutional corruption of pharmaceuticals and the myth of safe and effective drugs, *Journal of Law, Medicine and Ethics* 41(3), and Ross, J. S., *et al*., (2008) Guest Authorship and Ghostwriting in publications related to rofecoxib, *Journal of American Medical Association* 299: 1800–1912.

45 See, for example, Sah, S. and Fugh-Berman, A. (2013), Physicians under the influence: Social psychology and industry marketing strategies, *Journal of Law, Medicine & Ethics* 41(3); Sismondo, S. (2013) Key Opinion Leaders and the corruption of medical knowledge: What the Sunshine Act will and won't cast light on, *Journal of Law, Medicine & Ethics* 41(3); Lexchin, J. (2012) Those who have the gold make the evidence: How pharmaceutical industry biases the outcomes of clinical trials of medications, *Science and Engineering Ethics* 18(2); Sismondo, S. (2007) Ghost management: how much of the medical literature is shaped behind the scenes by the pharmaceutical industry? *PLoS Medicine* 4(9).

individuals and 650 organisations, including the Swedish Medical Association, had signed up to the campaign *All Trials*.[46]

The EMA is now of the opinion that there is essentially no commercially sensitive information in the key results reported by pharmaceutical companies and that these can therefore be made available.[47] In general terms, the Medical Products Agency shares this view and has provided information upon request and following assessment in accordance with the principle of public access to official records. The EMA has recently declared its clear intention to continue down the path towards greater transparency.[48] If the EMA's promised transparency becomes a reality, researchers and agencies producing knowledge about pharmaceutical treatment (e.g. the SBU and the National Board of Health and Welfare) will be able to access a more comprehensive evidence base.[49]

2.2 The closeness between government agencies and industry

The Medical Products Agency, SBU and the National Board of Health and Welfare appoint external experts who provide support during the development of treatment recommendations, literature reviews and national guidelines. These experts are highly-qualified researchers with long-standing experience within their area of expertise. They are expected to have good understanding of how different treatment methods function in a clinical context. The experts linked to the production of recommendations, literature reviews and guidelines at the Medical Products Agency and the National Board of Health and Welfare who were interviewed argue that proven experience has a particularly important function when the data in published studies is not deemed to be adequately reliable. However, SBU does not assign proven experience any weight as evidence.

The expert role's strength largely lies in the knowledge and experience the expert has. At the same time, however, this constitutes the expert role's weakness when viewed from the perspective of the ideal of evidence-based medicine. When there is a lack of documented evidence and the expert is one of the few authorities within their area of expertise, it may be difficult for the agencies to assess and challenge that expert's

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46 For more information, see the website www.alltrials.net., accessed 05/05/2016.

47 EMA (2014), *European Medicines Agency policy on publication of clinical data for medicinal products for human use*. EMA/240810/2013.

48 EMA (2015), *EMA ready to address challenges ahead: Support to innovative medicines, transparency and patient involvement will be among the priorities of new EMA Executive Director Guido Rasi*. Press release 09/12/2015.

49 See, for example, Wieseler, B. *et al*., (2013), Completeness of Reporting of Patient-Level Clinical Trial Outcomes: Comparison of Unpublished Clinical Study Reports with Publicly Available Data, *PLoS Medicine* 10(10).

opinions. This can result in individual experts having great influence, which in turn imposes major requirements on experts to act in an objective and impartial manner.

The closeness which exists between government agencies and industry has frequently been problematised in research and inquiries, both in general terms and with respect to pharmaceuticals more specifically. According to a report by the Expert Group on Public Economics (ESO), the Medical Products Agency is among those agencies that are most vulnerable to this so-called revolving door problem. In the report, the authors show that almost every second manager who left the Medical Products Agency between 2005 and 2009 has taken up employment within the industry. The corresponding proportion of all agency staff was approximately 40 per cent.[50]

A study of corruption in the healthcare sector published by the European Commission states that there is a risk of corruption when the national medicines agencies assess the pharmaceutical companies' applications for marketing authorisations for new medicines.[51] The study shows that the closeness between agencies and industry risks leading to a situation in which the agency more or less conciously promotes the industry rather than regulating and supervising it. When central government is promoting the interests it is charged with regulating, this can be considered as a form of institutional corruption.[52] Corruption of this kind is particularly serious within areas like pharmaceuticals where there may be a conflict between the commercial interest of generating profit and the pharmaceutical policy interest of promoting public health.[53]

There is a natural point of contact between the Medical Products Agency and those pharmaceutical companies that want to conduct clinical trials in Sweden or get a license to market a medicine within the EU. This point of contact is necessary if the Medical Products Agency is to fulfil its remit, but it also creates a risk of conflicts of interest. Such a risk occurs when public officials and managers leave their positions at the Medical Products Agency and move on to companies over which they had influence in their previous roles. A corresponding risk occurs when former employees of pharmaceutical companies take up employment at the Medical Products Agency. When employees move between the Medical Products Agency and the pharmaceutical industry, there is a risk that they give undue consideration to their future career or previous loyalties when performing their duties.[54]

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50 Lindström, L. & Bruun, N. (2012), *Svängdörr i staten – en ESO-rapport om när politiker och tjänstemän byter sida*, report to the Expert Group on Public Economics 2012:1, p. 75 f.

51 The European Commission (2013), *Study on Corruption in the Healthcare Sector*.

52 This form of corruption is also referred to as *state capture* or *regulatory capture*. See, for example, Carpenter, D. & Moss, D. (ed.) (2014), *Preventing regulatory capture: Special interest influence and how to limit it*, Cambridge University Press.

53 The European Commission (2013), *ibid*., p. 20.

54 Lindström, L. & Bruun, N. (2012), *ibid*.

The Medical Products Agency is among those Swedish agencies that have the most points of contact with industry.[55] In 2013, the magazine *Svensk Farmaci* conducted a review of the EMA's classification of the degree of risk of conflicts of interest for the foreign experts who had been engaged over the course of the year. The review showed that, compared to experts from other EU countries, Swedish experts are more likely to have direct interests in the pharmaceutical industry.[56]

[55] Lindström, L. & Bruun, N. (2012), *ibid.*

[56] Nygren, N. B. (2013), *Experter har kopplingar till läkemedelsindustrin* (Experts have links to the pharmaceutical industry), *Svensk farmaci*, 7 October 2013.

3 The Medical Products Agency's regulation of medicines

The Medical Products Agency's regulation of medicines is largely based on information submitted to the agency by pharmaceutical companies. The agency's assessments are therefore dependent on the reliability of this information. If the information is biased and the agency's assessments do not compensate for this, there is a risk that the medicine's product information (e.g. the SPC and patient information leaflets) will also contain bias. Since Sweden joined the EU, the Medical Products Agency has endeavoured to have a trusting working relationship with the pharmaceutical industry,[57] and pharmaceutical companies have great confidence in the agency. [58] However, if the agency has too much faith in companies there is a risk of this having a detrimental impact on the agency's role as an assessor and regulator.

Section 3.1 provides a description of the Medical Products Agency's remit, organisation and focus. Sections 3.2 to 3.4 focuses on the agency's handling of the assessments on which the SPC is based, namely:

- assessment of the application to conduct clinical trials,
- assessment of the application for marketing authorisation,
- assessment of the risk/benefit of authorised medicines.

Section 3.5 deals with how the Medical Products Agency handles the task of both assessing pharmaceutical companies' applications, at the same time as promoting the development of medicines. The comprehensive observations section (Section 3.6) concludes the chapter by discussing how the Medical Products Agency compensates for the industry's informational advantage and manages its closeness to the industry.

3.1 The Medical Products Agency's remit, focus and funding

3.1.1 The Medical Products Agency's remit

The principal duty of modern medicines regulation is to assess the benefits of a medicine in relation to its risks. The origin of this is usually attributed to the

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[57] Junker, S. (2014), *Att skapa gemenskap: Hur beslut fattas i en EU-myndighet* (Creating community – How decisions are made in an EU agency), Stockholm School of Economics, doctoral thesis.

[58] This is evident from interviews with representatives of pharmaceutical companies in Sweden and also in National Audit Office (2003), *Themes and comparisons in international medicines regulation*.

thalidomide catastrophe at the start of the 1960s. Prior to this, issues relating to pharmaceutical safety had been neglected both in Sweden and internationally. For example, there were no rules governing how clinical trials were to be performed. Since then, medicines regulation has continually been expanded through more stringent rules and new duties for central government (and also county councils/regions). Central government medicines regulation has gradually become both more far-reaching and more complex.

The amount of documentation companies are obliged to submit to the Medical Products Agency has increased. For example, in the mid-1980s an application for marketing authorisation would encompass approximately 100 A4 folders.[59] Today, employees at the Medical Products Agency compare the quantity of documentation to that which would fill a lorry, although the information is now delivered digitally.

The Medical Products Agency was established in 1990 with the intention being that the agency would focus on product safety (i.e. prospective and retrospective regulation of medicines) and on supervising the manufacture and distribution of medicines.[60] According to agency's directives, regulation and supervision are still its principal remit.[61] The agency also has other duties, for example pursuing assessment and development activities in order to improve the use of medicines and providing producer-independent information. According to its appropriation directions, the agency is also to promote innovation and the development of medicines.[62]

3.1.2 The Medical Products Agency promotes the development of medicines

Even before Sweden joined the EU, the Medical Products Agency chose to take a prominent role within EU-wide work in this area. One reason was to strengthen Sweden's influence over pharmaceutical policy in Europe. Today, the agency still highlights its strong position as a way for Sweden to exert influence on which medicines are available in the market. Another reason was that a well-developed national system of medicines regulation was considered to be beneficial to industrialised countries' export success.[63] The Medical Products Agency is now the

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59 Riksrevisionsverket (the National Audit Bureau, 1986), *Den statliga läkemedelskontrollen* (Central government medicines regulation). Audit report.

60 Govt. Bill 1989/90:99, *om en ny myndighet för kontrollen och tillsynen på läkemedelsområdet m.m.* (about a new agency for regulation and supervision in the area of pharmaceuticals, etc.), report. 1989/90:SoU21 *Ny myndighet för kontrollen och tillsynen på läkemedelsområdet m.m.* (New agency for regulation and supervision in the area of pharmaceuticals, etc.) decision 17 May, 1990.

61 Ordinance (2007:1205) with instructions for the Medical Products Agency.

62 Appropriation directions for the budget years 2014, 2015 and 2016 regarding the Medical Products Agency.

63 Alvan, G. and Broström, A. (2003), *1962–2003 En epok i svensk läkemedelskontroll* (1962–2003 An epoch in Swedish medicines regulation), p. 69; Medical Products Agency, (1992), *Särskild rapport – en framtidsanalys* (Special report – a future analysis), sent to the Ministry of Health and Social Affairs 24/02/1992, p. 9.

national agency that receives the largest number of assessment commissions (known as *rapporteurship*) within the EU.[64]

The Medical Products Agency assessed early on that there is a competitive relationship between national medicines agencies, with the preferences of pharmaceutical companies determining how well the different agencies cope with this competition. The Medical Products Agency's senior management emphasised how important it is for the agency to focus on proactively marketing itself to the pharmaceutical industry. Short turn-around times for assessments were identified as an important aspect of this effort at an early stage.[65] Today, the Medical Products Agency highlights the high quality of its assessments as a reason behind its success within the EU.

The EMA has been criticised in various contexts for giving excessive consideration to enterprise policy interests. For reasons including the highlighted potential for conflicts of interest, the European Parliament has questioned whether the agency is able to maintain an independent position in relation to the pharmaceutical industry. The European Court of Auditors (ECA) has levelled similar criticism.[66] The European Ombudsman has criticised the EMA for treating the results of clinical trials as trade secrets.[67] Even Germany's counterpart to SBU has openly criticised the EMA for this approach.[68] Patient and consumer organisations have expressed similar criticism.[69]

The European Commission has the explicit ambition to make it easier, in various ways, for the pharmaceutical industry to develop and get new medicines authorised in Europe.[70] In recent years, the Swedish Government has also pursued a pharmaceutical policy that promotes innovation. This desire to stimulate pharmaceutical development influences how the Government manages the Medical Products Agency. According to its annual report for 2015, the Medical Products Agency is to participate, on the basis of its areas of responsibility, in realising the national innovation strategy within the area life sciences and contribute to building up the evidence base throughout the entire process of pharmaceutical development.[71] The ambition to promote innovation in the

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64 The Medical Products Agency's annual report 2015.

65 Junker, S. (2014), *Att skapa gemenskap: Hur beslut fattas i en EU-myndighet*, Stockholm School of Economics, doctoral thesis, ff. 69-73.

66 European Court of Auditors (2012), "Selected EU agencies did not adequately manage conflict of interest situations" – EU Auditors, *Press release* 11/10/2012, ECA/12/39. See also Adams, B. (2011) EMA under fire from European Parliament, *Pharmafile*, 13/05/2011.

67 European Ombudsman (2014), Complaint O1/3/2014/(BEH)FOR, Strasbourg, 27/10/2014.

68 See, for example, IQWiG (2014), Just look, but don't touch: EMA terms of use for clinical study data are impracticable, Press release 27/05/2014.

69 Health Action International (HAI), International Society of Drug Bulletins (ISDB), Medicines in Europe Forum (2015), *Health Groups Call on European Medicines Agencies to Address Independence and Transparency Problems*, Press release, 02/07/2015.

70 Jonzon, B. & Dunder, K. (2014), *Godkännande av läkemedel* (Approval of medicines), *Läkemedelsboken*, the Medical Products Agency.

71 The Medical Products Agency's annual report 2015.

area of pharmaceuticals also appears in the national pharmaceutical strategy, where "attractiveness for innovation of products and services" was one of five target areas in 2014. In the strategy for 2016, innovation is instead a perspective that should be included in all targets and activities, when appropriate.[72] One example of a method that could be used to achieve the target is *adaptive licensing*, which involves it being possible to release medicines onto the market earlier than is currently the case, while simultaneously strengthening monitoring. The Medical Products Agency has been tasked by the Government with investigating the potential of adaptive licensing.[73]

The appropriation directions for 2014 require the Medical Products Agency to include in its annual report an account of how its work with innovation contributes to realising the national innovation strategy.[74] The Medical Products Agency is also to describe the areas in which there is a continued need for innovation.[75] In the Medical Products Agency's appropriation directions for 2016, the Government specifies measures to promote innovation as a separate target for the agency. The target means that the Medical Products Agency is to promote innovation by promoting access to and adequate use of new cost-effective and innovative products.[76]

In 2012, the Medical Products Agency established a separate innovation office that provides information and training to small pharmaceutical companies and research teams within the life sciences. The Government has not allocated specific resources for the agency's innovation promotion activities. According to the Medical Products Agency, this means that the agency allocated its own resources for this purpose.[77] In a communication to the Government in April 2016, the Medical Products Agency contends that the political desire to support innovation has contributed to certain other activities being under-financed.[78]

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72 Government Offices of Sweden (2014), *Nationell läkemedelsstrategi: Handlingsplan 2014*, (The national pharmaceutical strategy: action plan 2014), reference number S2014.003, p. 5; Ministry of Health and Social Affairs (2015), *Nationella läkemedelsstrategin 2016–2018* (The national pharmaceutical strategy 2016–2018), Memorandum 17/12/2015.

73 Medical Products Agency (2014), *Stegvist godkännande och införande av nya läkemedel* (Adaptive licensing and introduction of new medicines), NLS project 6.6, Final report from the Medical Products Agency, 12/12/2014.

74 Government Offices of Sweden (2012), *Den nationella innovationsstrategin* (The national innovation strategy), reference number. N2012.27.

75 Ministry of Health and Social Affairs (2013), Appropriation directions for the budget year 2014 regarding the Medical Products Agency. The reporting requirements are found in the appropriation directions for 2015 and 2016.

76 Ministry of Health and Social Affairs (2015), Appropriation directions for the budget year 2016 regarding the Medical Products Agency.

77 Meeting with the Medical Products Agency's head of administration and others, the Medical Products Agency 26/09/2013.

78 Medical Products Agency (2016), *Förslag till reviderad förordning (2010:1167) om avgifter för den statliga kontrollen av läkemedel*, (Proposal for revised Ordinance [2010:1167] concerning fees for the central government regulation of medicinal products), Communication 23/04/2016.

3.1.3 *The Medical Products Agency's funding*

Since it was established in 1990, the agency has been funded through fees from pharmaceutical companies, central government appropriations and grants. The agency has control over how the fees are spent. In 2015, 79 per cent of the agency's revenue consisted of fees from pharmaceutical companies, 17 per cent was central government appropriations and four per cent was grants. The turnover was SEK 735 million.[79] The appropriations may be allocated to expenditure on such activities as producer-independent medicines information,[80] which encompasses the Swedish medicines information service *Läkemedelsupplysningen*, the Swedish Poisons Information Centre, the book for healthcare personnel *Läkemedelsboken* and treatment recommendations. The agency's assessments of applications concerning clinical trials and marketing authorisation are funded entirely by fees from pharmaceutical companies.[81]

An ordinance regulates which fees companies pay. A company now pays SEK 400,000 for a complete application for marketing authorisation in Sweden and an annual fee of SEK 46,000 for assessments of the company's own monitoring of medicines that have already been authorised and registered.[82] The application fees for EU-wide marketing authorisation amount to EUR 278,200 or more. Of the total fees received, 60 per cent consist of annual fees paid by companies for medicines that are already on the market. The remaining 40 per cent are application fees. Total revenue from fees in 2015 was SEK 571 million.

Since August 2014, companies have also paid fees to the EMA for assessments of the company's safety reports. These fees are also to cover the cost of safety assessments conducted by the member states' medicines agencies, including the Medical Products Agency.[83] According to the Medical Products Agency, however, the work involving pharmaceutical safety (as is the case with environmental management and innovation support) is under-financed. [84]

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79 The Medical Products Agency's annual report 2015.

80 Govt. Bill 2015/16:1, Expenditure area 9.

81 The Medical Products Agency's annual report 2015.

82 Ordinance (2010:1167) concerning fees for central government regulation of medicinal products.

83 Regulation (EU) No 658/2014 of the European Parliament and of the Council of 15 May 2014 on fees payable to the European Medicines Agency for the conduct of pharmacovigilance activities in respect of medicinal products for human use. Text of importance for EEA (L 189/112, 27.6.2014, Celex 32014R0658).

84 Medical Products Agency (2016), *Förslag till reviderad förordning (2010:1167) om avgifter för den statliga kontrollen av läkemedel*, Communication 23/04/2016.

3.1.4 Points of contact between the Medical Products Agency and the pharmaceutical industry

Employees of the Medical Products Agency have to submit a conflict of interest declaration (see Info Box 3.1). The Swedish NAO assesses that, at a procedural level, the Medical Products Agency manages conflict of interest declarations in accordance with the agency's ethics handbook. The Swedish NAO has not conducted an assessment of whether assessors have filled in conflict of interest declarations in accordance with the actual conditions or if the actions taken in the event of suspected conflict of interest are reasonable in relation to the severity of the conflict of interest. This is because the focus of the audit is on the agency's closeness to industry, not how individuals deal with any potential closeness.

Info Box 3.1 Conflict of interest declarations at the Medical Products Agency
Every assessor at the Medical Products Agency has to fill in a conflict of interest declaration. This is to contain information about current secondary employment, previous employment and consultancy assignments over the past five years at companies which are affected by the Medical Products Agency's activities, research funding and participation in pharmaceutical companies' advisory bodies, as well as information about their own shareholdings. Conflict of interest declarations have to be submitted in conjunction with recruitment and thereafter annually or in conjunction with and change of duties. The line manager assesses whether the employee has a conflict of interest in relation to the cases that are being processed. The manager is responsible for ensuring that employees' duties are adapted so that a conflict of interest situation does not arise.[85] Rules and procedures are described in the Medical Products Agency's ethics handbook, which has largely been prepared by the agency's legal unit.[86]

Approximately half of the Medical Products Agency's assessors have previously had an involvement in a pharmaceutical company, usually in the form of employment. This is evident from the Swedish NAO's review of conflict of interest declarations from 97 assessors who were employed by the Medical Products Agency in November 2015. About half of the assessors declared that they have "current or previous interests in companies that are affected by the activities of the Medical Products Agency."[87] The results of the review are shown in Figure 3.1.

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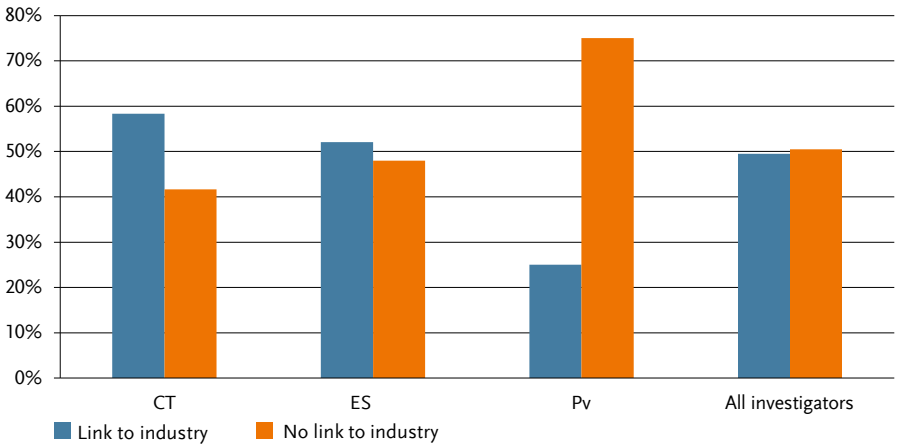
85 Medical Products Agency (2015), *Jävsdeklaration och redovisning av bisysslor* (Conflict of interest declaration and reporting secondary employment). The Medical Products Agency's instructions 01108 applicable as of 04/05/2015.

86 Medical Products Agency (2015), *Etikhandbok* (Ethics handbook). Handbook 01177, applicable as of 20/04/2015.

87 This is the formulation which is used in the Medical Products Agency's form for conflict of interest declaration and reporting secondary employment.

Figure 3.1 The number of assessors at the Medical Products Agency who have links to the pharmaceutical industry, distributed by the units for clinical trials (CT), for efficacy and safety (ES) as well as for pharmacovigilance (Pv).



Source: The Medical Products Agency, 2015, data processed by the Swedish NAO.

The proportion of assessors who have declared a link to the pharmaceutical industry is largest within the departments that assess companies' applications for clinical trials (CT) and marketing authorisations (ES). The proportion is smaller in the department for pharmaceutical safety, where two out of twelve investigators declared a link to a pharmaceutical company.

3.1.5 The Medical Products Agency's organisation of the cases addressed in the audit

The Medical Products Agency's functions are organised into departments and units, of which the following are addressed in the Swedish NAO's audit.

Table 3.1 Functions within medicines regulation that are addressed in the Swedish NAO's audit

Department	Units	Activity
Development	Scientific support	Quality assurance
Licensing	Efficacy and Safety (four units)	Assessment of marketing authorisation applications Assessment of companies' safety reports and risk management plans following authorisation Scientific advice
	Clinical Trials and Special Permissions	Scientific advice Assessment of clinical trials applications
Usage	Pharmacovigilance	Processing of side effect reports Signal management

The Swedish NAO's audit focuses on the case types within medicines regulation that involve more complex assessments influencing the content of the SPC (see table 3.1). Scientific advice, clinical trials, new applications, changes to the authorisation, and assessment of the company's safety reports[88] are examples of such activities. The management of side effect reports and quality assurance are also addressed.[89] The distribution between different types of case is presented in Figure 3.2.

Companies' applications for changes to the authorisation are the Medical Products Agency's most common type of case, but new applications utilise the most resources. Applications for changes often relate to amendments to the terms of the authorisation, for example new packaging or updates to the safety information.

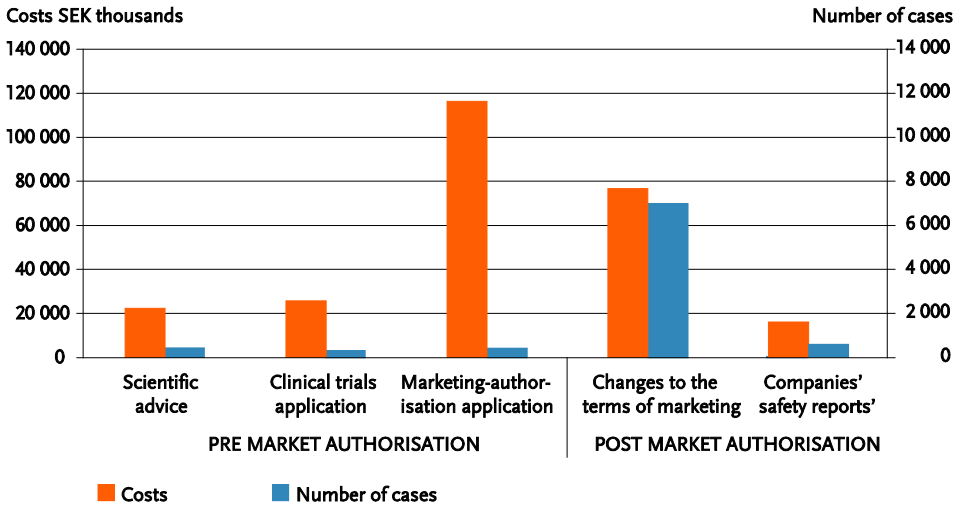
There are comparatively few new marketing authorisation applications, but assessing these requires substantial resources. Therefore, the cost per case is higher (see the diagram below). New applications encompass a large amount of documentation that the assessors use as the basis for their assessment of whether a medicine is sufficiently safe and effective to be authorised. The assessment of a new application involves an assessment of the company's reporting from pharmaceutical investigations, preclinical studies and clinical trials. Other available data (e.g. from literature sources) may also be

88 This refers to safety reports submitted by companies following marketing authorisation, known as *periodic safety update reports* (PSUR).

89 The Medical Products Agency does not report case and cost information for these activities. This is why it is absent in Diagram 2.

requested, depending on the question being addressed. Assessments are conducted in accordance with a formalised template with fixed assessment criteria.

Figure 3.2. The case types within medicines regulation addressed in the Swedish NAO's audit: number and cost (2015).



Source: The Medical Products Agency's annual report, 2015, data processed by the Swedish NAO.

Info Box 3.2 The SPC contains the information about the medicine that the Medical Products Agency/EMA approved.
When a pharmaceutical company gets marketing authorisation for a medicine, this means that the medicine's SPC has been approved. The SPC is a document that describes the medicine's characteristics and the terms of its marketing authorisation. One common term is that the medicine may only be prescribed and marketed to certain patient groups.

The SPC is the basis of the information about the product that may be disseminated further to prescribers, patients and the general public.[90] It forms the basis of FASS, which is the pharmaceutical industry's database of medicines information prepared for prescribers and healthcare personnel. The SPC is also a foundation of central government knowledge-based management, which begins once the medicine has been authorised and is described in Chapter 4.

Once authorisation has been obtained, the pharmaceutical company may want to change its terms and, for example, enable sales to several patient groups. In which case, the company submits a variation application, which is then assessed by the Medical Products Agency. The SPC is updated throughout the lifecycle of the medicine subsequent to assessment by the Medical Products Agency/EMA.

3.2 Assessment of applications to conduct clinical trials

Clinical trials are conducted initially on a small number of healthy people and then on increasingly large groups of people who have the illness that the medicine is supposed to treat. The planned number of test subjects in Sweden amounted to 20,000–30,000 patients per year in the period 2005–2013.

In order to start a clinical trial in Sweden, approval is required from a regional ethical review board and the Medical Products Agency. The ethical review boards are to examine applications on the basis of the aim of protecting the individual human being and respect for human dignity in research.[91] The Medical Products Agency grants authorisation for clinical trials on the basis of the Medicinal Products Act, which sets out the conditions under which a trial may be conducted.

Clinical trials are governed by international and national regulations, as well as international industry standards. The safety of test subjects is a key assessment criterion for both authorities. While the trial is taking place, the pharmaceutical company is obliged to submit documentation informing the ethical review board and the Medical Products Agency about potential side effects and any changes to the design of the trial. Table 3.2 contains examples of documents that are submitted to the Medical Products Agency during a clinical trial:

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90 European Commission (2009), *A Guideline on Summary of Product Characteristics*. The content of the SPC is also regulated in the Medical Products Agency's regulations (LVFS 2006:11) on marketing authorisation for medicinal products.

91 The Act (2003:460) concerning the Ethical Review of Research Involving Humans.

Table 3.2 Documents that companies submit to the Medical Products Agency in conjunction with clinical trials.

Documents	Time
Application for clinical trial	Before a clinical trial
Investigator's brochure (IB)	Before a clinical trial, updated continuously
Suspected Unexpected Serious Adverse Reaction (SUSAR) report	Within 15 days of the company becoming aware
Development Safety Update Report (DSUR)	Annually
Notification of substantial amendment	Before a substantial amendment to the trial's design
Clinical study report (CSR)	Within one year of the clinical trial's completion

3.2.1 Application turnaround times

Applications for authorisation to conduct clinical trials are processed by the Medical Products Agency's Clinical Trials and Special Permissions Unit. In 2015, approximately twelve assessors worked at the unit. The unit received 340 applications that year. The law states that the turnaround time for an application concerning a clinical trial shall be a maximum of 60 days. If the Medical Products Agency exceeds this time limit, the application is automatically approved.[92] In 2014, 98 per cent of applications were processed in time[93]; the corresponding proportion for 2015 was 94 per cent.[94] Almost 20 per cent of the applications were processed within 30 days, following what is known as a basic assessment. The head of the Clinical Trials and Special Permissions Unit says that the quality of many applications is so good that it is possible to process them on time and that it would be desirable if more applications were of the same quality.[95]

There is political pressure to reduce turnaround times in order to promote the development of medicines. For example, a Swedish Government inquiry investigated the conditions in which companies conduct clinical trials and proposed that the

92 Chapter 7, Section 9, the Medicinal Products Act (2015:315).
93 The Medical Products Agency's annual report 2014, p. 21.
94 The Medical Products Agency's annual report 2015, p. 20.
95 Email from the group head at the Medical Products Agency's Clinical Trials and Special Permissions Unit, 24/02/2015.

Medical Products Agency further develop the support it provides to pharmaceutical companies, so that more applications can be processed within 30 days.[96]

However, the Medical Products Agency is of the opinion that a fast turnaround has a negligible impact on the time it takes for a company to develop a medicine.[97] Nevertheless, several of the assessors interviewed claim that pharmaceutical companies have an interest in fast turnaround. Not to reduce the time it takes to develop a new medicine, but because it limits the opportunity the agency has to ask critical questions. Short turnaround times contribute to medicines being introduced onto the market earlier, but assessors argue that lack of time means that less knowledge about the medicine is built up prior to its marketing authorisation being granted. Ultimately, this constitutes a risk to the test subjects' safety.

3.2.2 Handling of safety reports (DSURs) during the trial

When a medicine is tested on human subjects in Sweden, the Medical Products Agency has to continuously monitor the clinical trial's development from a safety perspective. The Medical Products Agency is the only independent body that has the authority to independently terminate a clinical trial in Sweden, for example if the safety of test subjects is at risk.[98] Companies and researchers who are conducting a clinical trial are obliged to produce an annual safety report (this is called the *Development Safety Update Report*, DSUR). This report has to be sent to the regional ethical review board and the Medical Products Agency.[99] In the safety report, the company has to sum up all the serious side effects that have emerged in the past twelve months and make an overall assessment of the safety of test subjects. When a clinical trial is conducted in more than one country at the same time, all safety-related incidents are to be reported in the same DSUR, regardless of the country in which they have been detected.[100] When several ongoing trials are included, the safety report can become very large and amount to over one thousand pages. [101]

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96 SOU 2013:87, *Starka tillsammans, Betänkande av Utredningen om nationellsamordning av kliniska studier* (Strong together, Report of the Inquiry into national coordination of clinical trials).

97 This view emerged when the Medical Products Agency fact checked of the report.

98 Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, art. 12.

99 Chapter 8, Section 10 of the Medical Products Agency's regulations (LVFS 2011:19) on clinical trials of medicinal products for human use.

100 Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ L 121, 1.5.2001, Celex 32001L0020). See also EMA (2011), *ICH Guideline E2F on development safety update report*. EMA/CHMP/ICH/309348/2008.

101 Interview with pharmacovigilance expert at a global company with operations in Sweden, 08/02/2016.

The regional ethical review boards do not read the DSURs that companies submit.[102] They do not have any statutory obligation to do so and are of the opinion that they lack the resources and expertise to review these sizeable documents. Nor do they see any clear use for this information as they lack the authority to stop a trial. The representatives of the boards interviewed claim that it would be better if the companies were only obliged to report to the Medical Products Agency. In 2007, the Government inquiry also stated that it ought to be sufficient for the Medical Products Agency to receive the reports.[103] However, the Government chose not to abolish the requirement to report to the boards. The justification was that this reporting is stipulated in EU directives and that the reporting ought to contribute to raising the quality of ethical review board's assessment of applications concerning clinical trials.[104]

Pharmaceutical companies submit approximately 550 DSURs per year to the Medical Products Agency. There is a clear expectation that the Medical Products Agency will assess them. Representatives of global companies with operations in Sweden, and representatives of regional ethical review boards presume that the Medical Products Agency reviews the documents they submit, including the safety reports.[105]According to the chair of the Swedish Association of the Pharmaceutical Industry's (LIF's) expert group on pharmacovigilance, the system's credibility is based on the Medical Products Agency independently auditing the reports of pharmaceutical companies.

The Medical Products Agency has not conducted any systematic assessment of DSURs since 2010. A number of reports are assessed in connection with assessments of notifications of substantial amendments in the ongoing trials, but other submitted reports are not read.[106] Furthermore, the Medical Products Agency does not have any instructions that describe how DSURs are to be processed. DSURs contain a great deal of information and the Medical Products Agency's assessors may end up assessing a safety problem differently to the pharmaceutical company. By not reading DSURs, the Medical Products Agency is losing out on a channel through which to exert influence over pharmaceutical safety during ongoing clinical trials. According to the assessors interviewed, systematically disregarding DSURs results in it taking longer to detect the risks of medicines during their development.

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[102] This is evident from the interviews the Swedish NAO has conducted with two regional ethical review boards and two global pharmaceutical companies with operations in Sweden.

[103] SOU 2005:78, *Etikprövningslagstiftningen – vissa ändringsförslag* (Ethical review legislation – some proposals for amendments).

[104] Govt. Bill 2007/08:44, *Vissa etikprövningsfrågor, m.m.* (Some ethical review issues, etc.)

[105] Interviews with two regional ethical review boards and two global pharmaceutical companies with operations in Sweden, 07/02/2016 and 08/02/2016.

[106] Email from the group head at the Medical Products Agency's Clinical Trials and Special Permissions Unit, 17/02/2015. Interviews with assessors from the Clinical Trials and Special Permission Unit.

The Medical Products Agency points to a lack of resources as one reason for assessment not taking place. In February 2015, three of a total of eight clinical assessor posts were vacant and one doctor employed as a clinical assessor was seconded to the EMA. It is estimated that processing all safety reports would require one full-time employee.[107] The Medical Products Agency's senior management and the assessors interviewed are of the opinion that the safety reports should be assessed.

The officials at the Ministry of Health and Social Affairs who are responsible for this area do not express an opinion on which documents the Medical Products Agency should read.[108] However, the Government has rejected the Medical Products Agency's proposal to raise the fees levied on pharmaceutical companies in order to fund the assessment of DSURs (and other safety-related information that has emerged in conjunction with new safety legislation at the EU level).[109] In its written justification, the Government refers to critical comments on this proposal from LIF, the Swedish Agency for Economic and Regional Growth, Vinnova and the Swedish Research Council, all of whom warn that increases in fees would discourage companies from conducting clinical trials in Sweden. Instead these bodies are requesting a report on how the Medical Products Agency can further increase efficiency of its operations. This argument also appears in the Government's decision to reject the proposal.[110] In April 2016, the Medical Products Agency submitted a new proposal concerning increased fees to the Government.[111]

3.2.3 Other channels for safety monitoring

DSURs are not the only means by which the Medical Products Agency supervises the safety of test subjects while a trial is ongoing. Safety information is also specified in the investigator's brochure, which is assessed and approved by the Medical Products Agency. Companies also submit reports concerning unexpected and serious side effects, referred to as *suspected unexpected serious adverse reactions* (SUSARs). The Medical Products Agency also conducts inspections of clinical trials through which inadequate safety procedures can be detected.

The principal aim of the investigator's brochure is to provide guidance on what investigators should consider with respect to the safety of test subjects and to provide

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107 Email from the group head at the Medical Products Agency's Clinical Trials and Special Permissions Unit, 23/02/2015.

108 Meeting with the Ministry of Health and Social Affairs, 06/05/2015.

109 Medical Products Agency (2014), *Förslag till reviderad förordning om avgifter för den statliga kontrollen av läkemedel* (Proposal for revised Ordinance concerning fees for central government regulation of medicinal products), Communication 26/03/2014.

110 Government decision, 28/08/2014, S2014/2910/FS.

111 Medical Products Agency (2016), *Förslag till reviderad förordning (2010:1167) om avgifter för den statliga kontrollen av läkemedel*, Communication 23/04/2016.

investigators with the most up-to-date information about the efficacy and safety of the investigational product (i.e. the medicine being tested). The investigator's brochure, which the pharmaceutical company draws up and continuously revises, contains the pharmaceutical company's summary of the information available in the company's own annual safety reports (DSURs).[112] By assessing the investigator's brochure, assessors at the Medical Products Agency learn about the medicine's safety profile. In the Medical Products Agency's fact check of a draft of this Swedish NAO report, the Medical Products Agency advocates that the agency study all safety information by assessing and approving the investigator's brochure. However, assessing a summary instead of the complete document must, in all likelihood, mean that some information is lost. It would also be difficult to critically assess the company's own summary without seeing the information that is being summarised.

The pharmaceutical company has a legal obligation to immediately, within 15 days of detection, report all suspected unexpected serious adverse reactions (SUSARs) to the EMA's database of suspected adverse drug reactions.[113] SUSARs are defined as suspected adverse reactions which are not listed in the safety information contained in the investigator's brochure. The content of the database is confidential and only accessible by authorised medicines agencies within the EU, the EMA and the European Commission. Fatal and life-threatening adverse reactions have to be reported within seven days of the sponsor becoming aware of them. For other serious adverse reactions, the deadline is 15 days.[114]

Pharmaceutical companies have an obligation to report SUSARs that occur in Sweden to a regional ethical review board.[115] The ethical review boards register these adverse reaction reports but do not study them.[116] The Medical Products Agency studies SUSARs by searching in the EU's database of suspected adverse drug reactions. According to the assessors interviewed by the Swedish NAO, however, in order to assess whether a SUSAR is linked to the medicine, it is also important to have a more complete view, which is obtained by having read the DSUR.

The Medical Products Agency also conducts inspections of pharmaceutical companies' pharmacovigilance systems during ongoing clinical trials. In 2014, the Medical Products Agency conducted 15 such inspections. During these inspections, the Medical

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112 EMEA (2002), ICH Topic E 6 (R1) Guideline for Good Clinical Practice.

113 Chapter 6, Section 2 of the Medicinal Products Act (2015:315), and Chapter 8, Section 7 of the Medical Products Agency's regulations (LVFS 2011:19) on clinical trials of medicinal products for human use.

114 EudraVigilance Clinical Trial Module (EVCTM), see https://eudravigilance.ema.europa.eu/human/, accessed 25/04/2016.

115 Medical Products Agency (2013). *Vägledning till LVFS 2011:19* (Guide to LVFS 2011:19), version 2, 01/04/2013, p. 17.

116 Interview with the administrative director of the Central Ethical Review Board, the head of the Regional Ethical Review Board in Stockholm and members at the regional ethical review boards in Stockholm and Uppsala.

Products Agency found 63 major deviations from applicable regulations, five of which were judged to be critical.[117] Information from supervisory initiatives is rarely used as grounds for the agency to suspend or terminate a trial prematurely.[118]

The total number of inspections carried out by the Medical Products Agency in Sweden and abroad has declined significantly, from 302 inspections in 2013 to 200 inspections in 2015 (the number of inspection days decreased from 541 to 318).[119] The volume of international inspections is often governed by the demand generated in the European system. In 2015, the Medical Products Agency has not been able to meet the demand there has been for initiatives concerning clinical trials abroad. The Medical Products Agency states that this was due to lack of resources.[120]

3.2.4 Handling of companies' final reports

When a clinical trial has been concluded, the company has to submit a final report to the Medical Products Agency. This report (called the *clinical study report*, CSR), which is the most detailed description of a completed clinical trial, is to describe the trial's design, method and results. The report has to contain sufficient information about the study design, analytical technique and patient data to allow medicines agencies to replicate, if necessary, the analysis of the trial results.[121] Pharmaceutical companies have to submit the CSR within one year of the trial having been completed.[122]

CSRs contain information to which only the Medical Products Agency has access and that may be of interest to researchers and others. The Medical Products Agency does not conduct any assessment of CSRs and accordingly does not take advantage of the opportunity for learning and follow-up that processing the reports could entail. The relevant assessors and managers at the Medical Products Agency agree that CSRs could be used to learn more about predictable risks and thereby contribute to more efficient case management. What does happen, however, is that CSRs are requested internally

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117 Medical Products Agency (2014), *Tillsynsrapport från Läkemedelsverket, Område: Inspektion av Industri och Sjukvård* (Supervision report by the Medical Products Agency, Area: Inspection of Industry and Healthcare), p. 17.

118 Email from the group head at the Medical Products Agency's unit for inspection of industry and medical services, 10/08/2015.

119 The purpose of the Medical Products Agency's inspections of industry and healthcare is to audit the supervision object's quality management system and to investigate the systems pharmaceutical companies use in the manufacturing, distribution and handling of medicines so that these comply with established requirements. The inspections takes place both domestically and internationally. The Medical Products Agency supervises manufacturers (GMP), wholesale traders (GDP), clinical trials (GCP), pharmacovigilance (GVP), laboratories, blood centres and hospital-related objects such as dialysis units, radiopharmaceutical units and hospitals' pharmaceutical supplies. The information presented here relates to the overall supervision, not just the supervision of clinical trials.

120 The Medical Products Agency's annual report 2015, p. 28–29.

121 ICH (1996), *Topic E3: "Structure and Content of Clinical Study Reports". International conference of harmonisation of technical requirements for registration of pharmaceuticals for human use*. 30 November, 1995.

122 Chapter 6, Section 5, the Medicinal Products Act (2015:315).

within the Medical Products Agency, for example in connection with the emergence of a safety issue or when an issue occurs in connection with an application concerning a similar product. The head of the clinical trials unit says that it would be desirable to review the CSRs, but claims there are insufficient resources to do so.[123]

3.3 Assessment of marketing authorisation applications

When the clinical trials have ended, the pharmaceutical company applies for marketing authorisation for the medicine. The Medical Products Agency assesses and approves the application (see Info Box 3.3). Assessments of these applications constitute the bulk of the agency's work. This work is extensive, highly regulated and is now often conducted within the framework of a common EU assessment process. The Medical Products Agency has a leading role within the common EU process, which is illustrated by the agency having been allocated the largest number of assessment commissions (rapporteurship) by the EMA in 2015, in competition with other national medicines agencies.[124]

[123] Email from the group head at the Medical Products Agency's Clinical Trials and Special Permissions Unit, 23/02/2015.

[124] The Medical Products Agency's annual report 2015.

Info Box 3.3 Marketing authorisation applications at the Medical Products Agency[125]

The application has to contain scientific documentation concerning the medicine's pharmaceutical quality, previous studies conducted on animals and data about the medicine's clinical effects. Applications submitted to the Medical Products Agency have to contain a range of information in accordance with regulations and industry standards. In addition to the application, the company submits those parts of the final reports (CSRs) that cover methods and results. The company also has to append a plan for the management of safety risks.

Every subsidiary part of the assessment within each subject area undergoes internal scientific quality assurance at an assessors' meeting. The quality assured subsidiary assessments are then brought together to produce an assessment report that forms the basis of quality assurance at a joint quality meeting (Q meeting). This internal assessment report contains questions for the company, proposals for activities the company should undertake following authorisation and comments and changes in the SPC. The Q meeting then forms an opinion on how the SPC is structured, how the company intends to manage known and potential risks and which questions should be asked of the pharmaceutical company responsible.

If the medicine is to be approved across the whole EU and the Medical Products Agency is the principal national assessment agency, the report is then subject to a common EU process. Several committees within the EMA coordinate national agencies' assessments, after which the European Commission makes the formal decision concerning authorisation. The law requires the Medical Products Agency to process applications within a maximum of 210 days of the application being received.

Nothing has emerged from our interviews to indicate that the Medical Products Agency systematically assigns a lower priority to specific aspects of its operations in this area. However, it is difficult to judge how exhaustive the Medical Products Agency's evaluation of causation and any safety problems should be within the scope of an assessment prior to marketing authorisation. Here, as in all advanced research and assessment processes, there is scope to use discretionary judgement and, for obvious reasons, there are different ideas about how this scope should be utilised.[126] Most of the assessors interviewed express their confidence in the organisation's ability to strike the right balance when assessing marketing authorisation applications.

A small number of assessors express their concern about the decline in the quality of assessments in recent years. Some are of the opinion that the agency has been assigned too many duties over and above its core remit and that this has taken focus from the scientific work of weighing up and assessing risks in relation to benefits. Others say that safety issues are downplayed during the assessment process in order to prevent too

[125] For a more detailed description of the application procedure and approval process, see Jonzon, B. & Dunder, K. (2014,) *Godkännande av läkemedel*, *Läkemedelsboken 2014*, the Medical Products Agency.

[126] This is clear from interviews with investigators within the Medical Products Agency and its British counterpart, MHRA. See also, for example, Herder, M. (2014), Toward a jurisprudence of drug regulation, *Journal of Law, Medicine & Ethics* 42(2); Trotta, F. *et al.,* (2011), Evaluation of Oncology Drugs at the European Medicines Agency and US Food and Drug Administration: When differences have an impact on clinical practice, *Journal of Clinical Oncology* 29(6); Eichler, H-G, *et al.,* (2013), The risks of risk aversion in drug regulation, *Nature Reviews: Drug Discovery* (12).

many obstacles being put in the way of pharmaceutical companies' development of medicines.

3.4 Assessment of risk and benefit following marketing authorisation

Pharmaceutical companies are responsible for monitoring the safety of their authorised medicines. The company that has been issued a marketing authorisation for a medicine has to have a system in place to monitor its safety (known as a pharmacovigilance system). This means that the company has to monitor developments in the area of pharmaceuticals and, within the authorisation, make any necessary amendments to, for example, the product information for the medicine in question. The company also has to register, store, evaluate and report information about suspected adverse reactions to the medicine as part of the pharmacovigilance system.[127]

After a medicine has been authorised, the Medical Products Agency has a continued responsibility to inspect the company's monitoring of the medicine's risk-benefit balance. This is primarily conducted using documentation the company is obliged[128] to submit to the agency and the adverse reaction reports sent to the agency by healthcare personnel and members of the public. If the Medical Products Agency come to the conclusion that the harm revealed by the documentation has been caused by the medicine, the agency can, in consultation with other medicines agencies in the EU, either change the terms of the marketing authorisation or withdraw it.

The Medical Products Agency is responsible for assessing companies' *periodic safety update reports* (PSURs) and risk management plans and for managing and analysing the reports of adverse reactions received from the EMA and Swedish healthcare personnel, which is called *signal management*. The Medical Products Agency has a specific responsibility at the EU level for signal management with respect to just over 70 medicines and a general responsibility for assessing all adverse reactions that occur in Sweden.

3.4.1 Processing of companies' periodic safety update reports (PSURs)

After a medicine is authorised, pharmaceutical companies have to submit periodic safety update reports (PSURs). The frequency of these varies depending on how

[127] Chapter 6, Section 2, the Medicinal Products Act (2015:315).

[128] Companies are ordered to submit all documentation and knowledge which they become aware of after the approval.

uncertain the knowledge situation is.[129] The PSUR is to contain the company's synthesis of the safety-related information from a number of sources, for example studies that are ongoing or have been completed during the reporting period, the company's signal management, published scientific articles and reviews of particular risks linked to the specific medicine. A PSUR for a medicine can stretch to approximately 700 pages.[130] The Medical Products Agency has to assess these documents and establish whether there are new risks, if the risks have changed or whether the relationship between the benefit and risks of the medicine has changed.[131]

According to the Medical Products Agency's annual report for 2014, a large proportion of the national PSURs had not been processed within 70 days of the PSUR being received by the Medical Products Agency. [132] This is the limit the agency has set itself based on how long it usually takes to process these cases, how long it is reasonable for companies to wait for feedback and how urgent the content of these reports tends to be.[133] According to the head of one of the four units responsible for assessing PSURs, the unprocessed reports that have been presented have accumulated over the course of several years. One explanation for this is that in the period 2010–2013, the Medical Products Agency had a high workload when its finances were weak. In order to strengthen its finances, the agency undertook more common EU rapporteurship commissions, and there was therefore no scope to process PSURs. According to the unit head, the agency has now reviewed all reports without detecting any serious safety problems. New PSURs received today are processed on time.[134]

3.4.2 Adverse reaction reports from healthcare and the general public

Actors in the Swedish healthcare system are obliged to report all suspected adverse reactions to medicines to the Medical Products Agency.[135] It is particularly important that previously unknown and suspected adverse reactions are reported, irrespective of their severity. Post marketing authorisation safety evaluations also departs from reports

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129 Sections 10–11 (LVFS 2012:14), *The Medical Products Agency's regulations on safety monitoring of medicinal products for human use*.

130 Interview with clinical assessors at the Medical Products Agency's Efficacy and Safety Unit, 11/11/2014.

131 Chapter 4, the Medicinal Products Ordinance (2015:458). Compare with Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EU on the Community code relating to medicinal products for human use (L 348, 31.12.2010, p. 74, Celex 32010L0084). The regulation entered into force on 1 January 2016.

132 According to the Medical Products Agency's annual report 2014, p. 23, of the total 2,041 PSURs, 1,466 PSURs were not processed on time.

133 Email from the group head at the Medical Products Agency's regulatory unit, 18/12/2015.

134 The Medical Products Agency's annual report 2015.

135 Sections 10–11 (LVFS 2012:14), *The Medical Products Agency's provisions on safety monitoring of medicinal products for human use*.

from the general public, as well as published research and studies conducted on the company's own initiative or when the agency requires.

Pharmaceutical companies whose medicines have been approved for sale are required to have a system for safety monitoring. This means that they have to monitor developments in the area of pharmaceuticals and, within the scope of the authorisation, amend, for example, the product information for the medicine in question when necessary. Companies that have an authorised medicine also have to, as one aspect of their safety monitoring system, register, store, evaluate and report information about suspected adverse reactions to the medicine.[136]

The Medical Products Agency is also responsible for ensuring a safety monitoring system is in place, the purpose of which is to collect, register, store and scientifically evaluate information about suspected adverse reactions to medicines that have been granted marketing authorisation.[137] Each adverse reaction is registered by administrators in the Medical Products Agency's adverse reactions database. The administrators also conduct a preliminary assessment and quality assurance of the adverse reaction reports. Reports that are judged to be serious are subject to quality assurance at an adverse reactions meeting during which clinical assessors who judge how probable it is that the incident is caused the medicine specifically and not, for example, by the underlying illness.

The number of adverse reaction reports has increased in recent years, from 6,190 reports in 2013 to 8,365 reports in 2015.[138] At the Medical Products Agency, the general perception is still that the degree of reporting is much too low. The figures are said to equate to each doctor reporting one suspected adverse reaction every twenty years. Many patients are unaware that they can report adverse reactions themselves. According to the head of the Medical Products Agency's Pharmacovigilance Unit, a greater influx of reports would result in a substantial increase in the quality of the data used for signal management.

In 2013 the Medical Products Agency received a government commission which aims to increase the reporting of adverse reactions. The commission resulted in the project *Sjukvårdens elektroniska biverkningsrapportering* (the Swedish healthcare system's electronic adverse reaction reporting tool, SEBRA). The intention is to make it easy for healthcare personnel to report adverse reaction directly from the medical records system. In its final report, the Medical Products Agency states that SEBRA will probably lead to a higher number of reports and more informative adverse reaction reports and

136 Chapter 6, Section 1, the Medicinal Products Act (2015:315).
137 Chapter 6, Section 1, the Medicinal Products Act (2015:315).
138 The Medical Products Agency's annual report 2015, p. 42.

that in the long run this will contribute to improved pharmaceutical safety in Sweden and the EU.[139] The work to introduce SEBRA is still ongoing.[140]

New EU pharmacovigilance legislation came into force in July 2012, which resulted in an expansion of the Medical Products Agency's remit. For example, prior to this, the Medical Products Agency only dealt with adverse reactions that occurred when medicines are used correctly. The agency now has to deal with all adverse reactions, even those resulting from incorrect use. This entails greater volumes and more complex administration.

The head of the Pharmacovigilance Unit is of the opinion that this work is significantly more time consuming now than it was prior to the new legislation and that the unit is understaffed in relation to the amount of work involved. This has resulted in several reprioritisations including:

- some information from other databases (e.g. the WHO's) is no longer sought and documented in individual cases
- complete information about concomitant medication is not registered
- the time available for meetings and the telephone hours have been decreased.

The unit head is of the opinion that operations cannot be streamlined more without jeopardising patient safety.

The resource problems have also contributed to the unit being forced to lower the level of ambition in terms of processing adverse reaction reports. In autumn 2014, the Medical Products Agency stopped recording the description of the circumstances of or details concerning the reported adverse reaction, which is referred to as the *narrative*. By the third quarter of 2014, the narrative was absent from 2,688 reports (of which 731 were serious).[141] In concrete terms, this means that, in the reports in question, medicines agencies (including the EMA) that wanted to investigate an adverse reaction signal for a certain medicine did not have direct access to all details that the Medical Products Agency is responsible for registering. They must then request supplementary data from the Medical Products Agency. According to supplementary information from January 2016, routine registration of the narratives has now been reintroduced.[142]

Due to the lack of resources, the Pharmacovigilance Unit has also lowered its level of ambition with respect to information campaigns that aim to encourage healthcare

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139 Medical Products Agency (2014), *Elektronisk rapportering av läkemedelsbiverkningar – rapport från Läkemedelsverket,* (Electronic reporting of adverse drug reactions – report from the Medical Products Agency), 20/12/2014, p. 9.

140 Ministry of Health and Social Affairs (2015), Appropriation directions for the budget year 2016 regarding the Medical Products Agency.

141 Emails from the head of the Medical Products Agency's Pharmacovigilance Unit, 01/10/2014 and 07/10/2014.

142 Email from the head of the Medical Products Agency's Pharmacovigilance Unit, 21/01/2016.

personnel and the general public to report adverse reactions. The unit head is of the opinion that previous information campaigns have had a clear positive impact on the degree of reporting, but because the unit cannot cope with all of the adverse reaction reports currently being received, activities which aim to increase the degree of reporting have been reduced. Parallel to these problems, the Medical Products Agency has continued to work on the government commission SEBRA.

3.4.3 The Medical Products Agency's signal management

In addition to processing adverse reaction reports, the Medical Products Agency also has to analyse potential safety problems. This is known as signal management and is conducted in order to detect previously unknown risks. A signal is a safety problem that is considered to be supported by sufficient evidence[143] to justify further investigation. This further investigation can then form the basis of regulatory action. The action taken might be a decision to amend the descriptions of the medicine's properties in the SPC, a decision to amend the medicine's permitted area of use or, in some cases, a decision to withdraw a medicine. The Medical Products Agency is responsible for all domestic signal management and for approximately 70 medicinal products at the European level.

In brief, signal management involves the following steps for national medicines agencies:

- detection (detecting patterns in adverse reaction reports using statistical methods)
- validation (establishing whether the information about the potential signal is relevant, sufficient and should be investigated further)
- confirmation (the national agency's final assessment that there is sufficient evidence to regard the information as a signal)[144].

The Medical Products Agency detects approximately 300 potential signals per year. Of these, approximately five per cent (15 signals) lead to regulatory action (usually an amendment to the SPC). The number of signals detected by the Medical Products Agency decreased by nine per cent in 2014 and by seven per cent in 2015. In its annual report for 2014, the Medical Products Agency explains this decrease as being caused by the number of doctors at the agency being halved in the autumn of 2014 and that it is doctors who "have the initial responsibility for defining the potential signals that are

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[143] What is considered to be sufficient evidence is not clear-cut, which is illustrated by the definition of a signal used by the EMA and the Medical Products Agency: "Information that arises from one or multiple sources (incl. observations and experiments), which suggest a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.", *Practical Aspects of Signal Detection in Pharmacovigilance Report of CIOMS Working Group VIII*, Geneva 2010.

[144] Medical Products Agency (2014). *Signaldetektion och signalutredning på Läkemedelsverket* (Signal detection and signal assessment at the Medical Products Agency). Instruction 01047.

clinically relevant and will be processed further"[145]. According to the Medical Products Agency, the decrease in the number of signals detected in 2015 is the result of four signal assessors having been seconded for a period of time to register adverse reaction reports from healthcare actors and the public.

All confirmed signals have to be entered in the tracking system, the *European Pharmacovigilance Issues Tracking Tool* (EPITT), which is administered by the EMA. They are then sent to the EMA's *Pharmacovigilance Risk Assessment Committee* (PRAC) for an initial analysis and prioritisation.[146] This allows the EMA to make a prompt assessment and decide if any regulatory action is required. The EMA then has to immediately inform the concerned marketing authorisation holder (MAH) or holders of the PRAC's conclusions. Using EPITT to process signals also means that all national agencies within the EU can see which signals other countries have investigated or are currently being processed.

If a validated signal is deemed to require further analysis, it has to be confirmed as soon as possible, within 30 days of the signal being received. The national competent authorities and the EMA have to validate and confirm all signals that they have detected in conjunction with their continuous monitoring of adverse reactions within this timeframe. If a signal is not confirmed by the national authority, the authority is to be particularly attentive to further signals that concern the same medicine.[147] The EU's implementing regulation does not explicitly state how this is to be conducted, however. In the Medical Products Agency's local instructions, continued signal monitoring and monitoring of the signal within the company's safety reports (PSURs), which are submitted at various intervals, are two options specified. According to these instructions, in order to proceed with a validated signal, collaboration meetings are conducted between the Pharmacovigilance Unit, assessors from the efficacy and safety units and PRAC delegates (as well as a Q meeting, if necessary). Thereafter, the signal can be entered into the EPITT. Accordingly, there needs to be a consensus that the signal should be confirmed before it can be registered in the EPITT.

However, few of the signals that are validated are then confirmed and thus also registered in the EPITT. According to the Medical Products Agency's statistics, the agency has registered significantly fewer signals than the other medicines agencies that have a prominent role within the EMA. Between 2008 and May 2015, the Medical Products Agency registered nine signals in the EPITT and between 2014 and May 2015, not one signal was registered.[148] This can be compared to the United Kingdom and the Netherlands, which have each registered over 40 signals in the same period. However, these figures are not directly comparable as they do not take into account the fact that

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145 The Medical Products Agency's annual report 2014, p. 47.
146 Article 21, p. 5 of Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012.
147 Article 21 of Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012.
148 Email from the head of the Pharmacovigilance Unit, the Medical Products Agency, 04/05/2015.

national authorities assess signals and subject them to quality assurance in different ways. Nevertheless, the figures can be seen as an indication that the Medical Products Agency has a relatively more restrained practice when it comes to the confirmation of signals. This indication is strengthened by the statements provided in the interviews.

Unconfirmed signals are instead processed by the Medical Products Agency within the framework of the companies' safety reports (PSURs). As mentioned earlier, companies submit PSURs at various time intervals, often every six months where new drugs are concerned. Several assessors claim that the Medical Products Agency's processing of a validated signal through PSURs results in further analysis of the signal being conducted later than if it had been entered into the EPITT. In the long run, this may result in the detection adverse reactions being delayed. Accordingly, the assessors are implying that the Medical Products Agency does not register as many signals as would be justifiable. In its fact check of this Swedish NAO report, the Medical Products Agency claims, to the contrary, that the limited number of signals demonstrates the high quality of the agency's assessments. The Medical Products Agency also claims that different national agencies have different opportunities to conduct extensive background work prior to validation and confirmation.

3.5 Assessing while simultaneously promoting

The public administration inquiry's final report from 2008 highlighted how conflicting roles easily emerge when public authorities are charged with simultaneously promoting and critically assessing a specific sector or activity. The promoter is charged with making the activity function well, while the assessor's remit includes investigating whether it has been successful. If the assessor detects shortcomings, this may mean that the promoter has not done its job, which the assessor then needs to point out. For obvious reasons, assessing yourself may be problematic, both for the actual quality of the assessment, as well as for the credibility of the results. According to the public administration inquiry, the argument in favour of separating assessment from promotion is intuitive because of the obvious risk of a conflict of interest. That is why several government agencies have also more clearly defined their remits in recent years.[149]

Medicines regulation encompasses a critical assessment of information submitted to the Medical Products Agency by external actors. Consequently, the importance of maintaining a separation between critical assessment and promotion is probably also relevant here, particularly considering the signs of institutional corruption described in the introduction to this report. The following section describes how the Medical

[149] SOU 2008:118, *Styra och ställa – förslag till en effektivare statsförvaltning* (Governing and Ruling, Proposals for a More Efficient Central Government Administration). Final report of the Committee on Public Administration of 2006, Appendix 8, pp. 274-276.

Products Agency deals with the challenges involved in managing its simultaneous promotion and critical assessment of the pharmaceutical industry.

3.5.1 *The Medical Products Agency's organisation of safety assessment*

The Medical Products Agency's Pharmacovigilance Unit is a part of the operational area *Usage*. This operational area is organisationally separate from the operational area *Licensing*, which encompasses the efficacy and safety units. The Pharmacovigilance Unit has not been charged with making decisions on regulatory action with respect to approved medicines. Instead, such decisions are made and implemented via the operational area *Licensing*. This relationship between, on the one hand, assessment of safety and on the other, risk–benefit evaluation, has an equivalent within the EMA, where the committee responsible for assessing the safety of medicines, PRAC, issues recommendations to instances including the Committee for Medicinal Products for Human Use (CHMP), which is the committee that has the most significant influence on decisions concerning marketing authorisation.

The units that assess safety have fewer staff and less formal influence than the parts of the organisational that assess marketing authorisation applications. This is the case for both the Medical Products Agency and the EMA. This relationship is a problem that has been highlighted by researchers and special interest groups in both the EU and the US.[150] The same criticism has also emerged in the Swedish NAO's interviews.

Companies' safety reports (PSURs) are now assessed within the efficacy and safety units, which are the same units that assess the marketing authorisation applications. Prior to 2010, this assessment was conducted by the Pharmacovigilance Unit.

3.5.2 *The Innovation Office*

The Medical Products Agency established an innovation office in 2012. The purpose of the Innovation Office is to offer innovators, pharmaceutical companies and university-based researchers with a distinct channel through which to contact the agency. The Innovation Office's remit is to disseminate information about the agency's services for the promotion of innovation, for example, scientific and regulatory advice.[151] The reason why the office was established is described by the Medical Products Agency in

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[150] See, for example, Institute of Medicine (2006), *The future of drug safety – Promoting and protecting the health of the public*. The Institute of Medicine's Committee on the Assessment of the U.S. Drug Safety System; Carpenter, D. and Moss, D. (2014), *Preventing Regulatory Capture: Special Interest Influence and How to Limit it*, Cambridge, Mass.: Cambridge University Press; Goldacre, Ben (2012) *Bad Pharma: How drug companies mislead doctors and harm patients*. London: Fourth Estate; and Götzsche, Peter C. (2013) *Deadly medicines and organised crime: How big pharma has corrupted healthcare*. London: Radcliffe Publishing.

[151] Interview with the Medical Products Agency's innovation strategist, 29/04/2013. See also Medical Products Agency (2012), *Innovationskontor ska stödja life science företag* (Innovation office to support life sciences companies); Medical Products Agency (2012), *Vi rustar för att möta nya utmaningar inom hälso- och sjukvård* (We are preparing to meet new challenges within healthcare).

terms of the agency needing to become more receptive to new demands from society through actions such as developing research and innovation support strategies and strengthening the Swedish life sciences.

The Innovation Office organises lectures, seminars and courses at which representatives from pharmaceutical industry and universities are given the opportunity to meet assessors from the Medical Products Agency. In 2014, the Innovation Office also coordinated the agency's work to develop an innovation support strategy, which involved a large number of employees from various operational areas. Nevertheless, in the period in which the audit took place, the Innovation Office and those who work directly in it were organisationally separate from the Medical Products Agency's assessment activities. However, according to subsequent information, the Innovation Office will be closed and integrated into the rest of the organisation.[152]

The Innovation Office cost the Medical Products Agency just over SEK 6.4 million in 2014 and SEK 3.9 million in 2015.[153] Between two and five people worked there during 2015.

3.5.3 Scientific advice

Another promotional aspect of the agency's operations is *scientific advice*. In contrast to the Innovation Office, scientific advice is not organisationally separate from the assessment activities; instead it is assessors who are responsible for providing the advice itself.

The advice is subject to fees and can relate to all parts of the pharmaceutical development process. Companies can choose to purchase scientific advice, either nationally from the Medical Products Agency or internationally from the EMA. The EMA is legally obliged to provide scientific advice.[154] The fee paid by companies for the Medical Products Agency's scientific advice is SEK 45,000. The fee for the EMA's advice is from EUR 41,700 and upwards.[155]

The purpose of the EMA's scientific advice is "to facilitate access of medicinal products to patients and users of medicines by optimising Research and Development, reducing uncertainties in regulatory outcomes, and accelerating time to approval of a marketing

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152 Bergeå Nygren, N. (2016), Medical Products Agency: *Vi stärker innovationsarbetet* (We are strengthening innovation management), *Svensk farmaci*, 25/04/2016.

153 The Medical Products Agency's annual reports 2014 and 2015.

154 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, Celex 32004R0726).

155 Ordinance (SFS 2010:1167) concerning fees for the governmental control of medicinal products; EMA (2015), *Explanatory note on fees payable to the European Medicines Agency*, 30 July 2015, EMA/212803/2015.

authorisation application".[156] The national scientific advice is provided "in order to provide guidance to companies and researchers and facilitate a future approval of clinical trials or marketing authorisation".[157] Accordingly, the written descriptions of the scientific advice emphasise its role of in helping companies to conduct relevant studies so that no major obstacles arise during their development programmes.

Keeping down the cost of developing medicines can be seen as a shared interest of both the pharmaceutical industry and society as a whole. Neither pharmaceutical companies nor government agencies want to discover at a late stage in the development process that certain preclinical studies are missing or that clinical studies that have already been concluded should have been designed differently. By providing scientific advice, medicines agencies can work to ensure that pharmaceutical companies detect such shortcomings earlier.[158] The Medical Products Agency also emphasises that scientific advice can prevent studies being performed on human subjects unnecessarily.[159]

In 2014, the EMA provided scientific advice on 550 occasions. The Medical Products Agency participated on each of these occasions and had a specific coordinating role in 85 of them. The Medical Products Agency also provided national scientific advice on 199 occasions. In principle, all assessors who provide scientific advice also assess marketing authorisation applications. A total of 125 assessors from the Medical Products Agency participated in providing scientific advice in 2014.[160] Scientific advice is strategically important to the Medical Products Agency and is highlighted as a factor that contributes to the Medical Products Agency being appointed so frequently as the assessor of marketing authorisation applications in competition with other medicines agencies in the EU.[161]

According to the managers at the Medical Products Agency responsible for this area, it is generally necessary for the assessor to have good experience of the marketing authorisation assessment process within the area in question in order to provide relevant advice. According to these managers, the fact that the same assessor both provides advice and assesses the application for marketing authorisation does not carry any risk of divided loyalty as the advice is not binding for either the agency or the company. It is also claimed that the fact that many assessors are involved in both providing advice and assessing applications, both at the Medical Products Agency and

156 EMA (2012), *Mandate, objectives and rules of procedure of the scientific advice working party (SAWP)*, 23/08/2012, EMEA/CHMP/SAWP/69686/04Rev 9.

157 Medical Products Agency (2011). *Nationell vetenskaplig rådgivning* (National scientific advice). Instruction 634, Applicable from 12/04/2011.

158 Jonzon, B. & Dunder, K. (2014), *Godkännande av läkemedel*, *Läkemedelsboken*, the Medical Products Agency, p. 1376 f.

159 Information during the Medical Products Agency's factual examination of the report.

160 Email from the head of the Medical Products Agency's Scientific Expertise Unit, 26/05/2015.

161 The Medical Products Agency's annual report 2015, p. 15.

within the EU, means there is no risk of any one individual providing a piece of advice and then enforcing this incorrectly at the time of approval.[162]

At an institutional level, however, the provision of scientific advice may come into conflict with the Medical Products Agency's role as a regulatory and supervisory agency. If a company follows the advice provided, the agency can be regarded as a co-developer of the medicine. This may make it more difficult for assessors, as well as others who have participated in providing the scientific advice, to restrict or reject the marketing authorisation. The Swedish Agency for Public Management identified such a risk in an analysis of the Medical Products Agency in 2009.[163] The Medical Products Agency's scientific advice is not formally binding, but it can still have a more subtle impact on the agency's assessments and decisions. The local instructions for assessing applications for marketing authorisation state that investigators are to describe how the application is consistent with scientific advice.[164] The discussions that take place during the Q meeting also relate to what has been stated in the scientific advice.[165]

In June 2014, the EMA received similar criticism from a range of international organisations representing patient and consumer interests. They claimed that, in practice, scientific advice provides companies with an opportunity to pay for advice about the lowest possible level for marketing authorisation. They also pointed to the fact that the scientific advice is confidential, which means that it is not possible for a third party to assess whether the advice has been provided with sufficient integrity.[166]

3.5.4 The Q group as a standard-setter

The Medical Products Agency's highest quality assurance body (the Q group) addresses all fundamentally important assessment issues within the agency, for example marketing authorisations for medicines, authorisation to conduct clinical trials, pharmacovigilance cases of principal importance and the publication of monographs for medicinal products and treatment recommendations. One important function of the Q group is ensuring that the agency's cases are processed consistently over time.

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[162] Email from the head of one of the Medical Products Agency's efficacy and safety units, 18/06/2015.

[163] Swedish Agency for Public Management(2009), *Analys av Läkemedelsverkets verksamhet och ekonomi*, (Analysis of the Medical Products Agency's operations and finances, 2009:18), p. 10.

[164] Medical Products Agency (2013), *Praktisk vägledning vid CHMP och PRAC-(co-)rapportörskap – Centrala godkännandeproceduren för humanläkemedel – Nyansökan,* (Practical guidance for CHMP and PRAC-(co-)rapporteurship – The central approval procedure for medicinal products for human use – New application), the Medical Products Agency's instruction 707, applicable as of 03/12/2013.

[165] The Swedish NAO's observation of a Q meeting at the Medical Products Agency, 09/05/2014.

[166] Healthcare and social benefits for all, International society of drug bulletins, Medicines in Europe Forum, Health Action International (2014), *Parallel scientific advice: the first step towards undermining independent Health Technology Assessment (HTA)?* Joint response to the EMA's public consultation on its "Best practice guidance for Pilot EMA HTA parallel scientific advices procedures", Brussels, 14/06/2014.

Standards for the decisions made by the Medical Products Agency are set in this way. Approximately 390 cases per year are subject to quality assurance by the Q group.[167]

In the Swedish NAO's interviews, criticism is directed at of how parts of the Q group conduct their assessments by assessors from several parts of the organisation. This criticism concerns attitudes to the management of adverse reaction signals and attitudes to pharmacovigilance. An external consultancy report from spring 2013 describes how the team of doctors at the Clinical Trials and Special Permissions Unit is of the opinion that the Q group's stance is not based sufficiently clearly on a patient safety perspective. According to the report, doctors believe that decisions are sometimes made on "political" rather than scientific grounds. However, according to an internal survey in January 2014, answered by 32 investigators, it is clear that the Q group's work is valued highly with respect to "benefit, significance, clarity, constructive dialogue and reception."[168]

In terms of adverse reactions, it is difficult to prove causal links between a specific incident and the use of a certain medicine, particularly if a patient has one or more underlying diseases. It is difficult to prove what is caused by the medicine and what is caused by the underlying disease and assessors claim that there is a tendency to downplay the incident and say it is caused by the underlying disease when such uncertainty exists. These assessors have provided detailed statements that corroborate this criticism. These statements concern not just the approach of members of the Q group, but also how its activities are governed on a more general level. Several of these assessors have taken the initiative to contact the Swedish NAO and do not want their identity to be revealed to the agency's senior management.

3.5.5 Senior management's role

The Medical Products Agency's senior management group as a whole contends that there is no clear incompatibility between, on the one hand, regulating medicines and, on the other, promoting their development, and that both of these activities promote the ultimate objective of safeguarding public health. However, different members of the group have different approaches to relationships with pharmaceutical companies. One points to the large influx of staff from industry having resulted in the agency having a clearer "customer focus". Another, however, reflects on how much a part of companies' pharmaceutical development the Medical Products Agency can be and is of

[167] Medical Products Agency (2014), *Utvärdering intern kvalitetssäkring QT och QP 2013-14* (Evaluation internal quality assurance QT and QP 2013-14), Internal rapport from the Medical Products Agency 20/03/2014, Preliminary version.

[168] Medical Products Agency (2014), *Utvärdering intern kvalitetssäkring QT och QP 2013-14* (Evaluation internal quality assurance QT and QP 2013-14), Internal rapport from the Medical Products Agency 20/03/2014, Preliminary version.

the opinion that is not good if the agency appears to be acting as a consultant to the pharmaceutical industry.

The Medical Products Agency's senior management points out that the innovation remit it has been given by the Government is not sufficiently concrete. For example, it is unclear how much the agency should prioritise activities that promote innovation.

The senior management group is aware that there are tensions between parts of the organisation and is working actively to deal with the part that is judged to have the most conflict. The senior management group believes it is vital to the agency that there are shared values encompassing respect for different areas of expertise. The agency admits that the fact that its employees have taken the initiative to meet with the Swedish NAO while stressing that their identity should not be revealed to senior management, is an alarming sign and a work environment issue the agency needs to deal with.

One member of the senior management group claims that the tensions within the organisation can be partly explained by the fact that different groups of assessors have different knowledge about patient benefit and about the potential of new medicines. Depending on their knowledge profile and role in the organisation, different groups of assessors may place greater emphasis on either the development of medicines or safety assessment. Both approaches are compatible with a desire to promote patient benefit, but they result in different conclusions concerning how the Medical Products Agency should act to achieve this aim. The senior management group's attitude is that the agency should strive for good relations with the pharmaceutical industry in order to promote the development of new medicines, which is also in line with the agency's innovation promotion remit. The consequences of this include the agency's prioritisation of the rapid turnaround of all cases, including pharmacovigilance cases.[169]

A recurring problem for the Medical Products Agency is the difficulty of recruiting staff with clinical expertise, i.e. assessors with a medical background. Clinical assessors are expected to have medical degree and clinical experience, but because of circumstances such as the shortage of doctors, experienced pharmacists are now also working as clinical assessors. The difficulty in recruiting and retaining doctors is chronic and has existed ever since the National Board of Health and Welfare was responsible for medicines regulation (1971–1990).[170] Clinical assessors with a medical background are important as doctors are best equipped to assess a medicine's clinical relevance and can also expected to be particularly well qualified to assess the medicine on the basis of a patient perspective.

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[169] Meeting with the Medical Products Agency's senior management group, 18/05/2015.

[170] See, for example, Ds S 1978:12, *Den statliga läkemedelskontrollen: uppgifter, organisation och finansiering*, (Central government medicines regulation: remit, organisation and funding) and SOU 1987:20, *Läkemedel och hälsa: betänkande av 1983 års läkemedelsutredning* (Medicines and health: report of the medicines inquiry of 1983).

Several explanations for the chronic staffing problem emerge from the Swedish NAO's interviews with managers and assessors. One explanation is that many doctors look for employers where there appears to be better opportunities to conduct research and take part in further academic training. Many doctors also want to meet with patients, which they do not have the opportunity to do as assessors at the Medical Products Agency. The clinical assessors interviewed also believe that the Medical Products Agency does not offer competitive salaries.

3.6 Summary of findings

3.6.1 The Medical Products Agency has lowered the priority of certain assessments of medicines' risks

The Medical Products Agency is of the opinion that there is a lack of resources at the Clinical Trials and Special Permissions Unit, the unit for pharmacovigilance unit and the Supervision Department. What these units have in common is that they are responsible for those aspects of the agency's work that are more purely safety-oriented.

The Swedish NAO has also found that the Medical Products Agency assigns a lower priority to assessments of certain purely safety-oriented tasks. Safety reports submitted during ongoing clinical trials (DSURs) are not processed, there have been delays to the processing of safety reports submitted following the medicine's authorisation (PSURs), the number of inspections of clinical trials has decreased and the level of ambition with respect to the assessment of adverse reaction reports from healthcare personnel and the general public has decreased. The causes of this are said to be a shortage of personnel and resources. The Medical Products Agency has also questioned the value of some of the afore-mentioned activities. In addition, the Swedish NAO is of the opinion that there is a risk that chronic shortage of clinical assessors has an impact on the agency's ability to assess the safety of medicines.

The fees paid by companies have to cover the cost to the Medical Products Agency of assessing these companies' applications. The Medical Products Agency has requested that the fees be increased so that the agency is able to assess the safety reports submitted by companies during ongoing clinical trials. At the same time as the agency points to inadequate resources, its funds are used for innovation promotion activities for which it is not compensated through appropriations.

The Medical Products Agency's senior management has a challenging task of steering towards the right balance between, on the one hand, getting medicines onto the market quickly and, on the other, ensuring that there is sufficient knowledge about the risks of medicines. Senior management's attitude is that the agency aim to have good relations with companies, the consequences of which include an explicit prioritisation of the

quick turnaround of companies' applications. However, the endeavour to process applications quickly may have had an impact on the agency's ability to conduct purely safety-oriented tasks.

3.6.2 The Medical Products Agency does not maintain sufficient separation between its promotional and regulatory duties

The Medical Products Agency is primarily a regulatory and supervisory authority. This means that the agency must ensure that pharmaceutical companies' economic interests are not pursued at the expense of pharmaceutical safety. In addition to regulation and supervision, the agency is tasked with making it easier for pharmaceutical companies to develop new medicines. This takes place mainly through the provision of scientific advice and innovation support to pharmaceutical companies. Simultaneously regulating and promoting the companies' activities means that conflicts of interest may arise at the agency. A common way to deal with potential conflicts of interest is to maintain a separation in central government between promotional and regulatory activities so that they can operate independently of one another. One example of this is when the Health and Social Care Inspectorate (IVO) took over the supervisory responsibilities of the National Board of Health and Welfare. However, in the Medical Products Agency there is a tendency towards less separation of these duties. For example, the Innovation Office is to be closed down and its work integrated more clearly into the agency. Another example is that certain safety assessments, which were previously conducted by the Pharmacovigilance Unit, are now being moved to the units for efficacy and safety where assessments prior to market authorisation are performed.

3.6.3 The Government's management of the Medical Products Agency sends mixed messages

In recent years the Government has pursued a pharmaceutical policy that actively promotes innovation and involves the Medical Products Agency. The Government has gradually changed the role of the Medical Products Agency from regulation and supervision to also encompassing the promotion of the development of new medicines. In some respects this policy has made the Medical Products Agency's already difficult task of striking a balance between various ways of promoting public health even more difficult. The conflict of interest that exists in the area of pharmaceuticals has thus been more clearly incorporated into the agency. The change also involves a shift in roles that may impair the agency's ability to maintain a sufficient degree of integrity in relation to the pharmaceutical industry.

3.6.4 The model for the Medical Products Agency's fee-based funding may lead to the wrong priorities

The bulk of the Medical Products Agency's revenue comes from the fees paid by pharmaceutical companies for the agency's assessments. By acting to ensure a large allocation of assessment commissions from the EMA, the agency can increase its revenues. Even before Sweden joined the EU, the Medical Products Agency assessed that a large number of EMA commissions (rapporteurships) is a key measure through which to safeguard the agency's turnover. The Swedish NAO's audit shows that the Medical Products Agency has lowered the priority of purely safety-oriented tasks for a period of time in favour of more EU rapporteurships that generate revenue. That it is possible for a regulatory and supervisory agency to increase its revenue by lowering the priority of work involving safety may justify a review of the agency's funding model.

3.6.5 Significant closeness to pharmaceutical companies challenges the integrity of the Medical Products Agency

The Swedish NAO's assessment is that the agencies manage the risk of individual conflicts of interest correctly at a procedural level, for example through conflict of interest declarations. Each year, all assessors have to submit a conflict of interest declaration that is assessed by their line manager. About half of the assessors have stated that they have current or previous interests in companies that are affected by the activities of the Medical Products Agency. About half the assessors who have left the agency have taken up employment with a pharmaceutical company.

It is, of course, not necessarily the case that assessors with clear links to industry are more inclined to promote the interests of pharmaceutical companies. However, when a large proportion of assessors have links to the pharmaceutical industry, this may, at an overarching level, impair the agency's ability to safeguard its integrity and strike the correct balance between positive values.

4 Central government knowledge-based management

4.1 Greater ambition for knowledge-based management

As is the case for other treatments delivered in the Swedish healthcare system, pharmaceutical treatment is to take place based on scientific knowledge and proven experience. The central government provides support for evidence-based prescribing of medicines by publishing product information, knowledge support and recommendations. However, it is up to prescribers to determine which medicine is to be prescribed to which patient, what dose they are to receive and how the medicine is to be administered.

The quantity of medical academic literature has increased. The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) assesses that approximately 1.4 million scientific articles evaluating different treatment methods are published each year.[171] According to a report from the National Board of Health and Welfare, the increase in the quantity of knowledge, combined with improved efficiency requirements in the healthcare system, have resulted in "a change to the professional culture that involves doctors becoming increasingly dependent on recommendations, the basis of which they are increasingly unfamiliar with".[172] In view of this, it is particularly important that the knowledge that central government agencies produce and provide to healthcare is based on sound assessments of information and knowledge, and has a high level of credibility.

In recent decades, central government has gradually raised its level of ambition in terms of knowledge-based management within the healthcare system. For example, the Government's special inquiry into care efficiency proposed in December 2014 that national guidelines be made mandatory within the healthcare system and a central government inquiry has proposed that central government initiate a new form of

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171 SBU (2014), *Utvärdering av metoder i hälso- och sjukvården: En handbok.* (Evaluation of methods in the healthcare system: A handbook). 2 ed. Stockholm: The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU), p. 7.

172 National Board of Health and Welfare & Swedish Association of Local Authorities and Regions (2009), *Mot en effektivare kunskapsstyrning – Kartläggning och analys av nationellt och regionalt stöd för en evidensbaserad praktik i hälso- och sjukvården* (Towards more effective knowledge-based management – Survey and analysis of national and regional support for evidence-based practice in healthcare), p. 54.

national treatment recommendations directed at healthcare personnel.[173] The Government has also recently established a new advisory body, the Council for Knowledge-based Management, in order to increase cooperation between agencies that are charged with knowledge-based management in the area of health and social care.[174]

4.2 Knowledge-based management in the area of pharmaceuticals

When a medicine is approved and the SPC is published, researchers and pharmaceutical companies continue to generate new knowledge about the medicine. This knowledge results in, for example, articles published in scientific journals. In order to assist the healthcare system to choose priorities on the basis of the sum of this knowledge, central government produces guidance documents that are public. The documents in focus in this audit are: the Medical Products Agency's treatment recommendations, SBU's literature reviews and the National Board of Health and Welfare's national guidelines.

Based on the description of the problem presented in Chapter 2, the agencies need to deal with two problems: 1) bias in published material and 2) conflicts of interest among external experts. We have audited what steps the agencies take to minimise the negative consequences of these problems when developing recommendations, literature reviews and guidelines for the healthcare system.

Table 4.1 Central government knowledge-based management tools included in the Swedish NAO's audit

Documents	Agency in charge
Treatment recommendations, summary of product characteristics (SPC)*	The Medical Products Agency
Systematic literature reviews	SBU
National guidelines	The National Board of Health and Welfare

**The work involved in establishing these is described in Chapter 3.*

[173] Ministry of Health and Social Affairs (2014), *Diskussions-PM från utredningen En nationell samordnare för effektivare resursutnyttjande inom hälso- och sjukvården* (Discussion memo from the inquiry A national coordinator for more efficient use of resources within the healthcare system, S 2013:14), pp. 22 f.

[174] Ordinance (2015:155) on central government knowledge-based management of healthcare and social services.

4.2.1 *The National Board of Health and Welfare's national guidelines*

The instructions for the National Board of Health and Welfare state that the board is to contribute to healthcare and social services being managed in accordance with scientific evidence and proven experience through knowledge development, knowledge support and regulation.[175] These instructions also refer to the new ordinance that regulates government agencies' knowledge-based management within healthcare and social services.[176] This states that central government knowledge-based management takes place through means including non-binding knowledge support with the purpose of contributing to healthcare and social services being managed in accordance with scientific evidence and proven experience. This knowledge is aimed at supporting the authorities responsible (county councils/regions and municipalities) and the various professions responsible for ensuring that patients and service users are provided with a good standard of care in accordance with the Health and Medical Services Act (1982:763). In its appropriation directions for 2016, the National Board of Health and Welfare has also been charged with reporting on initiatives that promote innovation within the agency's area of responsibility.[177]

The National Board of Health and Welfare publishes *national guidelines* containing recommendations on priorities that concern the major widespread diseases. These recommendations are to serve primarily as guidance for decision makers when prioritising the organisation of care, but they can also constitute a basis for the design of county councils' care programmes. As of July 2015, when the new knowledge-based management ordinance[178] came into force, SBU is now drawing up the evidence base for national guidelines.[179] Previously the National Board of Health and Welfare used literature reviews from sources including SBU, when these were available for the subject in question. In other cases, the National Board of Health and Welfare conducted its own systematic review of the scientific literature, often with the aid of a large number of external experts.[180]

In line with the increased ambitions, the number of knowledge overviews and guidelines produced by central government has increased and more experts have been involved. For example, the National Board of Health and Welfare's first national guidelines (for diabetes care) were written by two experts in 1996. Now there are fifteen

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175 Ordinance (2015:284) with instructions for the National Board of Health and Welfare.

176 Ordinance (2015:155) on central government knowledge-based management of healthcare and social services.

177 Ministry of Health and Social Affairs (2015), Appropriation directions for the budget year 2016 regarding the National Board of Health and Welfare.

178 Ordinance (2015:155) on central government knowledge-based management of healthcare and social services.

179 SBU's annual report 2015, p. 5.

180 National Board of Health and Welfare (2013), *Rutin 4.1 Vetenskapligt underlag. Ledningssystem Rut (Procedure 4.1 Scientific Evidence. Management System Procedure)*.

current guidelines, each of which has involved up to one hundred external experts. The National Board of Health and Welfare now directs over 2,600 recommendations at the healthcare system.[181]

4.2.2 *The Medical Products Agency's treatment recommendations*

The Medical Products Agency has effects on the prescription of medicines through means including the *treatment recommendations* that the agency publishes for certain selected disease areas.[182] These are principally directed at prescribers and primarily concern pharmaceutical treatment, but may also cover other treatment methods. The treatment recommendations do not relate to individual medicines, rather to entire groups of medicines, for example medicines that reduce blood pressure. The treatment recommendations are primarily based on external expert knowledge and published studies, not on the evidence the Medical Products Agency used in connection with, for example, decisions concerning the marketing authorisation of a medicine. However, staff from the Medical Products Agency participate in the production of treatment recommendations and the approved product information serves as a foundation for this work.[183]

4.2.3 *SBU's systematic literature reviews*

The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) is tasked with scientifically evaluating the use of current and new medical methods in the healthcare system from a medical, economic, social and ethical perspective.[184] SBU is also given more specific commissions through its appropriation directions. For example, the agency runs an information service to which healthcare personnel can turn when they have clinical questions that require a quick evaluation of the scientific evidence. SBU is also charged with reviewing and disseminating international literature reviews and medical evaluations and with identifying knowledge gaps of strategic importance.[185]

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[181] Swedish NAO (2013), *A Greater Patient Perspective in Healthcare – Are National Guidelines a Method of Achieving This?* RiR 2013:4, pp. 13, 36, 48; Swedish Agency for Health and Care Services Analysis (2015), *Lång väg till patientnytta – en uppföljning av nationella riktlinjers inverkan på vården i ett decentraliserat system*, (Long path to patient benefit – a follow-up of national guidelines' impact on care in a decentralised system), p. 43.

[182] Other important documents include monographs for medicinal products and information from the Medical Products Agency.

[183] Medical Products Agency (date missing), *Utarbetande av behandlingsrekommendationer och kunskapsunderlag Instruktion* 00680 (Preparation of treatment recommendations and evidence bases Instruction 00680).

[184] Ordinance (2007:1233) with instructions for SBU.

[185] Ministry of Health and Social Affairs (2014), Appropriation directions for the budget year 2016 regarding SBU.

SBU publishes *literature reviews* that are to function as guidance for healthcare personnel and decision makers at various levels. They constitute an important basis for the National Board of Health and Welfare's national guidelines, but also have a direct impact on priorities within the healthcare system.[186] The literature reviews are produced by conducting systematic reviews of the scientific literature and assessment of the effects and risks associated with different treatment methods. Alongside the scientific literature, external experts have an important function.

SBU describes itself as an independent agency that produces impartial and scientifically reliable evidence on which to base decisions. The agency has an explicitly critical attitude to the pharmaceutical industry's informational advantage and has provided concrete examples of when the agency has acted to nuance information from pharmaceutical companies that has been "entirely positive and biased".[187]

4.3 Government agencies' correction of bias in published material

As seen in Chapter 2, there is bias in the published research concerning medicines. Literature reviews and guidelines that are based exclusively on published studies therefore risk suffering from the same bias.[188] The assessors and experts interviewed by the Swedish NAO are well aware of this problem. Public officials and experts at the three agencies concerned point to an investigation conducted at the Medical Products Agency in 2003. This showed that the documentation companies submit to the Medical Products Agency in conjunction with marketing authorisation applications provides a more comprehensive and balanced view than the published material to which other agencies, prescribers and researchers have access.[189]

4.3.1 The Medical Products Agency

Several circumstances indicate that the Medical Products Agency's treatment recommendations are not particularly affected by bias in published material. When the Medical Products Agency draws up treatment recommendations, it has access to all the documentation from clinical trials submitted by pharmaceutical companies in conjunction with marketing authorisation applications. The agency's internal experts also have thorough knowledge of this material. Each treatment recommendation is subject to quality assurance by the same group of assessors (Q group) as is responsible

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186 SBU (2014), *Utvärdering av metoder i hälso- och sjukvården: En handbok*. (Evaluation of methods in the healthcare system: A handbook).

187 SBU (2012), *SBU påverkar vården – ett försök att värdera effekterna av kunskapsspridning* (SBU has an impact on care – an attempt to evaluate the effects of knowledge dissemination), order number: 902-17.

188 See, for example, Schroll, J. & Bero, L. (2015), Regulatory agencies hold the key to improving Cochrane Reviews of drugs [editorial]. *Cochrane Database of Systematic Reviews* 2015(4).

189 Melander, *et al.,* (2003), Evidence b(i)ased medicine – selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications, *British Medical Journal* 31(326).

for the quality assurance of assessments of applications for marketing authorisation and clinical trials. This team is thus able to react if a treatment recommendation clearly deviates from the view that has emerged in the previous assessment material. At the same time, there are indications that there is the potential to make more use of the Medical Products Agency's internal knowledge and expertise in work involving treatment recommendations.

An important element of the formulation of the treatment recommendation is a seminar that is dominated by external experts, but at which the Medical Products Agency's own assessors also participate. Normally, some of the external experts are commissioned to write a background chapter based on their own literature search and proven experience prior to this meeting. Sometimes the Medical Products Agency's assessors are also engaged to write a background chapter.[190]

The main evidence base for the experts' background chapter consists of articles published in scientific journals. The chapter's authors are responsible for the literature search, but can receive help with finding published literature from the Medical Products Agency's information specialist. If SBU or any other agency has produced a systematic literature review, the Medical Products Agency uses this in the process of drawing up a specific treatment recommendation. In such cases, the Medical Products Agency is dependent on the agency that conducted the search having corrected for any problems pertaining to selective publishing.[191] According to an expert at the Medical Products Agency's medical information unit, the EMA's publically accessible assessment reports are also used as a basis of treatment recommendations. However, the internal instructions contain no indication as to whether assessment reports, be they public or internal, should be included in the evidence base.[192]

The Medical Products Agency has published 18 treatment recommendations since 2012. The Swedish NAO's review of these documents indicates that the participation of internal experts as authors of the material has declined. In the first two years of the period, internal experts were authors in five out of seven (71 per cent) of the recommendations that were published. In the last two years, the corresponding proportion was three out of eleven (27 per cent). The Swedish NAO's interviews with external experts and the Medical Products Agency's assessors confirm that relatively limited use is made of internal expertise and internal assessment material.[193] Nobody

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190 Medical Products Agency (date missing), *Utarbetande av behandlingsrekommendationer och kunskapsunderlag*. Identity number 00680, version 2.

191 Ibid.

192 Email from an expert at the Medical Products Agency's medical information unit, 21/01/2016.

193 This is evident from interviews with marketing authorisation assessors, interviews with senior experts at the Medical Products Agency's medical information unit and the Medical Products Agency's internal instructions for the preparation of treatment recommendations: Medical Products Agency (date missing), *Utarbetande av behandlingsrekommendationer och kunskapsunderlag*. Identity number 00680.

has been able to provide examples where internal experts have supplied essential information from the Medical Products Agency's own assessments.

4.3.2 *The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)*

The SBU demonstrates an awareness of bias in published material and also takes concrete action to counter this. This is evident in both the interviews and the handbook in which the SBU describes its work involving systematic literature reviews. For example, it is pointed out in the handbook that "studies sponsored by the industry or other actors with vested interests in their results exaggerate the efficacy of their products".[194] The handbook also emphasises the importance of forming an opinion as to whether the literature review has captured all relevant articles.[195]

The SBU requested unpublished information from various pharmaceutical companies on one occasion. However, it took a long time to obtain responses from the companies and it became clear that at least one company failed to provide a large unpublished trial which showed that the medicine in question did not have the intended effect. Two of the companies demanded that the SBU sign a confidentiality agreement that was so comprehensive it would have, in practice, made the material unusable. The assessors realised that this initiative was very time-consuming and resource-intensive and did not provide any material of value.[196]

As a rule, the SBU does not request any information directly from companies or ask the Medical Products Agency for any unpublished information. Instead, statistical methods are used to estimate the risk of the published material being biased. The methods are based on the assumption that the largest studies provide the most reliable assessment of the effects of a medicine. If all the studies have been published, the results of smaller studies are expected to be distributed evenly around the largest studies. This means that the number of studies that are more positive is deemed to correspond to the number of studies that are more negative. However, if the majority of the smaller studies are more positive, this is seen as an indication of bias, i.e. there are a number of negative studies that have not been published. SBU then downgrades the value of the smaller studies that have been published.[197]

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194 SBU (2014), *Utvärdering av metoder i hälso- och sjukvården. En handbok*, p. 147.

195 Ibid., p. 55.

196 Eliasson, M. & Bergqvist, D. (2001), *Forskningsresultat bör vara allmänt tillgängliga! Fallbeskrivning visar hinder vid kontakt med läkemedelsindustrin* (Research results should be freely accessible! Case reports demonstrate obstacles in contact with the pharmaceutical industry), *Läkartidningen* 98(37), p. 3913–3916.

197 Interview with a head of programme and two project managers at SBU, 02/12/2014. The statistical methods for this are referred to as *funnel plots* and *trim and fill* and are described in SBU(2014), *Utvärdering av metoder inom hälso- och sjukvården. En handbok*, pp. 124 ff.

Accordingly, this method contributes to the detection of potential problems of bias in published research and their rectification using statistical methods. However, it can be questioned whether this method is adequately effective. The fact is that it is based on a number of assumptions that are rarely completely fulfilled. One such assumption is that selective publication mainly applies to small studies and that large studies are almost always published, irrespective of the results. However, research has shown that it is also not uncommon for large studies to remain unpublished.[198] The SBU has itself had this experience in connection with a literature review.[199]

When a large study remains unpublished, you can assume that the results are mostly negative as positive results would have been good marketing for those behind the study. The consequence of a large study not being published is that the large studies which *are* published risk constituting an incorrect reference point.

Another assumption is that bias in published material primarily arises because some of the scientific evidence is unpublished, i.e. selective *publication*. According to research, however, significant bias arises as a result of the studies that are published reporting an elevated effect for the medicines studied.[200] Such selective *reporting* cannot be corrected using statistical methods. In order to detect and rectify this, documentation that more correctly represents the results of clinical trials must be read. For reasons such as this, researchers and certain European agencies request access to the regulatory material companies have produced in connection with, for example, applications for marketing authorisation.[201]

4.3.3 The National Board of Health and Welfare

According to officials at the National Board of Health and Welfare and experts linked to the board's work with guidelines, the board does not have access to the results reports received from pharmaceutical companies by the Medical Products Agency in conjunction with assessments marketing authorisation applications. As a rule, the National Board of Health and Welfare does not attempt to access this information through either the Medical Products Agency or the pharmaceutical companies

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198 See, for example, World Health Organization (2015), *WHO Statement on Public Disclosure of Clinical Trial Results* and Jones C. *et al.,* (2013), Non-publication of large randomized clinical trials: cross sectional analysis, *British Medical Journal* 347.

199 Eliasson, M. & Bergqvist, D. (2001), *Forskningsresultat bör vara allmänt tillgängliga! Fallbeskrivning visar hinder vid kontakt med läkemedelsindustrin, Läkartidningen* 98(37).

200 See, for example, Melander, H. *et al.,* (2003), Evidence b(i)ased medicine – selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications, *British Medical Journal* 31(326).

201 See, for example, Köhler, M. (2015), Information on new drugs at market entry: retrospective analysis of health technology assessment reports versus regulatory reports, journal publications, and registry reports, *British Medical Journal* 350(796), and Hart, B. *et al.,* (2012), Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses, *British Medical Journal* 2012:344.

concerned. As is the case for the Medical Products Agency, the National Board of Health and Welfare uses the SBU's literature reviews, when available, and thus relies on the SBU having corrected any potential bias.

The National Board of Health and Welfare's internal procedure for the production of scientific evidence states that only studies published in full text are to be reviewed, but that unpublished material can provide important information for answering questions about publication bias. However, this does not provide more detail as to which type of unpublished documentation is being alluded to, how the board's external experts are to gain access to it or how it is to be used.[202]

According to officials from the Government Offices of Sweden, it is up to the National Board of Health and Welfare and the SBU to define which evidence base is to form the foundation knowledge-based management.[203]

4.3.4 *New opportunities to correct bias*

There are two registers of clinical trials that are particularly relevant to Swedish agencies and researchers: the EMA's register *EudraCT* and the FDA's register *ClinicalTrials.gov*. Both of these registers have been developed with the aim of creating transparency and overview of the trials being conducted. The intention is to enable researchers and government agencies to find unpublished trials in the registers and put pressure on companies to share the results of these trials.[204]

EudraCT primarily covers trials that have been conducted in Europe since 2004.[205] However, the evidence base for the medicines currently being prescribed is largely derived from trials conducted prior to 2004 and the results of these trials are not in EudraCT. Furthermore, many clinical trials have been conducted outside of Europe and are therefore not included in the register. Consequently, the Swedish experts that the Swedish NAO has interviewed rarely refer to EudraCT, but instead refer to ClinicalTrials.gov, which is considered to be more comprehensive.

ClinicalTrials.gov primarily covers trials that have been conducted in the US since 1997. To a certain extent, this also includes trials that have been conducted outside of the US, but the degree of coverage in this respect is uncertain. In accordance with US legislation, registration has been mandatory since 2007, but research shows that, in spite of this, the degree of reporting of trial results is still low. Of the close to 13,000 registered US studies that have been concluded since 2008, the results of only 13 per

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202 National Board of Health and Welfare (2013), *Rutin 4.1 Vetenskapligt underlag. Ledningssystem Rutin*.
203 Meeting with public officials at the Ministry of Health and Social Affairs, 04/12/2014.
204 Dickersin, K. & Rennie, D. (2012), The Evolution of Trial Registries and Their Use to Assess the Clinical Trial Enterprise, *Journal of the American Medical Association, JAMA* 307(17), p. 1861.
205 See EudraCT's website: www.clinicaltrialsregister.eu/about.html, accessed 21/12/2015.

cent had been reported to the register one year after completion of the study.[206] Other studies also show similar results.[207]

If it is to be possible to use the registers to correct for selective publication, government agencies and experts need to search in the registers, note which completed studies have not been published, study the reported results and incorporate them into their assessments of the properties of the medicine in question. If the results are not reported, agencies and experts need to request that the companies responsible disclose information about them.

The Swedish NAO's interviews with experts and officials at the agencies audited show that these registers are not used in a systematic manner. All of the interviewees are also hesitant about requesting information concerning unpublished studies directly from companies.

The EMA publishes assessment reports (*European public assessment reports*, EPARs) concerning authorised medicines on its website. EPARs provide a comprehensive view of which trials have been conducted for a certain medicine, the methodological format of these trials and what effects and adverse reactions have emerged in the trials. Several experts that the Swedish NAO has interviewed claim that this has contributed considerably to combating the problem of bias in published material.[208] However, the same experts state that they do not use these reports in their literature reviews and national guidelines, which appears to be contradictory. Representatives of the National Board of Health and Welfare's work with national guidelines justify this by stating that regulatory material (e.g. EPARs) falls outside of the agency's definition of what can be included in their evidence bases. Representatives of the SBU's literature reviews are of the opinion that EPARs contain less detailed information than published studies and that it can therefore be difficult to include data from these documents in the evidence base of a literature review. However, the SBU may use EPARs to obtain information about which relevant studies have been conducted and which studies might be missing from the SBU's evidence base.

4.3.5 British and German agencies have made more progress ...

The dominant perception among the Swedish agency experts and assessors interviewed by the Swedish NAO is that the existence of clinical trial registers and assessment reports means that the problem of bias in published material primarily is a thing of the

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206 Saito, H. & Gill, C. (2014), How frequently do the results from completed US clinical trials enter the public domain? A statistical analysis of the ClinicalTrials.gov database, *PLoS One*. 2014;9(7).

207 See, for example, Prayle, A. *et al.,* (2012), Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study, *British Medical Journal* 2012(344).

208 Interview with a head of programme at SBU, 02/12/2014; interviews with two senior experts linked to the National Board of Health and Welfare's work on guidelines, 10/02/2015 and 18/02/2015.

past. The Swedish NAO is of the opinion that this perception can be called into question based on examples of how British and German agencies manage bias in published material.

The SBU and the National Board of Health and Welfare's German and British counterparts have been more active in pointing out how their literature reviews are affected by bias in their evidence base.[209] In the United Kingdom, the *National Institute for Health and Care Excellence* (NICE) produces literature reviews and issues national guidelines. The NICE routinely asks pharmaceutical companies to submit reports concerning unpublished results that relate to the medicines the agency is evaluating.[210] If the company is global, the NICE demands that the company's British branch declare that all relevant results have been reported.[211]

The NICE has some opportunities to impose sanctions if a company does not submit the requested data. It can, for example, defer the publication of a literature review or a guideline, or fail to recommend treatment using a certain medicine, referring to the fact that unpublished data has not been made available as grounds for the decision. When the NICE does not receive commitments from the company at a global level, it relies on the assessment reports (EPARs) published by the EMA subsequent to marketing authorisation.[212]

The SBU's German counterpart, the *Institute for Quality and Efficiency in Health Care* (IQWIG), demands that pharmaceutical companies share results of all trials they have financed. If a company does not submit material within the stipulated time, the agency does not conduct an assessment of the company's medicine and comments on this in the published literature review. The IQWIG also routinely accesses regulatory material from the German equivalent of the Medical Products Agency, preferably in the form of final reports from clinical trials, i.e. the reports described in Chapter 3.2.4.[213]

4.3.6 ... but are still subject to criticism

Several parliamentary committees of inquiry in the United Kingdom and also the National Audit Office (NAO), which is the British equivalent of the Swedish NAO, have criticised NICE for not fully ensuring that it has complete information about medical treatments prior to the publication of literature reviews and national guidelines. The NAO is of the opinion that the NICE should also demand a statement from companies at a global level in order to ensure that all relevant trial results have been provided to

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209 EMA (2014), Overview of comments received on "Publication and access to clinical-trial data", EMA/240810/2013, pp. 58 ff., pp. 67 ff.

210 NICE (2013), *Guide to the methods of technology appraisal 2013, Process and methods guides*, http://publications.nice.org.uk/pmg9, p. 24, accessed 20/04/2015.

211 NAO (2013), *Access to clinical trial information and the stockpiling of Tamiflu*, p. 19.

212 Ibid.

213 IQWIG, (2015), *General Methods,* version 4.2.

the agency. The NAO is also critical of the fact that the NICE does not gain access to regulatory information about medicines that is held by the British medicines agency, the *Medicines and Healthcare Products Regulatory Agency* (MHRA). Therefore, the NAO recommends that these agencies initiate collaboration on information sharing. According to the NAO, the lack of such information sharing means that companies are encumbered with unnecessary information requirements when the MHRA and NICE request the same information and that the NICE risks receiving incomplete information on which to base its assessments.[214]

In 2013 the parliamentary committee of inquiry, the *Committee of Public Accounts*, concluded that results of clinical trials constitute the most important evidence when doctors, researchers and agencies assess how effective and safe medicines are. The committee recommends that NICE:

1. ensure it receives full methods and results of all clinical trials for all illnesses which are covered by the guidelines, including final reports (CSRs) if necessary
2. make this information available for independent scrutiny
3. routinely audit the completeness of the information received

The committee also recommends that the NICE and the MHRA draw up a formal information sharing agreement in order to ensure that the NICE has access to all regulatory information to which the MHRA has gained access to through the application procedures.[215]

4.4 Conditions for information sharing between Swedish government agencies

Based on the above reasoning, researchers and organisations that provide knowledge-based guidance to the healthcare system, government agencies such as the National Board of Health and Welfare and the SBU may have an interest in gaining access to the clinical study reports pharmaceutical companies submit to medicines agencies. These reports contain the most detailed results and are not affected by the bias there is in published material. However, this documentation is extensive, often covering several thousand pages, and it may be difficult to obtain access to. Both pharmaceutical companies and the EMA have also been unwilling to share these reports (see Chapter 2).

When the Medical Products Agency is responsible for assessments within the EMA, the agency prepares its own assessment reports. These reports are not published, but the

[214] NAO (2013), *Access to clinical trial information and the stockpiling of Tamiflu*, p. 9.
[215] House of Commons Committee of Public Accounts (2014), *Access to clinical trial information and the stockpiling of Tamiflu, Thirty-fifth Report of Session 2013–14*, p. 5.

Medical Products Agency can, upon request, provide the documents to the SBU and the National Board of Health and Welfare following a confidentiality assessment.[216] Researchers have recently shown that the use of such more easily-accessible regulatory material may be one of the most time-efficient measures of counterbalance bias in published material.[217]

According to the Swedish NAO, there are no conclusive legal obstacles to such information sharing between government agencies in Sweden.[218]

4.5 Government agencies' view of external experts and the risk of harming trust in government

The fact that experts engaged by government agencies have worked for pharmaceutical companies risks having an impact on both the agencies' ability to act in accordance with the Instrument of Government's requirements for objectivity and impartiality and on public trust in the agencies' activities. The public officials at the National Board of Health and Welfare, the SBU and the Medical Products Agency that the Swedish NAO has interviewed view this risk of harming the trust seriously and therefore give careful consideration to which experts it is appropriate to appoint.

In September 2014, the Swedish Union of Civil Servants (ST) reviewed conflict of interest declarations from 55 experts who were engaged within the framework of the Medical Products Agency's work on treatment recommendations. Of these 55 experts, 30 reported links to, primarily, pharmaceutical companies. In a comment in the union's magazine *Publikt*, the Medical Products Agency states that it is difficult to find independent experts and that the requirements imposed by the Government and the Riksdag that researchers are to collaborate with industry have contributed to this problem.[219]

In several cases, agencies have acted to limit the harm that may be done to the trust in government when the independence of experts is called into question. One example is that the Medical Products Agency cancelled a meeting of experts concerning treatment recommendations for ADHD; according to the official responsible at the Medical Products Agency, all these experts were a part of strategic advisory teams at companies that market ADHD medicines. The same thing happened with another meeting of experts concerning treatment recommendations for thromboembolic disease among

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216 Interview with chief statistician at the Medical Products Agency, 27/04/2015.

217 Schroll, J. *et al.*, (2015), The Food and Drug Administration reports provided more data but were more difficult to use than the European Medicines Agency reports, *Journal of Clinical Epidemiology*, 68(1).

218 See Appendix 4 for justification of this statement.

219 Bjärvall, K. (2014), *Forskare på dubbla stolar* (Researchers wearing two hats), *Publikt*, 16/09/2014, http://www.publikt.se/artikel/forskare-pa-dubbla-stolar-17047, accessed 20/08/2015.

children; in this case, half of the experts were judged to have strong links to pharmaceutical companies. It was possible to hold the ADHD meeting at a later date, but there has been media criticism because several of the experts had links to pharmaceutical companies.[220] According to the same official, it has not yet been possible to hold the meeting about thromboembolic diseases.[221]

The experts and officials at the National Board of Health and Welfare, the SBU and the Medical Products Agency interviewed are worried that the agencies' credibility may be affected by suspected links among external experts. However, the Swedish NAO notes that they are not as worried that the content of their agencies' documents may be influenced in an inappropriate manner. The Medical Products Agency maintains that it does not know of any examples of such influence.

4.6 Summary of findings

4.6.1 The Medical Products Agency, the SBU and the National Board of Health and Welfare have insight into the problem of bias in published material, but do not adequately compensate for it

Central government knowledge-based management, which forms the basis of the healthcare system's priorities, is based on different types of evidence: scientific literature, expert knowledge and, to a small degree, regulatory material. The emphasis on articles published in scientific journals means that the evidence risks being influenced by the bias there is in published material. The agencies have insight into the problem of bias in the scientific literature, but claim that it only has limited consequences for their work of producing recommendations, literature reviews and guidelines.

The agencies audited only partially utilise the opportunities there are to combat the probable consequences of proven bias. While it is true that SBU makes statistical corrections in its evaluations of the efficacy and harmful effects of medicines, this does not tackle the entire problem. The SBU and the National Board of Health and Welfare do not request unpublished information from the Medical Products Agency or pharmaceutical companies. Nor do they use clinical trial registers in a systematic way.

When the Medical Products Agency is drawing up treatment recommendations, it has access to unpublished information from pharmaceutical companies, which can counteract the bias to a certain extent. At the same time, there are signs that the

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220 See, for example, Petersson, C. (2011), *Har gjort fel* (Mistakes have been made), Aftonbladet 30/09/2011, and Petersson, C. (2911), *Läkarnas dubbelspel* (The double-dealing of doctors), Aftonbladet 30/09/2011.

221 Interview and email correspondence with a senior expert at the Medical Products Agency's medical information unit, 20/11/2014.

internal assessors who have insight into the regulatory material have little involvement in this work.

4.6.2 *External experts create conflicts of interest that are difficult to resolve*

The agencies take a serious view of the risk of reducing trust that may arise if there is a perception from the outside that the agency engages experts with strong links to the pharmaceutical industry. On the other hand, the risk of these conflicts of interest having material consequences seems to be regarded as less of a problem. At the same time, the conflicts of interest are difficult to resolve as the foremost experts in the area of pharmaceuticals tend to have or to have had some involvement with pharmaceutical companies.

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List of interviews and meetings

Workplace	Title/role	Date
The Swedish Association of the Pharmaceutical Industry (LIF)	Official in charge of patient safety and Regulatory Affairs	27/08/2013
The Swedish Association of Local Authorities and Regions (SALAR)	Medical coordinator	28/08/2013
The Medical Products Agency	Head of the Regulatory Administration Unit, controller and representative of the management office	04/09/2013
Roche Sverige AB	Head of Regulatory affairs, Regulatory Affairs Manager and Medical Director	17/09/2013
AstraZeneca	Representatives from Governmental Affairs, Regulatory Affairs and pharmacovigilance	23/09/2013
The Medical Products Agency	Deputy Director General, head of administration, assessor 1 from one of the efficacy and safety units, assessor 1 from the Clinical Trials and Special Permissions Unit	26/09/2013
The Dental and Pharmaceutical Benefits Agency	Chief pharmacist	02/10/2013
Drug and Therapeutics Committee, Stockholm County Council	Chairperson	08/10/2013
The National Board of Health and Welfare	Project secretary national guidelines	10/10/2013
Drug and Therapeutics Committee, Stockholm County Council	Member 1	17/10/2013
Drug and Therapeutics Committee, Stockholm County Council	Member 2	04/11/2013

Workplace	Title/role	Date
Drug and Therapeutics Committee, Stockholm County Council	Member 3	05/11/2013
Eli Lilly Sweden AB	Market Access Manager	11/11/2013
Drug and Therapeutics Committee, Stockholm County Council	Member 4	18/11/2013
The Medical Products Agency (former)	Professor Emeritus the Medical Products Agency, former senior expert	18/11/2013
Stockholm County Council	Head of the Unit for Monitoring and Evaluation	19/11/2013
The Nordic Cochrane Institute	Head and professor of Clinical Research Design	21/01/2014
Lund University, Department of Experimental Medical Science	Shai Mulinari, sociology researcher	21/01/2014
Drug and Therapeutics Committee, Region Skåne	Members 4, 5 and 6	22/01/2014
The Swedish Network for Pharmacoepidemiology (NEPI)	Head	12/02/2014
The Medical Products Agency	Project manager of the National Pharmaceutical Strategy	10/03/2014
The Medical Products Agency	Assessor 2 from one of the efficacy and safety units	12/03/2014
The Medical Products Agency	Swedish delegate on the EMA's Pharmacovigilance Risk Assessment Committee (PRAC)	19/03/2014
The Medical Products Agency	Assessor 3 from one of the efficacy and safety units	25/03/2014
The Medical Products Agency	Chair of the EMA's Committee for Medicinal Products for Human Use (CHMP)	07/04/2014
The Medical Products Agency	Assessor 4 from one of the efficacy and safety units	07/04/2014
The Medical Products Agency	Swedish delegate on the CHMP	08/04/2014
The Dental and Pharmaceutical Benefits Agency	Chief economist and scientific coordinator	24/04/2014
The Medical Products Agency	Chief legal officer and collaboration strategist	28/04/2014

Workplace	Title/role	Date
The Medical Products Agency	Assessor 5 from one of the efficacy and safety units	28/04/2014
The Medical Products Agency	Innovation strategist	29/04/2013
The Medical Products Agency	Assessor 2 from the Clinical Trials and Special Permissions Unit	29/04/2014
The Medical Products Agency	Chair of the Q group	05/05/2014
The Medical Products Agency	Quality assurance meeting of the Q group, observation	09/05/2014
London School of Hygiene and Tropical Medicine, London	Ben Goldacre, researcher and epidemiologist	12/05/2014
The European Medicines Agency (EMA)	Head of Inspections and Human Medicines, Head of Audit (Pharmacovigilance Division), and two scientific administrators (Regulatory Affairs)	13/05/2014
King's College, London	Courtney Davis, medical sociologist	13/05/2014
The National Audit Office (NAO), London	Two auditors who, among other things, audited the pharmaceutical industry's influence over the activities of MHRA and NICE	14/05/2014
Medicines and Healthcare Products Agency (MHRA), London	Five representatives of the Policy Division	14/05/2014
The Medical Products Agency	Assessor 6 from one of the efficacy and safety units	16/05/2014
Stockholm County Council's Drug and Therapeutics Committee	Members	11/06/2014
The Medical Products Agency	Signal assessor 1 from the Pharmacovigilance Unit	12/06/2014
The Medical Products Agency	Head of and two assessors from the Market Supervision Unit	26/08/2014
The Medical Products Agency	Head of the Clinical Trials and Special Permissions Unit	19/09/2014
The Medical Products Agency	Swedish delegate 2 on the EMA's Pharmacovigilance Risk Assessment Committee (PRAC)	19/09/2014
The Medical Products Agency	Head of the Pharmacovigilance Unit	29/09/2014

Workplace	Title/role	Date
The Medical Products Agency	Signal assessor 2 from thePharmacovigilance Unit	10/10/2014
The Medical Products Agency	Adverse reactions administrator 1 from the Pharmacovigilance Unit	20/10/2014
The Medical Products Agency	Adverse reactions administrator 2 from the Pharmacovigilance Unit	20/10/2014
The Medical Products Agency	Signal assessor 3 from the Pharmacovigilance Unit	20/10/2014
The Medical Products Agency	Signal assessor 4 from the Pharmacovigilance Unit	20/10/2014
The Medical Products Agency	Assessor 7 from one of the efficacy and safety units	11/11/2014
The Medical Products Agency	Assessor 8 from one of the efficacy and safety units	11/11/2014
The Medical Products Agency	Assessor 9 from one of the efficacy and safety units	11/11/2014
The Medical Products Agency	Assessor 10 from one of the efficacy and safety units	11/11/2014
The Medical Products Agency	Assessor 11 from one of the efficacy and safety units	11/11/2014
The Medical Products Agency	Assessor 12 from one of the efficacy and safety units	11/11/2014
The Medical Products Agency	Former Director General	19/11/2014
The Medical Products Agency	Assessor 3 from the Clinical Trials and Special Permissions Unit	20/11/2014
The Medical Products Agency	Assessor 4 from the Clinical Trials and Special Permissions Unit	20/11/2014
The Medical Products Agency	Assessor 5 from the Clinical Trials and Special Permissions Unit	20/11/2014
The Medical Products Agency	Statistician from the Clinical Trials and Special Permissions Unit	20/11/2014
The Medical Products Agency	Senior expert medical information	20/11/2014
Medical Association	Union representative with responsibility for the Medical Products Agency	01/12/2014
The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)	Head of the literature reviews department	02/12/2014

Workplace	Title/role	Date
The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)	Project manager of literature review	02/12/2014
The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)	Project manager of literature review	02/12/2014
The Government Offices of Sweden	Public officials with responsibility for the management of the Medical Products Agency, management of the Dental and Pharmaceutical Benefits Agency, e-health issues, clinical trials and the National Pharmaceutical Strategy.	04/12/2014
Medical Association	*Läkarförbundets råd för läkemedel, IT och medicinteknik* (RLIM, the Swedish Medical Association's council for pharmaceuticals, IT and medical technology)	09/12/2014
The Regional ethical review board Uppsala	Member	14/01/2015
The National Board of Health and Welfare	Medical expert adviser for national guidelines	10/02/2015
The National Board of Health and Welfare	Project manager for national guidelines	12/02/2015
The National Board of Health and Welfare	Deputy head of unit, National Guidelines Unit	12/02/2015
The National Board of Health and Welfare	Principally responsible for medical scientific evidence in national guidelines	18/02/2015
The Medical Products Agency	Group head the Clinical Trials and Special Permissions Unit	20/02/2015
The Medical Products Agency	Group head of the Supervision Department	02/03/2015
The National Board of Health and Welfare	Chair of the working groupfor fact checking national guidelines	31/03/2015
The National Board of Health and Welfare	Chair of the prioritisation group for national guidelines	31/03/2015
The Medical Products Agency	Chief statistician	27/04/2015
The Medical Products Agency	Assessor 13 from one of the efficacy and safety units	27/04/2015

Workplace	Title/role	Date
The Government Offices of Sweden	Public officials from the Ministry of Health and Social Affairs	06/05/2015
Unknown university	Anonymous telephone call from researchers	13/05/2015
The Medical Products Agency	The Medical Products Agency's senior management group	18/05/2015
The Swedish Association of the Pharmaceutical Industry (LIF)	Managing director	26/05/2015
The Medical Products Agency	Head of the one of the efficacy and safety units	09/12/2015
The Medical Products Agency	Assessor 6 from the Clinical Trials and Special Permissions Unit	22/01/2016
The Swedish Society of Medicine	Chair of the committee for pharmaceutical matters	01/02/2016
AstraZeneca	Regulatory Affairs Manager	05/02/2016
GlaxoSmithKline	Pharmacovigilance Lead	06/02/2016
Roche Sverige AB	Regulatory Affairs Manager	09/02/2016
Central Ethical Review Board	Administrative Director	09/02/2016
The Regional ethical review board Stockholm	Head of unit	10/02/2016
Karolinska Institutet/Linnaeus University	Paul Hjemdahl, professor of clinical pharmacology and Staffan Andersson, docent and senior lecturer at the Department of Political Science	10/02/2016
The Regional ethical review board Stockholm	Head of agency	11/02/2016
Stockholm centre for organizational research (Score)	Svenne Junker, PhD in business administration	12/02/2016
The Medical Products Agency	Assessor 7 from the Clinical Trials and Special Permissions Unit	13/02/2016