Regulatory benefit-risk assessment
Different perspectives

Arna Hrund Arnardóttir
Regulatory benefit - risk assessment

Different perspectives
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Chapter 1:

General introduction
The strict regulations of the pharmaceutical industry are aimed at ensuring that only safe, effective and high quality drugs reach the market. Regulators are under increasing pressure to balance the desire for rapid market access to new drugs with the need for having an acceptable knowledge of the benefits and risks of new drugs at time of approval. (1) A productivity decline in the pharmaceutical industry has been observed where increased investment in pharmaceutical research and development did not result in an increased number of new active substances approved each year. (2) This development is in part caused by what has been called “the cautious regulator problem”; where regulators continue to lower their risk tolerance in response to safety issues or scandals, raising the bar for introduction of new drugs which increases development costs. (3) This development is of concern as new drugs might become too expensive to develop or unaffordable to pay for by consumers or insurers. (4) While there are still diseases for which no pharmaceutical treatments are available, or considered inadequate, the new drugs coming to the market usually do not target these unmet medical needs. (5,6) In fact, many of the new drugs have only limited added value to what is already available. Pharmaceutical companies might prefer to avoid risks and focus on areas they are familiar with and that have higher probability of success. The industries view may be understandable, as the success rate for drugs entering phase III clinical trials is estimated at 64%. (7) In 2009, only 60% of new drug applications received a positive opinion by the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP). (8) Drugs for which industry sought scientific advice from the EMA were more successful than those for which this was not the case. Some of these failures might have been prevented by improving the dialogue during drug development and by better adherence of the industry to the scientific advice given by regulators. (9) In this context TI-Pharma initiated the Escher project. It aims at improving science-driven drug regulation and innovative research throughout phased drug development. Top Institute Pharma is a public private partnership where universities and partners from the pharmaceutical industry work together on multidisciplinary research. The Escher project also involves co-operation from the Dutch Medicines Evaluation Board with the aim “to evaluate and remove regulatory bottlenecks hampering the efficiency in pharmaceutical innovation and stimulate factors helping innovation”. (10) The research presented in this thesis was performed within this project.
**Regulatory procedures to help meet unmet medical need**

For many diseases with unmet medical need, new therapeutic options are essential. For those cases, the regulators have established special registration procedures that either accelerate the approval procedure (e.g. Accelerated Approval procedure in the USA) or reduce the requirements for the amount of data to be presented at registration (e.g. the Exceptional Circumstances (EC) or Conditional Approval (CA) procedures in Europe). (11-13)

**Regulatory mechanisms for continuous safety ascertainment**

When a drug is approved, a new phase of its life cycle begins. The population using the drug is no longer the limited trial population from the clinical development, but includes also patients that might not have been included in the trials. (1,14) To meet the challenges of continuous safety ascertainment, regulatory agencies have moved from a reactive system monitoring, mostly spontaneous ADRs, to a proactive system of Risk Management Plans which is a mandatory part of the marketing application since 2005. (15) An important part of risk management and risk minimization is timely and accurate risk communication of serious safety concerns identified post marketing. (16) In Europe the risk communication can have the form of a Direct Healthcare Professional Communication (DHPC), a letter sent out by the marketing authorisation holder, in collaboration with the regulators, to physicians, pharmacists and other healthcare professionals involved in the use of the particular drug. Safety related market withdrawal and DHPCs are regarded as safety related regulatory actions. (17)

**Regulatory learning and drug class effects**

Adverse drug reactions that were discovered post-marketing have sometimes triggered recalling drugs from the market. (18,19) Review of registration dossiers showed that some adverse events could have been predicted at time of approval. (20) Adverse drug reactions (ADRs) related to the drug’s mechanism of action can potentially be identified pre-approval while ADRs that are due to off-target (unexpected) pharmacological effects are often unpredictable and are likely only identified post-approval. Thus, for certain drug classes safety issues may be relevant for subsequent new drugs in the same class. These should be monitored in the clinical development program and, where necessary, long term, using appropriate methods. (21) Determining ADRs for novel drugs as compared to next-in-class (or ‘me-too’) drugs seems more difficult as there is no class experience. This is acknowledged
in the new European pharmacovigilance legislation which stipulates that first-in-class or novel drugs could be subject to additional monitoring post-marketing or will be subject to restricted medical prescription. (22) This raises the question whether more DHPCs are being issued for drugs that lack safety knowledge at time of approval and should be subject to additional monitoring post marketing.

**Patient involvement in regulatory decision making**

Today, the importance to take the patients’ perspective into account in health care is acknowledged as the most important next step in developing quality of health care. In management of chronic diseases, patient self-management and participation in treatment decisions is an integral part. (23) Active patient involvement in monitoring and reporting of side effects is also increasing and is becoming an important source for detection of ADRs. (24,25) Also regulating agencies also recognize this development as illustrated by the increasing interest in patient reported outcomes. (26) Regulators have accepted that patients are not only important in reporting of ADRs, but can also contribute to work within the regulatory agencies. As a platform for patient co-operation the European Medicines Agency has set up a framework for collaboration with qualified patient organisations with the Patients’ and Consumers’ Working Party (PCWP) and the US Food and Drug Administration has established the Patient Representative Program. (27,28)

Throughout the years, patient involvement in the European Medicines Agency has been of an advisory nature. Patient organisations do have representatives in the Committee for Orphan Medicinal Products and the Paediatric Committee, where they are active participants in the discussions and decisions made. However, these representatives are assigned by patient organisations and are not necessarily patients themselves. The CHMP decides on whether a drug should be granted market authorisation and occasionally invites patient representatives for consultation. The input of patients or their representatives to the CHMP is purely of an advisory nature and they are not allowed to participate in scientific deliberations. As patients are now more involved in the activities of the European Medicines Agency, the Agency believes their scientific committees are encouraged to reflect about the real-life implications of regulatory decisions. (27) However, whether that is the case has not yet been established and it is unclear whether regulators share the same values of benefits and risks as patients or healthcare professionals. Additionally, formal assessment of patient
or healthcare professional preferences has to date not been a part of the regulatory decision making.

**Research aim and outline of the thesis**

In line with the general aim of the Escher project, this thesis aims at evaluating the balance of benefit and risk ascertainment, as seen in the regulatory system. This thesis focuses on two issues that the regulatory system is grappling with, the uptake of knowledge about safety issues when deciding on market approval (part I), and the agreement on decision criteria between regulators and the decision makers in daily life about actual use of drugs (part II).

**Part I** of this theses focuses on timely uptake of safety issues. Here we look at whether the regulatory system provides sufficient tools to evaluate drug safety at time of approval.

**Chapter 2** explores whether safety issues arising for HIV drugs result in changes in the development and assessment of other HIV drugs that arrive later to the market. The question will be addressed of whether regulators considered class experience sufficiently.

**Chapter 3** evaluates whether market registration of drugs using procedures that allow less data to be submitted, results in an increased probability of safety issues. The question will be addressed on whether regulatory systems to approve drugs for unmet medical need are sufficiently robust to ensure that safe (and effective) drugs reach the market.

**Chapter 4** assesses the association of highly innovative drugs with the probability of safety issues arising post marketing. Innovative drugs may need more monitoring post-approval as there is no class experience and we hypothesize that this may lead to more detection of safety issues post-marketing.

**Part II** focuses on the perception of stakeholders in diabetes care regarding benefits and risks of drugs and their preferences for benefit-risk balance. Diabetes is one of the most important health problems today, in terms of its prevalence and in terms of availability of pharmacotherapy options.

Global prevalence of diabetes is high and is still increasing. In the year 2000 it was estimated that between 154 and 171 million persons had diabetes with estimates up to over 360 million for the year 2030. (29,30) Among patients with diabetes, the annual mortality is 2.9%,
mostly related to cardiovascular disease. In fact having diabetes is an independent risk factor for a number of cardiovascular disease (CVD) and once a diabetes patient develops CVD survival prognosis diminishes significantly. (31,32)

Several drug groups are available for the treatment of type 2 diabetes, each with their own ADR profile. Some of the more common side effects associated with diabetes drugs include gastro-intestinal upset and hypoglycaemias. (33) However, more serious ADRs have also been associated with these drugs. Rosiglitazone, for example, has been shown to increase the very risk it was intended to decrease; the risk of myocardial infarction, and pioglitazone seems associated with an increased risk of bladder cancer. (34,35)

Although diabetes is a disease for which multiple treatment options are available, regulators acknowledge the need for new drugs with improved benefits and risks. Still many patients are not adequately controlled with currently available treatments, that are also associated with several important ADRs. (35-37) It is unknown whether regulators are in agreement with patients and doctors in their value of benefits versus risks and the field of diabetes seems appropriate to assess the (dis)agreement between the groups.

Chapter 5 describes the method used to compile a list of drug effects to use in creating choice sets for measurement of preferences.

Chapter 6 assesses the preferences of benefit-risk balance of patients with type 2 diabetes. We sought to evaluate the importance of short term glucose regulation and long term cardiovascular benefits of oral anti-diabetes drugs relative to symptomatic ADRs and serious ADRs when choosing a drug.

Chapter 7 compares the benefit-risk preferences of assessors working at the Dutch medicines evaluation board with doctors and patients with type 2 diabetes. Regulators make their decisions on a population level and doctors and patients on an individual level and some regulatory decisions have been criticised as the conclusion on a drug’s benefit/risk balance are not always shared by doctors, patients or society at large. The question is addressed whether the difference between regulators on one hand and doctors and patients on the other is just the result of making decisions at a different, more population oriented level, instead of the individual patient level, or whether regulators genuinely value benefits and risks of drugs differently from other stakeholders.

Chapter 8 is a summary of the results presented in this thesis and a discussion on their implication in regulatory policy and practice, as well as perspectives for future research.
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Part I

Uptake of safety knowledge in regulatory practice
Chapter 2:

Does safety information on newer HIV drugs benefit from experience with older HIV drugs?
A regulatory perspective

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Chapter 2

ABSTRACT

Background: Knowledge on the safety of new medicines is limited at the time of market entry. Nearly half of all drugs used to treat HIV registered in the EU required at least one Direct Healthcare Professional Communication (DHPC) in the past 10 years for safety issues identified post-approval.

Objective: The aim was to evaluate the extent to which regulators and industry have addressed the risk of safety issues for HIV drugs based on prior experience with other drugs in the same class and whether doing so impacts development time of these drugs.

Methods: HIV drugs receiving $\geq 1$ DHPC in the Netherlands between January 1999 and December 2008 were identified. Each drug with a DHPC (‘index’ drug) was paired with subsequently approved HIV drug(s) in the same class (Anatomical Therapeutic Chemical [ATC] 4th level) [‘follow-on’ drugs]. Characteristics of safety issues were extracted from the DHPCs of the ‘index’ drugs. European Public Assessment Reports (EPARs) were reviewed regarding whether the safety issues had been considered during development and approval. Consideration of previously identified safety issues in ‘follow-on’ drug applications was assessed regarding attention paid to adverse drug reaction (ADR) symptoms in pre-marketing studies, Summary of Product Characteristics (SmPC) and postmarketing commitments, and whether size of the safety population was in accordance with Regulatory guidelines. ‘Index’ drugs were also paired with drugs in the same class already on the market (‘older’ drugs). For ‘older’ drugs, we identified whether the safety issue led to appropriate changes in the current SmPC (January 2011) compared with the SmPC at the time of marketing authorization.

Clinical development time was assessed using time from first patent application to market authorization as proxy, and comparison was made between ‘index’ and ‘follow-on’ drugs.

Results: For 9 (43%) of the 21 centrally authorized HIV drugs, 11 serious safety issues that required a DHPC were identified. Two drugs were excluded from our analysis (DHPCs related to contamination/medication error). Six ‘index’ drugs were paired, each with one to six ‘follow-on’ drugs. Three concerned drug-drug interactions (DDIs); the other three were intracranial haemorrhage, neuromuscular weakness and severe skin/hepatic reactions. All but one ‘follow-on’ drug had information in the EPAR on that specific ADR (i.e. attention was paid to the ADR). The DDIs were addressed in pre-marketing studies and/or the SmPC. Two of the other ADRs were addressed by post-marketing surveillance commitments; intracranial haemorrhage was not addressed. Three safety issues for two safety issues could not be
paired with a ‘follow-on’ drug as no drug in the same class was approved after the corresponding DHPCs were issued.

Five of the nine safety issues were added to at least one of the current SmPCs for the ‘older’ drugs already on the market at the time of DHPC issue. Two safety issues were already in the SmPC of the ‘older’ drugs at time of market approval and two were not introduced into the SmPC of ‘older’ drugs.

Population size to assess short-term safety complied with the guidelines for four ‘index’, seven ‘follow-on’ and three ‘older’ drugs; population size to assess long-term safety complied for one, three and two drugs, respectively. For five drugs, EPARs did not provide adequate information on population size. No statistically significant difference in development time between ‘index’ and ‘follow-on’ drugs was found.

**Conclusion:** Generally, safety issues were taken into account in the approval process of other drugs in the class. The approaches were different and determined by the nature of the ADR. Taking safety issues into account in the approval process did not seem to impact on the time taken to perform the pre-approval clinical programme.
INTRODUCTION

As new drugs enter the market, their full safety profile is usually not fully established. (1-4) Clinical trials on which marketing applications are based are primarily designed to assess efficacy, have a relative short duration, include sometimes low-risk patients with narrowly defined co-morbidities, and generally do not include enough patients to identify safety issues that are relatively rare (incidence less than 1:1000). (5) Thus, it seems almost inevitable that new safety issues emerge post-approval. Serious safety issues requiring regulatory action are identified in approximately 10% of all marketed drugs, with higher rates for specific classes of drugs, such as drugs to treat HIV (referred to hereafter as HIV drugs). (6)

Most (serious) adverse drug reactions (ADRs) related to the drug’s mechanism of action can be predicted and identified pre-approval. In contrast, the ADRs identified post-approval are often unpredictable (idiosyncratic) or due to off-target (unexpected) pharmacological effects. It is, therefore, important that for pharmacologically related new drugs (similar drug class or molecule) coming to the market, the risk of ADRs that could be class-related are thoroughly evaluated in the drug development programme, in particular during the market authorization process. (7)

The evaluation of idiosyncratic ADRs may be particularly challenging in therapeutic areas with a large unmet medical need and the accompanying pressure to prevent unnecessary delay in access to new drugs. HIV/AIDS is still considered a disease with such high unmet medical need by the European Medicines Agency (EMA). Prolongation of the development phase for HIV drugs to evaluate a potential but rare risk might negatively affect public health by delaying access to potentially beneficial drugs. (8) Also, additional study requirements will add to the costs that are associated with development of new drugs, further hampering their development. (9) Therefore, for HIV drugs, ‘accelerated approval’ in Europe is possible through approval procedures under Exceptional Circumstances or Conditional Approval, allowing drugs to be approved with more limited clinical data packages. (10-12)

However, a considerable number of new serious ADRs have been identified with these HIV drugs post-approval. The EMA has acknowledged this risk and stipulated that safety issues based on class experience may be relevant for subsequent new HIV drugs and should be monitored long term using appropriate methods. (7,13)

In this study, we aim to evaluate the extent to which regulators and industry have addressed the risk of safety issues for HIV drugs based on experience with other drugs in the same class.
In a separate exploratory analysis we assessed the impact of (increasing) regulatory requirements on development times for new HIV drugs.

**METHODS**

**Study Drugs**

All HIV drugs approved by the EMA from the start of the EMA Central Procedure on 1 January 1995 until 31 December 2008 were reviewed. We identified those HIV drugs with new important safety issues that required a Direct Healthcare Professional Communication (DHPC) in the period 1 January 1999 to 31 December 2008, referred to as ‘index’ drugs. DHPCs are paper-based letters sent by the Marketing Authorization Holder (MAH), in cooperation with the regulatory authorities, to relevant healthcare professionals. In the US, the equivalent of DHPCs are Dear Healthcare Professional Letters. (14) We excluded those DHPCs with safety issues that were related to the production process, route of administration or to the device. First, HIV drugs from the same drug class (Anatomical Therapeutic Chemical [ATC] 4th level). (13) that received marketing approval after the initial safety issue with the ‘index’ drug were studied (referred to as ‘follow-on’ drugs) [figure 1].

**Figure 1** Definition of ‘index’, ‘follow-on’ and ‘older’ drugs. ‘Index’ HIV drugs are defined by a Direct Healthcare Professional Communication (DHPC) issued for a new drug safety issue. ‘Follow-on’ drugs are HIV drugs in the same class (Anatomical Therapeutic Chemical [ATC] 4th level) as the ‘index’ drug that were granted marketing authorization after the date of the DHPC. ‘Older’ drugs were HIV drugs in the same ATC-4 class as the ‘index’ drug that were granted Marketing Authorization (MA) before the DHPC was issued.
Second, we studied those HIV drugs that were already approved at the time the ‘index’ drug received a DHPC (referred to as ‘older’ drugs).

**Characteristics of Safety Issues**

DHPCs were retrieved from the Dutch Medicines Evaluation Board (MEB) website. (15) The data extracted from DHPCs was as follows: (6)

- type of ADR;
- incidence rate of the ADR;
- the research method by which the safety issue was identified (e.g. clinical trials, spontaneous ADR reports or epidemiological studies);
- precursory symptoms or markers identified.

**Review Procedure**

European Public Assessment Reports (EPARs), which contain publicly available summary reports of the clinical dossier that was the basis for the marketing authorization, were retrieved from the EMA website. (16) Two reviewers (AHA and PGMM) evaluated the clinical studies, as presented in the EPARs, and independently extracted the data. Discrepancies were resolved by consensus. This was done for both the HIV drugs for which the safety issue was initially communicated postmarketing (‘index’ drugs) and for the HIV drugs of the same class (ATC 4th level) [‘follow-on’ drugs] (13) that received a marketing authorization after the safety issue was communicated by the DHPC.

**Data Extracted**

The EPARs were reviewed to establish if an earlier-identified safety issue had been critically addressed in the pre-clinical (animal) studies, pharmacokinetic studies and clinical trials. This was done for both ‘index’ and ‘follow-on’ drugs. Each issue was scored on pre-specified criteria regarding the identification of the ADR of interest, in line with the EMA guideline for clinical development of HIV drugs. (7) The score ranged from – (insufficient) to +++ (excellent) with respect to the effort put in establishing and describing these ADRs pre-approval [table 1].
We compared the size of the study population of the ‘index’ drugs with their respective ‘follow-on’ drugs, as well as for ‘older’ drugs. Both short- and long-term safety populations were identified for which minimal requirements were set by the EMA as being 1500 subjects exposed and 100 patients treated for at least 1 year, respectively. (7,17,18)

We recorded whether the safety issue identified was also reflected in the initial Summary of Product Characteristics (SmPC) of each product at the time of marketing authorization, as retrieved from the European Commission website. (19) The SmPC is a document that includes information for the health professional on how to use the drug effectively and safely. For the ‘older’ drugs we identified whether the safety issue led to a change in the current SmPC (January 2011) compared with the SmPC at the time of marketing authorization that was approved before the safety issue in the ‘index’ drug had occurred.

Finally, it was recorded whether the drugs obtained a marketing authorization through the Exceptional Circumstances or Conditional Approval procedure. (20,21)

Table 1 Scoring system of European Public Assessment Reports

<table>
<thead>
<tr>
<th>Grade</th>
<th>Markers/symptoms of the ADR seen or evaluated</th>
<th>Markers/symptoms linked to the possibility of the ADR</th>
<th>Investigation or discussion on the presence or absence of the ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>– (insufficient)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>+</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>++</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>+++ (excellent)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ADR = adverse drug reaction.

Clinical Development Time

A patent search in the Newport Horizon Global™ database (22) was performed. The clinical development time was defined as the time from the date of first patent application until the date of marketing authorization. Patent time was used as proxy for clinical development time as developers of drugs generally apply for a patent when the development process of the drug has not reached the point of clinical trials. (23)
Regression analysis was used to probe for a possible trend in clinical development time, and the Mann-Whitney U test was used to probe for a difference in clinical development time between the ‘older’, ‘index’ and their ‘follow-on’ drugs.

RESULTS

Characteristics of Safety Issues

For 9 (43%) of the 21 centrally authorized HIV drugs, 11 serious safety issues that required a DHPC were identified [figure 2]. We excluded two safety issues since they did not concern an ADR related to the pharmacology of the drug. Three of nine safety issues were drug-drug interactions (DDIs), which resulted in subtherapeutic plasma levels of the antiviral drug or loss of virological response due to mutation of the virus. Another three safety issues were idiosyncratic ADRs, including intracranial haemorrhage, neuromuscular weakness and severe skin/liver reaction. Assessment of incidence rate was only possible for two of the safety issues. Three safety issues could not be paired with a ‘follow-on’ drug as no drug in the same class was approved after the corresponding DHPCs were issued; these concerned drug hypersensitivity, myocardial infarction (MI) and renal disorder [table 2].

Evaluation of Identified Safety Issues for Class-Related Drugs

The impact of six safety issues could be evaluated in the EPARs of one to six ‘follow-on’ drugs per safety issue [table 3].

In the case of a drug-drug interaction with St John’s wort by indinavir, described in table 2, all ‘follow-on’ drugs underwent non-clinical (in vitro) and/or clinical pharmacokinetic investigations to assess the metabolism of the active compounds [table 3]. All these drugs were determined to be cytochrome P450 (CYP) 3A4 substrates as well as inhibitors or inducers of the isoenzyme and received a contraindication for concomitant use with St John’s wort at the time of market authorization. (33-38) All three of the ‘older’ drugs did not mention an interaction with St John’s wort in their original SmPC (39-41) but received a contraindication in the SmPC valid in January 2011. (32-44)
Figure 2: Timeline of approvals and safety risk communication (Direct Healthcare Professional Communication [DHPC]) of HIV drugs. EC = Exceptional Circumstances market authorization; CA = Conditional Approval market authorization; Arrows above the x-axis represent the date of marketing approval and arrows below the x-axis represent the date of the DHPC.
Atazanavir’s pH-dependent absorption, leading to lower plasma levels when co-administered with proton pump inhibitors (PPIs), was studied in appropriate pharmacokinetic interaction studies for the ‘follow-on’ drugs, i.e. tipranavir and darunavir. No discernable interaction was observed for concomitant administration of darunavir with a PPI and, as a consequence, no contraindication was included in the SmPC. An interaction study with an antacid but not with a PPI was performed for tipranavir. Based on the lowered plasma levels of tipranavir, a warning was included in the SmPC (37) to separate intake of antacids and tipranavir by 2 hours. Four of the seven ‘older’ drugs had a comment on acid-reducing agents but no comment on PPIs in the ‘interactions’ section of their original SmPC. (33,36,41,45) In the current January 2011 version of the SmPC, all drugs, except indinavir, had a comment on either acid-reducing agents or PPIs in their ‘interactions’ section. (42-44,46-48)

Intracranial haemorrhage was reported as a serious ADR of tipranavir. The ‘follow-on’ drug, darunavir, showed some effects on platelets in rats. It was claimed that this effect did not lead to bleeding and no further specific investigation of bleeding or the occurrence of intracranial haemorrhage was performed in clinical trials. For the eight ‘older’ drugs, none had any mention of haemorrhage or bleeding, except in patients with haemophilia, in neither the original SmPC (33-36,39-41,45) nor the version valid in January 2011. (42-44,46-50)

Regarding neuromuscular weakness that occurred with stavudine, a discussion on lactic acidosis (a precursory symptom) in clinical trials was present in the EPARs for both ‘follow-on’ drugs, tenofovir and emtricitabine, and a warning was included in their SmPCs. (51,52) Lamivudine, one of two ‘older’ drugs, had no mention of lactic acidosis or neuromuscular weakness in its original SmPC. (53) The original SmPC for abacavir was not available on the European Commission website, but there was a mention of lactic acidosis in its original patient information leaflet. (54) Both drugs have a discussion of lactic acidosis in the SmPC valid in January 2011. (55,56)

For tenofovir, where a pharmacodynamic interaction with lamivudine/abacavir or lamivudine/didonasine was observed, the ‘follow-on’ drug, emtricitabine, was tested in vitro for resistance of the known mutation type virus but only for lamivudine alone and not for the combination of lamivudine with abacavir or didonosine. The SmPC mentions that combination therapy with lamivudine cannot be recommended as specific interaction studies have not been performed. (52) For the three ‘older’ drugs, there was no mention of the mutated virus strain in the SmPC of stavudine and lamivudine, (53,57) while it could not
Table 2: Characteristics of the study drugs and adverse drug reactions (ADRs)

<table>
<thead>
<tr>
<th>Drug (approval date)</th>
<th>DHPC date</th>
<th>ADR</th>
<th>Symptoms and/or mechanism of ADR</th>
<th>Discovery of ADR as presented in DHPC</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indinavir (Oct 1996)</td>
<td>Mar 2000</td>
<td>DDI with St John’s wort</td>
<td>Plasma levels of indinavir lowered significantly Interaction is via the CYP metabolic pathway</td>
<td>ADR was discovered in a post-approval clinical trial (DDI study)</td>
<td></td>
</tr>
<tr>
<td>Atazanavir (Mar 2004)</td>
<td>Dec 2004</td>
<td>DDI with omeprazole</td>
<td>Plasma levels of atazanavir lowered significantly Uptake of atazanavir is inhibited by the change in acidity Other PPIs and preparations that increase gastric pH are likely to have a similar effect</td>
<td>ADR was discovered in a post-approval clinical trial (DDI study)</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir (Jan 1998)</td>
<td>(i) Jun 2007&lt;sup&gt;a&lt;/sup&gt; (ii) Jul 2007&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(i + ii) Therapeutic product contamination</td>
<td>Excluded from analysis</td>
<td></td>
<td>Not related to pharmacology</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (Mar 2001)</td>
<td>(i) Sep 2006&lt;sup&gt;a&lt;/sup&gt; (ii) Aug 2007&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(i + ii) Information capable of leading to medication error</td>
<td>Excluded from analysis</td>
<td></td>
<td>Not related to pharmacology</td>
</tr>
</tbody>
</table>

<sup>a</sup> These DHPCs were excluded from the assessment of European Public Assessment Reports.

c.a. = approximately; CYP = cytochrome P450; DDI = drug-drug interaction; DHPC = Direct Healthcare Professional Communication; MI = myocardial infarction; MoA = Mechanism of Action; PPI = proton pump inhibitor.
**Table 2 (cont’d):** Characteristics of the study drugs and adverse drug reactions (ADRs)

<table>
<thead>
<tr>
<th>Drug (approval date)</th>
<th>DHPC date</th>
<th>ADR</th>
<th>Symptoms and/or mechanism of ADR</th>
<th>Discovery of ADR as presented in DHPC</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tipranavir (Oct 2005)</td>
<td>Aug 2006</td>
<td>Intracranial haemorrhage</td>
<td>Increased risk of bleeding and prolonged bleeding</td>
<td>ADR was discovered in a post-approval clinical trial (DDI study). 14 cases (8 fatal) were reported, giving the incidence rate of 0.23%.</td>
<td></td>
</tr>
<tr>
<td>Stavudine (May 1996)</td>
<td>Sep 2001</td>
<td>Neuromuscular weakness mimicking Guillain Barré syndrome</td>
<td>Non-specific symptoms and signs compatible with the acidosis syndrome appeared to precede the development of neuromuscular problems. Early symptoms of the lactic acidosis syndrome include nausea, vomiting, diarrhoea and abdominal pain, rapid and deep breathing, cramps, myalgia and paresthesia</td>
<td>The DHPC did not mention how the ADR was discovered. However, it was noted that 14 cases (5 fatal) have been reported</td>
<td></td>
</tr>
<tr>
<td>Nevirapine (Feb 1996)</td>
<td>(i) Apr 1999 (ii) Apr 2000 (iii) Feb 2004</td>
<td>i + ii + iii) Severe skin/liver reaction</td>
<td>Changes in liver tests and rash in the first weeks of treatment High count of CD4+ cells is a risk factor</td>
<td>Changes in liver tests and rash in the first weeks of treatment High count of CD4+ cells is a risk factor</td>
<td></td>
</tr>
</tbody>
</table>

a These DHPCs were excluded from the assessment of European Public Assessment Reports.

C.a. = approximately; CYP = cytochrome P450; DDI = drug-drug interaction; DHPC = Direct Healthcare Professional Communication; MI = myocardial infarction; MoA = Mechanism of Action; PPI = proton pump inhibitor.
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<tr>
<th>Drug (approval date)</th>
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<th>ADR</th>
<th>Symptoms and/or mechanism of ADR</th>
<th>Discovery of ADR as presented in DHPC</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir (Jul 1999)</td>
<td>Mar 2008</td>
<td>Drug hypersensitivity</td>
<td>HLA-B*5701 genotypes are sensitive to this ADR only. Patients should be genotyped before initiating abacavir treatment</td>
<td>The PREDICT-1 double-blind clinical trial demonstrated that this already known ADR occurred in 48–61% of HLA-B*5701 genotypes and in &lt;4% of non-carriers</td>
<td>No subsequent drug approved</td>
</tr>
<tr>
<td></td>
<td>Apr 2008</td>
<td>Myocardial infarction</td>
<td>No established MoA, but MI had been identified as a possible risk in the pre-approval programme. Cardiovascular risk factors such as hypertension, dyslipidaemia and/or diabetes should be monitored</td>
<td>ADR was confirmed in a postmarketing cohort study.[24] The absolute MI rate was 6.1/1000 patient years</td>
<td>No subsequent drug approved</td>
</tr>
<tr>
<td>Tenofovir (Feb 2002)</td>
<td>(i) Jul 2003 (ii) Oct 2003 (iii) Mar 2005</td>
<td>(i + ii + iii) Decreased efficacy: pharmacodynamics interaction with lamivudine + abacavir combination and lamivudine + didanosine combination</td>
<td>Mutation in the virus resulted in resistance and lack of virological response Seems to be related to the same types of mutations in the virus, and genotyping of the viral load was advised</td>
<td>ADR was discovered in a post-approval clinical trial (combination trials). 80 cases (c.a. 50%) of patients also using lamivudine + abacavir combination and 22 cases (c.a. 90%) of patients also using lamivudine + didanosine combination suffered virological non-response</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(iv) Mar 2006 (v) Apr 2008a</td>
<td>(iv + vi) Renal disorder; (acute) renal failure, nephrogenic diabetes insipidus</td>
<td>Creatinine clearance and serum sodium phosphate should be monitored</td>
<td>ADR was discovered with postmarketing data surveillance (spontaneous ADR reporting)</td>
<td></td>
</tr>
</tbody>
</table>

a These DHPCs were excluded from the assessment of European Public Assessment Reports.

c.a. = approximately; CYP = cytochrome P450; DDI = drug-drug interaction; DHPC = Direct Healthcare Professional Communication; MI = myocardial infarction; MoA = Mechanism of Action; PPI = proton pump inhibitor.
be determined for abacavir since the original SmPC was not available. The mutated virus strain is discussed in the January 2011 version of the SmPC for lamivudine and abacavir, but not stavudine. (55,56,58)

Following the severe skin and/or hepatic reaction of nevirapine, rash was reported in clinical trials of the ‘follow-on’ drug, etravirine, and hepatic events were slightly more frequent than for placebo. Rash was included as a common adverse effect in the SmPC. (59) For efavirenz, the single ‘older’ drug, a rash was listed as a possible adverse effect in both the original and January 2011 versions of the SmPC. (60,61)

Three safety issues could not be paired to a ‘follow-on’ drug and were only assessed for ‘older’ drugs, already on the market when the DHPC was issued. All three safety issues were for nucleoside and nucleotide reverse transcriptase inhibitors.

For the drug hypersensitivity associated with abacavir and described in table 2, all four ‘older’ drugs did have a contraindication for the use of the drug when the patient was known to have hypersensitivity to the drug in both the original and January 2011 versions of their SmPC. (51-55,57,58,62,63)

For the MI associated with abacavir, and described in table 2, none of the four ‘older’ drugs had any discussion on MI or precursory symptoms in either the original or January 2011 version of their SmPC. (51-55,57,58,62,63)

For the renal disorder associated with tenofovir and described in table 2, three of the ‘older’ drugs had no mention of renal disorders in the ‘undesired effect’ section of either the original or January 2011 version of their SmPC. (52,53,55,57,58,63) For abacavir, the original SmPC could not be accessed and its patient information leaflet had no mention of renal disorders in the ‘adverse effect’ section. (54) Abacavir did have renal failure listed as a possible undesired affect in the SmPC valid in January 2011. (56)
Table 3  Evaluation of identified adverse drug reactions (ADRs) for study drugs in drug development and product information

<table>
<thead>
<tr>
<th></th>
<th>Pre-clinical studies</th>
<th>Pharmacokinetic studies</th>
<th>RCTs</th>
<th>Warning or contra-indication in SmPC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir (DDI with St Johns wort)</td>
<td>+</td>
<td>−</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>amprenavir</td>
<td>+</td>
<td>+</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>lopinavir/ritonavir</td>
<td>+</td>
<td>+</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>atazanavir</td>
<td>+</td>
<td>+</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>fosamprenavir</td>
<td>+</td>
<td>−</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>tipranavir</td>
<td>+</td>
<td>−</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>darunavir</td>
<td>+</td>
<td>−</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Atazanavir (DDI with omeprazole)</td>
<td>−</td>
<td>+</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>tipranavir</td>
<td>+</td>
<td>+</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>darunavir</td>
<td>−</td>
<td>+</td>
<td>++</td>
<td>No&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tipranavir (intracranial haemorrhage)</td>
<td>++</td>
<td>−</td>
<td>++</td>
<td>Yes</td>
</tr>
<tr>
<td>darunavir</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>No</td>
</tr>
<tr>
<td><strong>Nucleoside and nucleotide reverse transcriptase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine (neuromuscular weakness)</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>No</td>
</tr>
<tr>
<td>tenofovir</td>
<td>++</td>
<td>−</td>
<td>++</td>
<td>Yes</td>
</tr>
<tr>
<td>emtricitabine</td>
<td>−</td>
<td>−</td>
<td>++</td>
<td>Yes</td>
</tr>
<tr>
<td>Tenofovir (DDI with lamivudine/abacavir or lamivudine/didanosine)</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>emtricitabine</td>
<td>+++</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Non-nucleoside reverse transcriptase inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine (liver/skin reaction)</td>
<td>+</td>
<td>−</td>
<td>++</td>
<td>Yes</td>
</tr>
<tr>
<td>etravirine</td>
<td>+</td>
<td>−</td>
<td>++</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<sup>a</sup> Source: EPARs.
<sup>b</sup> EPAR has shown that a warning in SmPC is not required.

**DDI** = drug-drug interaction; **EPAR** = European Public Assessment Report; **NA** = not applicable; **RCTs** = randomized controlled trials; **SmPC** = Summary of Product Characteristics; − indicates not mentioned in the EPAR or SmPC; + indicates evidence is present, but discussion is poor or follow up on the evidence is not performed; ++ indicates discussion present on evidence of the ADR or evidence that suggests the ADR is not likely; +++ indicates a good discussion on the ADR, either that the ADR is possible or not at all likely.
## Table 4  Evaluation of population exposed to study drugs and the duration of drug development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Population</th>
<th>Safety population</th>
<th>Time from patent to MA (y)</th>
<th>Approval type</th>
<th>Year of approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir (O)</td>
<td>Inadequate information</td>
<td>374</td>
<td>2.7</td>
<td>EC</td>
<td>1996</td>
</tr>
<tr>
<td>Saquinavir (O)</td>
<td>&gt;180</td>
<td>574</td>
<td>5.8</td>
<td>EC</td>
<td>1996</td>
</tr>
<tr>
<td>Indinavir (I)</td>
<td>~100</td>
<td>~2000</td>
<td>3.4</td>
<td>Regular</td>
<td>1996</td>
</tr>
<tr>
<td>Nelfinavir (O)</td>
<td>24</td>
<td>819</td>
<td>3.3</td>
<td>EC</td>
<td>1998</td>
</tr>
<tr>
<td>Amprenavir (F)</td>
<td>&gt;100(^d)</td>
<td>&gt;1000</td>
<td>7.1</td>
<td>EC</td>
<td>2000</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (F)</td>
<td>Inadequate information</td>
<td>2000</td>
<td>7.2</td>
<td>EC</td>
<td>2001</td>
</tr>
<tr>
<td>Atazanavir (I)</td>
<td>&gt;200</td>
<td>2244</td>
<td>6.9</td>
<td>EC</td>
<td>2004</td>
</tr>
<tr>
<td>Fosamprenavir (F)</td>
<td>&gt;470</td>
<td>&gt;1000</td>
<td>6.3</td>
<td>Regular</td>
<td>2004</td>
</tr>
<tr>
<td>Tipranavir (I)</td>
<td>57</td>
<td>3195</td>
<td>10.5</td>
<td>EC</td>
<td>2005</td>
</tr>
<tr>
<td>Darunavir (F)</td>
<td>1056</td>
<td>1783</td>
<td>13.5</td>
<td>CA</td>
<td>2007</td>
</tr>
<tr>
<td><strong>Nucleoside and nucleotide reverse transcriptase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine (I)</td>
<td>&gt;100(^d)</td>
<td>&gt;13 000</td>
<td>8.4</td>
<td>Regular</td>
<td>1996</td>
</tr>
<tr>
<td>Lamivudine (O)</td>
<td>Inadequate information</td>
<td>18 889</td>
<td>6.5</td>
<td>Regular</td>
<td>1996</td>
</tr>
<tr>
<td>Abacavir (O)</td>
<td>147</td>
<td>4400</td>
<td>10.0</td>
<td>Regular</td>
<td>1999</td>
</tr>
<tr>
<td>Tenofovir (I)</td>
<td>75</td>
<td>1050</td>
<td>15.8</td>
<td>EC</td>
<td>2002</td>
</tr>
<tr>
<td>Emtricitabine (F)</td>
<td>1348</td>
<td>2136</td>
<td>12.8</td>
<td>Regular</td>
<td>2003</td>
</tr>
<tr>
<td><strong>Non-nucleoside reverse transcriptase inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine (I)</td>
<td>~450</td>
<td>906</td>
<td>7.6</td>
<td>EC</td>
<td>1998</td>
</tr>
<tr>
<td>Efavirenz (O)</td>
<td>408</td>
<td>2437</td>
<td>5.8</td>
<td>Regular</td>
<td>1999</td>
</tr>
<tr>
<td>Etravirine (F)</td>
<td>279</td>
<td>1041</td>
<td>8.8</td>
<td>CA</td>
<td>2008</td>
</tr>
</tbody>
</table>

\(a\) Number of patients exposed to the drug for at least one year.

\(b\) Number of patients and healthy volunteers exposed to the drug.

\(c\) EPAR did not provide sufficient information to estimate the population.

\(d\) Information in EPAR is unclear and the population was estimated.

\(CA\) = Conditional Approval; \(EC\) = Exceptional Circumstances; \(EPAR\) = European Public Assessment Report; \(F\) = ‘follow-on’ drug; \(I\) = ‘index’ drug; \(O\) = ‘older’ drug; \(MA\) = Marketing Authorization.
**Size of Safety Population**

Less than 1500 subjects (patients and healthy volunteers) were included in the clinical development programme of six (two ‘index’, one ‘follow-on’ and three ‘older’) HIV drugs in our study. The programme of two ‘follow-on’ drugs (amprenavir and fosamprenavir) included more than 1000 subjects, but for these two we could not assess properly whether the number exceeded 1500 subjects [table 4]. Two of the ‘index’ drugs did not have the required long-term population of 100 patients treated for at least 48 weeks. Both drugs were licensed under exceptional circumstances. For one ‘follow-on’ drug the information in the EPAR was not sufficient to assess the number of the long-term participants. One ‘older’ drug did not have the required long-term population of 100 patients treated for at least 48 weeks and for two ‘older’ drugs the information in the EPAR was not sufficient to assess the number of the long-term participants. For the remaining 12 drugs, the EPARs indicated that at least 100 patients were treated for 48 weeks with the new HIV drug.

Eleven (61%) of the 18 HIV drugs were approved under Exceptional Circumstances or Conditional Approval; four were ‘index’, four were ‘follow-on’ and three were ‘older’ drugs. These drugs were more likely (81.8%) than the regularly approved drugs (28.6%; p = 0.024) to be non-compliant with the guidelines on safety population and long-term population [table 4].

**Clinical Development Times**

The median time from patent application to marketing authorization approval for all study drugs was 8.4 years, ranging from 2.7 to 15.8 years. No significant difference was shown in the median time from patent application to marketing authorization approval between the ‘older’ drugs and ‘index’ drugs (median 6.7 years, interquartile range [IQR] 4.6–9.2) and their ‘follow-on’ drugs (median 8.8 years, IQR 7.1–12.8; p = 0.689). Clinical development time (years) did significantly increase over time for the studied HIV drugs per year of market approval, on average by 0.49 years per calendar year (95% CI 0.04, 0.93; p = 0.033) [table 4].
DISCUSSION

Our study shows that in the clinical development for the majority of new HIV drugs, attention is paid to previously identified ADRs of drugs approved earlier in the same pharmacological class without significantly affecting drug development time. The ADRs are discussed in the EPARs and, if appropriate, relevant information is included in the SmPC. For drugs already on the market, the occurrence of a safety issue for a drug of the same drug class seems to result in a re-evaluation of the safety information in the SmPC for most of the ‘older’ drugs.

In our study, we show that EMA guidelines for development of HIV drugs, requiring that ADRs that have been observed for earlier-approved drugs are evaluated in clinical development programmes of new HIV drugs, were followed. (7,17,18) Pre-marketing clinical trials are generally considered insufficient to establish the full safety profile of a drug. Furthermore, when ADRs have been identified they are not translated into clear warnings or usable knowledge for the healthcare professional. (5) However, we find the latter is not the case for the class-related safety issues we studied. All but one of these ADRs were generally carefully evaluated pre-approval and resulted in appropriate warnings in the SmPC. (7) In the case of intracranial haemorrhage, identified with tipranavir, this issue was not discussed in the EPAR of darunavir, the only subsequently approved protease inhibitor in our study. (25) We cannot rule out that evaluation of class-related safety issues was triggered by something other than the DHPC. A general effect of acid-reducing agents was described for four of seven ‘older’ protease inhibitors, but none specifically mentioned PPIs. Most of the SmPCs valid in January 2011 do mention PPIs specifically as is the issue evaluated in pharmacokinetics programmes of the ‘follow-on’ drugs.

Most SmPCs of ‘older’ drugs did change to include class-related safety issues at sometime between approval and January 2011. This suggests that a re-evaluation of the safety of ‘older’ drugs is performed and SmPCs change as a result. However, there were exceptions. No change to the SmPC of indinavir was made, despite evidence that the absorption of indinavir is also dependent on the pH. (26) Since all other protease inhibitors do have a comment on possible interaction with acid-reducing agents, this seems clearly a class-related safety issue. On the other hand, no ‘older’ drug had a comment on intracranial haemorrhage in their January 2011 SmPC, and since the ‘follow-on’ drug did not have investigation on intracranial haemorrhage in its EPAR this suggests that the safety issue is regarded as idiosyncratic rather than class-related. The MI associated with abacavir could
also be regarded as idiosyncratic, (24) thus explaining the lack of SmPC changes for ‘older’ drugs. Where the safety issue is already included in the original SmPCs of ‘older’ drugs, e.g. in the case of hypersensitivity of abacavir, it could be that there is always a hypothetical possibility of the safety issue and the comment is added as routine.

Development time of the ‘follow-on’ drugs – drugs sharing the same pharmacological class – did not significantly increase compared with the ‘index’ drugs and ‘older’ drugs. There was one exception; indinavir had a shorter development time than all its ‘follow-on’ drugs, although slightly longer than the ‘older’ drug ritonavir. Indinavir and ritonavir were two of the first protease inhibitors to be approved. They opened up the route for new potent treatment combinations that became known as highly active antiretroviral therapy (HAART). (27) Thus, indinavir and ritonavir were regarded as an important breakthrough in the treatment of HIV and this may have led to their very short clinical development time. As for other drugs, development times over the studied years are observed to be increasing. (28)

Our research showed that HIV drugs are likely to be licensed under Exceptional Circumstances or Conditional Approval and are more likely to receive a DHPC than other centrally approved drugs. (6,29) This finding suggests that because of the complex nature of the disease or the pressure put on regulators to approve the marketing applications quickly, (12,30,31) HIV drugs are more at risk of safety issues arising post-approval. The size of the safety population was, in the majority of the study drugs, in line with the regulatory guidelines. (18) Licensing under Exceptional Circumstances or Conditional Approval creates the possibility of including fewer subjects in clinical trials, and we found that the size of safety population did significantly correlate with the type of marketing authorization of HIV drugs. In general, drugs licensed under Exceptional Circumstances and Conditional Approval are less likely to fulfil the requirements of more than 1500 subjects exposed. However, in another study, we showed that for all centrally approved drugs in the EU, drugs approved through these procedures were no more likely to receive a DHPC than were drugs approved through the standard procedure. (32) Furthermore, in this study, we did not find a correlation between evaluation of safety issues for drugs approved through the Exceptional Circumstances/Conditional Approval versus standard procedure.
Limitations of the study

We collected most of our data from EPARs that do not provide access to confidential data. However, one may assume that all relevant clinical efficacy and safety data are present in the EPARs; the available data should therefore be sufficient to draw conclusions. The use of patent application dates is a weak proxy for clinical development time. The time from patent application to the beginning of pre-clinical or clinical research can vary depending on several issues, but generally companies do apply for patents before requesting ethics approval of their clinical trials. (23) We are not aware of a central database of clinical trial applications covering our study period; therefore, time from first patent application to marketing authorization was the best available proxy for clinical development time. The study evaluated only HIV drugs and cannot be extrapolated to other types of drugs. However, we could expect comparable results for other drug classes. Regulatory guidelines for clinical development of various drug classes or disease areas acknowledge class-related adverse effects. Finally, we only had access to DHPCs issued after 1 January 1999 (6) and cannot evaluate if any DHPCs were issued for HIV drugs between 1995 and 1998 and how this was followed up.

CONCLUSION

We found that in the case of HIV drugs, knowledge on ADRs gained from earlier-approved drugs has been used in the development of new drugs in the same class. We were not able to demonstrate that this affects clinical development times.

ACKNOWLEDGEMENTS

The authors would like to thank Margje Monster-Simons for her help with the EPAR assessment.
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Does safety information on newer HIV drugs benefit from experience with older HIV drugs?


Chapter 3:

Additional safety risk to exceptionally approved drugs in Europe?

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Flora M Haaijer-Ruskamp
Sabine MJ Straus
Hans-Georg Eichler
Pieter A de Graeff
Peter GM Mol
ABSTRACT

Aims: Regulatory requirements for new drugs have increased. Special approval procedures with priority assessment are possible for drugs with clear ‘unmet medical need’. We question whether these Exceptional Circumstances (EC) or Conditional Approval (CA) procedures have led to a higher probability of serious safety issues.

Methods: A retrospective cohort study was performed of new drugs approved in Europe between 1999 and 2009. The determinant was EC/CA versus standard procedure approval. Outcome variables were frequency and timing of a first Direct Healthcare Professional Communication (DHPC). An association between approval procedure and the time from market approval to DHPC was assessed using Kaplan-Meyer survival analysis and Cox-regression to correct for covariates.

Results: In total 289 new drugs were approved. Forty-six (16.4%) were approved under EC or CA of which seven received a DHPC (15%). This was similar to the standard approval drugs (243) of which 33 received one or more DHPC (14%, p=0.77). The probability of acquiring a DHPC for standard approval drugs versus EC/CA drugs during 11 years follow-up is 22% (95%CI: 14% ; 29%) and 26% (95%CI: 8% ; 44%) respectively (Log-Rank p=0.726). This difference remained not significant in the Cox-regression model: hazard ratio 0.94 (95%CI: 0.40 ; 2.20). Only drug type was identified as a confounding covariate.

Conclusion: The EC/CA procedure is not associated with a higher probability of DHPCs despite limited clinical development data. These data do not support the view that early drug approval increases the risk of serious safety issues emerging after market approval.
**INTRODUCTION**

Increasingly, society has become aware that drugs not only cure or prevent diseases but also can lead to considerable patient harm. Adverse drug events, whether or not due to (in)correct use of drugs, have been estimated to be a leading cause of unplanned hospital admission. (1,2) New drugs are allowed to the market based on relatively limited knowledge of their benefit-risk profile due to inherent and well known limitations in pre-approval clinical trials. (3) Those trials are typically performed in carefully selected patient populations not fully representing ‘real world’ patients, are of relatively short duration, and are primarily developed to determine efficacy. (4) They are not powered to detect rare adverse events, adverse events with a high background incidence or those related to the disease. (5) It is therefore not surprising that both in Europe and the USA for approximately 10% of all marketed drugs, serious adverse drug events were identified post approval that had to be communicated to healthcare professionals or patients. (6,7) Consistently, cardiovascular adverse events including QT prolongation and hepatotoxicity were leading causes for safety withdrawals of drugs. (6,7) Acknowledging this situation regulatory authorities have increased their pre-approval requirements over time. For example, thorough QT studies have become part of many new drug applications since QT prolongation and associated life-threatening arrhythmias have led to several drugs being withdrawn from the market. (8,9) More recently, the debate on rosiglitazone has led FDA to step up its pre-approval requirements for new drugs for diabetes, to demonstrate absence of an excess risk of cardiovascular events. (10) The negative consequences are that drug development times may increase, as do costs that are estimated upward of 800 million USD for the development of a new drug, limiting development of all but the most lucrative drugs. (11)

This development may not be in the interests of patients with a shortage of available treatment options for their disease, such as HIV/AIDS, cancer and many orphan diseases with unmet medical need. This is why the Food and Drug Administration (FDA) introduced the Accelerated Approval (AA) procedure in the USA and the European Medicines Agency (EMA) the Exceptional Circumstances (EC) or Conditional Approval (CA) procedures in Europe to approve drugs based on more limited clinical data sets. In Europe, the EC and CA procedures do not shorten the approval procedure itself, as is a common misconception. In the case of AA and CA procedures companies are required to perform confirmatory studies post approval, whereas in case of EC approval this is sometimes considered not realistic, e.g.
due to the (extreme) rarity of the disease. (12,13) However, an earlier effort by the FDA to streamline the regulatory process, the Prescription Drug User Fee Act (PDUFA) that restricted review times of new drugs, was criticised as it may have lead to unsafe drugs being approved. (14) Since the EC procedure has been used since 1995 and the CA procedure since 2007, it seems opportune to evaluate whether these special approval procedures have led to more safety issues identified after the drugs were marketed.

Our study evaluates whether the early approval under exceptional circumstances or conditional approval has led to a higher probability of new serious safety issues post approval than for drugs approved with the standard procedure of the EMA.

**METHODS**

**Study design & study population**

A retrospective cohort study was performed including all new active substances approved under the European Centralised Procedure (CP) from 1 January 1999 to 31 December 2009, using a limited definition of new active substances, by excluding biosimilars as defined by Eichler et al.. (15,16) The determinant was whether the drug product was approved using EC/CA or the standard procedure. Regulatory and scientific information on drugs was obtained from the European Public Assessment Report (EPAR) which is a summary report of the application. EPARs are issued for drugs that have received a marketing authorisation under the European Centralised Procedure (CP). EPARs are publicly available and can be retrieved from the EMA website. (17)

**Outcome**

The primary outcome was the identification of a first serious safety issue post approval. A serious safety issue was defined as an issue requiring regulatory risk communication in the form of a Direct Healthcare Professional Communication (DHPC) or a safety-related withdrawal of the marketing authorisation.

A DHPC contains information aimed at ensuring safe and effective use of medicinal products. It is delivered directly to individual healthcare professionals by a Marketing Authorisation Holder, or by a Competent Authority. DHPCs issued for drugs approved with the European
CP were retrieved from the Dutch Medicines Evaluation Board website. (18) We included European DHPCs issued from 1 January 1999 to 31 December 2009 and excluded DHPCs, where the safety issues were related to the administration of the drug, the pharmaceutical quality of the product or to malfunctioning in a device for the administration of the drug.

Time to DHPC or safety related market withdrawal, defined as the time in months from the date of market approval to the date of a first DHPC or withdrawal, was assessed. Whether a withdrawal was safety-related or not, was determined from the EMA press release regarding each drug withdrawal, as retrieved from the EMA website.

**Covariates**

Covariates were defined that could be considered as potential confounders. These were related to the drug, procedural issues and the clinical development and were obtained from the EPAR. The factors related to the drug were drug class (on anatomical therapeutic and chemical (ATC) code, (19) ATC-2 level, where more than 5 drugs were approved through the EC or CA procedure), whether it was first in class (y/n) and the type of drug (small molecule or biological including vaccines) as these might influence the likelihood of receiving EC or CA marketing authorisation as well as potentially increase the risk of serious safety issues post approval. The procedural issue was orphan drug status (y/n), because orphan drugs could be more prone to receiving EC or CA market approval and might be less prone to issuance of DHPCs. Another potentially important factor in the marketing authorisation application dossier related to the clinical development process was the size of safety population (less than 1500 subjects, y/n). EC/CA drugs can more often be approved with less than 1500 subjects exposed and drugs with smaller exposure in patients / healthy volunteers before approval may lead to more adverse drug reactions only being identified after approval. This number of 1500 has been specified by the E1 document published by the Internal Conference on Harmonisation (ICH) – agreement between USA, European and Japanese regulators - as a minimum number of subjects/patients that are expected to be exposed pre-approval to any new drug product. (20)

**Analysis**

Differences between baseline characteristics were analysed using chi-square and are presented in table 1. The probability for EC/CA and drugs approved with standard procedure to receive a DHPC or to be withdrawn for safety reasons was evaluated by Kaplan Meyer
analysis correcting for follow-up duration and by the Log-rank test. A follow-up duration of 11 years was deemed appropriate, as 73% of DHPCs are issued in the first ten years after market approval. (7)

Our study had 80% power at a 5% alfa-level to detect a difference of 10% between EC/CA and drugs approved with standard procedure of identifying safety-related issues requiring a DHPC during the 11-years follow-up. This is considering that 280 new drugs obtained marketing authorisation during the study period and had a 20% baseline chance for acquiring a DHPC, which is approximately in between the estimation for biologicals (29%) (21) and for all drugs (10%) (6) during 10 years follow-up.

A multivariable Cox proportional hazard model (HR and 95% CI) was used to evaluate the association between approval type and time to first DHPC, correcting for confounding covariates (p<0.1 in the chi-square analyses). A sensitivity analysis was also performed including all covariates in the Cox model.

As the research did not involve any patient data or other confidential material, no ethics approval was necessary for the performing of the study.

**RESULTS**

Of the 289 new drugs that obtained a marketing authorisation between 1 January 1999 and 31 December 2009, 46 (16%) were approved under EC/CA of which 38 with EC approval and 8 with CA. In the study period two to ten EC/CA drugs were approved annually, without any obvious pattern [Figure 1]. Sixteen drugs were withdrawn from the market for commercial reasons, all approved with standard procedure. The medium follow up of those withdrawn drugs was 45 months.

In total 74 DHPCs were issued for 49 drugs of the 289 drugs included, with 16 drugs receiving more than one DHPC. Five drugs, all approved with standard procedure, were withdrawn because of safety concerns; inhaled insulin, efalizumab, rimonabant, valdecoxib and a combination vaccine (Hexavac™). Eleven DHPCs for nine drugs were excluded; for five drugs the safety issues were related to the administration of the drug, for three drugs to the pharmaceutical quality of the product and for one drug to a malfunction in a device for the administration of the drug. A list of all DHPCs is presented in the appendix. Of the 46 drugs with EC/CA approval seven received a DHPC (15%) in comparison to 33 of 243 standard
Table 1: Approval procedures and issuance of a DHPC for new active substances approved between 1 January 1999 and 31 December 2009 and drug, procedural issues and clinical development characteristics.

<table>
<thead>
<tr>
<th>Drug classes (ATC-2 levelc)</th>
<th>Approval procedures</th>
<th>DHPC</th>
<th>HR (95% CI)***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All NAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EC/CA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Standard</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>289 (100)</td>
<td>46 (100)</td>
<td>243 (100)</td>
</tr>
<tr>
<td>Drug classes (ATC-2 levelc)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug classes (ATC-2 levelc)</td>
<td>Alcohol and drug metabolism – other (A16)</td>
<td>13 (5)</td>
<td>7 (15)</td>
</tr>
<tr>
<td></td>
<td>Direct acting antivirals (J05)</td>
<td>19 (7)</td>
<td>8 (17)</td>
</tr>
<tr>
<td></td>
<td>Antineoplastics (L01)</td>
<td>38 (13)</td>
<td>11 (24)</td>
</tr>
<tr>
<td></td>
<td>Other drug classes #</td>
<td>219 (76)</td>
<td>20 (44)</td>
</tr>
<tr>
<td>First in class (y)</td>
<td>37 (13)</td>
<td>5 (11)</td>
<td>32 (13)</td>
</tr>
<tr>
<td>Biologics (y)</td>
<td>109 (38)</td>
<td>14 (30)</td>
<td>95 (39)</td>
</tr>
<tr>
<td>Procedural issues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orphan drugs (y)</td>
<td>55 (19)</td>
<td>20 (44)</td>
<td>35 (14)</td>
</tr>
<tr>
<td>Clinical development</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety population &lt;1500 (y)¥</td>
<td>157 (56)</td>
<td>38 (83)</td>
<td>119 (51)</td>
</tr>
</tbody>
</table>

NAS New Active Substance; DHPC Direct Healthcare Professional Communication (as proxy for safety issues) after excluding non-safety related DHPCs; EC Exceptional Circumstances; CA Conditional Approval; * Percentages are expressed within NAS, approval type and DHPC (column); ** p-value of Chi square; *** Cox-proportional Hazard Ratio corrected for covariates presented; § Drug classes are selected to over-represent EC/CA procedure (≥5 drugs registered through EC/CAA procedure); # All drugs that are not categorized on ATC-2 level as A16, J05 or L01; c Variable is categorical and ratio of values adds up to 100%; (y) Variable is dichotomous and value represents the “yes”; ¥ EPARs were not available for nine drugs thus the size of the safety population. The ratio refers to if those drugs are excluded.
approvals (14%, p=0.77). DHPCs for three EC approved drugs (drotrecog alfa, atazanavir and tenofovir) regarded lack of efficacy concerns in certain subpopulations. All other DHPCs concerned safety issues.

The mean follow-up duration, from the date of approval to a first DHPC, withdrawal or end of study period, for EC/CA and standard approved drugs was 52 months (95% CI: 42 ; 62) and 55 months (95% CI: 50 ; 60), respectively. The Kaplan Meyer derived probability for drugs receiving a DHPC was similar for both types of approval processes [Figure 2, log-rank p=0.726]. At 3 years follow-up drugs under EC/CA approval had a 7% (95% CI: 0% ; 15%) risk of receiving a DHPC, while standard approvals had a 10% (95% CI: 6% ; 14%) risk of receiving a DHPC. At 11 years follow up this risk was 26% (95% CI: 8% ; 44%) for EC/CA approved drugs and 22% (95% CI: 14% ; 29%) for standard approved drugs.

The unadjusted hazard ratio (HR) for EC/CA drugs to receive a DHPC during the follow-up was 1.16 (95% CI: 0.51 ; 2.62). When correcting for confounders the EC/CA drugs had a 0.94
(95% CI: 0.40 ; 2.20) hazard ratio (HR) to receive a DHPC during the follow-up in the Cox proportional hazards model. From the confounders hypothesised to be present, the distribution of ‘drug classes’ (ATC-2 level) was significantly different between drugs approved under EC/CA and standard conditions (p<0.001), as the drug classes were specifically selected to have more than five drugs licensed under EC/CA. As could be expected EC/CA drugs were more likely to be orphan drugs (44%) than the drugs approved with standard procedure (14%, p<0.001) and more EC/CA drugs (83%) had safety populations that did not meet the ICH threshold of 1500 patients exposed to a new drug before approval than drugs approved with standard procedure (51%, p<0.001). For nine drugs we were unable to retrieve the variable ‘size of the safety population’ as scientific discussion of the EPARs was no longer available on the EMA website. All these drugs have

Figure 2: Proportion of new active substances authorised under exceptional circumstances/conditional approval (EC/CA) or standard conditions with a subsequent Direct Healthcare Provider Communication.

NAS       New active substances
DHPC    Direct Healthcare Professional Communication
EC/CA   Exceptional circumstances and conditional approval marketing authorisations
been withdrawn from the market. However, only drug class was associated with the issuance of a DHPC (p=0.014) and was subsequently included in the Cox model as a potential confounder [Table 1]. In the sensitivity analysis that incorporated all covariates the results were similar. The approval procedure did however not affect the issuance of DHPCs, for example 38% (3 of 8) EC/CA and 36% (4 of 11) HIV AIDS drugs approved with standard procedure received a DHPC. HIV/AIDS drugs had an increased risk of a DHPC, HR 3.07 (95% CI: 1.28 ; 7.37) independent of the approval procedure.

**DISCUSSION**

In the EU drugs receiving approval through the Exceptional Circumstances or Conditional Approval procedure have a similar probability of a first serious safety issue requiring a DHPC as drugs approved with standard procedure in our 11 year follow-up study; 26% and 22% respectively. None of the EC/CA, but five of the drugs approved with standard procedure were withdrawn from the market because of safety concerns.

In this direct comparison of approval procedures no association could be found between approval procedure and identification of serious safety issues post approval. Recent examples have shown the need for continuous monitoring of the benefit risk balance during the lifecycle of a drug. (7) This has led to a more proactive approach of pharmacovigilance through risk management plans. In the risk management plan, based on the knowledge of the drug’s characteristics at the time of the approval gaps in data are identified, companies are required to obtain additional data on benefits and risks of the drug in daily practice or in post-marketing trial settings. (22,23) Since the EC/CA drugs have been approved on preliminary evidence, regulators usually require even stricter risk management plans. (12,13,24) This close follow-up is expected to be more sensitive in picking up important safety issues than routinely collecting spontaneous adverse drug reactions, which is the usual approach for drugs approved with standard procedure.

Balancing this effect of close follow-up is that EC/CA drugs are generally intended to treat rare diseases and not all European countries reimburse conditionally approved drugs. Therefore, the population exposed to these drugs post-approval may still not be sufficiently large to detect less common adverse drug reactions. Heemstra et al. consider this a likely explanation for their observation of orphan drugs having fewer safety issues post approval.
than biologicals or [all] new drugs in cross study comparisons. (24) Supportive for their explanation is that they observed an association of safety-related regulatory action for drug classes with the highest expected use, those orphan drugs used within oncology and gastroenterology and metabolic indications (ATC classes L01/L02 and A respectively). In our study these drug classes and drugs to treat HIV/AIDS (ATC class J05) were also over-represented in the EC/CA group. Moreover, drug classes and specifically those involving the HIV/AIDS drugs, were shown to truly confound the results - for which we corrected in the Cox-proportional hazard model - as they also more frequently led to a DHPC. HIV/AIDS drugs are the most commonly used EC/CA drugs, which may indeed explain that rare but serious safety issues are picked up relatively early. Our data, however, also showed that for both HIV/AIDS and anti-cancer [data not shown] drugs the approval procedure did not predict whether serious safety issues were identified more readily post-approval. Unfortunately, data on drug usage could not be obtained. Many of the EC and CA licensed drugs are used in hospital setting and hospital drug consumption data is not readily available in the Netherlands or for the EU as a whole. Also, reimbursement is different across EU countries and associated prescription data difficult to obtain. This needs further study, perhaps in a setting where comprehensive total drug usage is available. Our results are in line with Richey et al. (25) who concluded that anti-cancer drugs approved with the accelerated approval were safe because none was withdrawn. They also confirm the more limited analyses by Boon et al.. (26) However, Boon et al. included in their assessment all withdrawals, not discriminating between withdrawals due to safety issues and withdrawals for commercial reasons.

Our finding that EC/CA drugs that were approved with more limited clinical data sets are as safe as drugs approved with standard procedure seems at odds with the current societal demand for more pre-approval ascertainment of harms and benefits of new drugs. (10,11,27,28) This finding has important societal implications. The request for large-scale outcome studies for e.g. new drugs for diabetes may already be prohibitive even in a field with a large target population. Therefore, it is reassuring to learn that EC/CA registration with limited clinical data sets seems to have been safe in the past decade for drugs with high unmet medical need.
Reassuringly, only 3 DHPCs were issued because of efficacy concerns from confirmatory trials, indicating that the objective to allow early access of potentially effective drugs meets its expectations.

Although we showed in an earlier study that approximately 10% of all marketed drugs throughout their life-cycle required safety-related regulatory action (7), we found in this study that for more recently approved drugs within 11 years after that approval the probability of requiring a DHPC is 26%. This is higher than reported earlier by Lasser et al., (6) but in line with Giezen et al who reported similar probabilities for biologicals. (21) Lasser included all drugs on the market in the USA from 1975 to 1999, while the study done by Giezen was more recent and included only biological drugs approved in Europe and the USA between 1995 and 2007. Our finding is consistent with the increasing trend of regulatory risk communications (DHPCs) per year that we observed in our earlier study. (7) The difference between our results and Giezen et al.’s on one hand, and those of Lasser on the other, could be due to increasing risk awareness, or to the implementation of more sensitive pharmacovigilance tools.

With this apparent growing risk-awareness, it was remarkable that 51% of all drugs with regular authorisation did not meet the ICH guideline of at least 1500 subjects exposed to the drug in pre-approval trials (safety population), in particular because this ratio is rather constant throughout the study period [data not shown]. It would be a topic of future research to explore why the safety population is so limited in the marketing authorisation procedure. However, one must keep in mind that the safety requirements in the EU and ICH guidelines are merely a guide. A complete cure for a rapidly fatal disease would require relatively few patients, while, to establish clinical benefit, and an absence of harm, for a new surrogate endpoint may take many thousand patient years.

**Limitations of the study**

DHPCs might not be the most sensitive proxy for safety issues and could be handled or perceived differently for EC/CA drugs addressing ‘unmet medical needs’. The acceptability of serious safety issues in the overall benefit/risk balance may be higher and could have a higher threshold for issuing a DHPC resulting in less strong safety-related regulatory action such as a change in the Summary of Product Characteristics. However, this does not become apparent when the observed safety issues reported for EC/CA are considered versus those
for regularly approved drugs. [Appendix] Furthermore, The DHPC is recommended as risk communication tool to guarantee continued safe use of a drug. (29) Other studies have used the DHPC as the most important proxy of serious safety issues. (6,21,24) It is the best we have as an overall measure that is going through a careful evaluation procedure at the EU level.

We cannot be completely sure that drugs withdrawn from the market for commercial reasons do not also have a safety issue prompting the company’s decision to withdraw the drug. However, in the reported cases the EMA press releases explicitly mentioned either that safety concerns were not the reason for withdrawal or that commercial reasons prompted the withdrawal.

As mentioned, EC/CA drugs are used in relatively small patient populations, which reduces the chance of finding rare adverse events. Therefore, our conclusion for the EC/CA procedure does not imply that this procedure would be appropriate for all drugs.

**Conclusion**

Our study showed that the risk of receiving a DHPC is similar for those drugs licensed using Exceptional Circumstances and Conditional Approval and the drugs that were licensed using the standard procedure in the past 11 years in the EU.

The use of Exceptional Circumstances and Conditional Approval should be continued, as it is valuable in allowing earlier entry to the market for eligible drugs that are mostly intended for rare diseases, without an apparent increased risk of unexpected serious side effects.
LIST OF REFERENCES:


Additional safety risk to exceptionally approved drugs in Europe?


(27) Jones TC. A call to restructure the drug development process: government over-regulation and non-innovative late stage (Phase III) clinical trials are major obstacles to advances in health care. Sci Eng Ethics 2005 Oct;11(4):575-587.


### APPENDIX: DRUGS WITH SAFETY ISSUES

<table>
<thead>
<tr>
<th>Drug name</th>
<th>ATC</th>
<th>Approved</th>
<th>Warning</th>
<th>System Organ Class</th>
<th>Time to DHPC (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard approval</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rimonabant *</td>
<td>A08AX01</td>
<td>Jun-06</td>
<td>Depression</td>
<td>Psychiatric disorders</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Depression</td>
<td>Psychiatric disorders</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Depression</td>
<td>Psychiatric disorders</td>
<td>2.4</td>
</tr>
<tr>
<td>insulin human (inhalation) *</td>
<td>A10AF01</td>
<td>Jan-06</td>
<td>Lung carcinoma cell type unspecified recurrent</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>2.4</td>
</tr>
<tr>
<td>rosiglitazone</td>
<td>A10BG02</td>
<td>Jul-00</td>
<td>Macular oedema</td>
<td>Eye disorders</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Fracture</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>6.6</td>
</tr>
<tr>
<td>pioglitazone</td>
<td>A10BG03</td>
<td>Oct-00</td>
<td>Fracture</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug ineffective</td>
<td>Surgical and medical procedures</td>
<td>7.7</td>
</tr>
<tr>
<td>tipranavir</td>
<td>J05AE09</td>
<td>Oct-05</td>
<td>Haemorrhage intracranial</td>
<td>Nervous system disorders</td>
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<td>abacavir</td>
<td>J05AF06</td>
<td>Jul-99</td>
<td>Drug hypersensitivity</td>
<td>Immune system disorders</td>
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<td>Myocardial infarction</td>
<td>Cardiac disorders</td>
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<td>entecavir</td>
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<td>Jun-06</td>
<td>Pathogen resistance</td>
<td>Infections and infestations</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Drug therapy changed</td>
<td>General disorders and administration site conditions</td>
<td>4.9</td>
</tr>
<tr>
<td>diptheria, tetanus, acellular pertussis, poliomyelitis, hepatitis B and haemophilus influenza type b vaccine *</td>
<td>J07CA</td>
<td>Oct-00</td>
<td>Drug ineffective</td>
<td>General disorders and administration site conditions</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cardiotoxicity</td>
<td>Cardiac disorders</td>
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<td></td>
<td>Cardiotoxicity</td>
<td>Cardiac disorders</td>
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<tr>
<td>trastuzumab</td>
<td>L01XC03</td>
<td>Aug-00</td>
<td>Tracheo-oesophageal fistula</td>
<td>Congenital, familial and genetic disorders</td>
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<tr>
<td>bevacizumab</td>
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<td>Eye disorders</td>
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<tr>
<td>imatinib mesilate</td>
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<td>Nov-01</td>
<td>Urinary bladder adenoma</td>
<td>Renal and urinary disorders</td>
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<td></td>
<td></td>
<td>Cardiac failure</td>
<td>Cardiac disorders</td>
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<td>temsirolimus</td>
<td>L01XE09</td>
<td>Nov-07</td>
<td>Anaphylactic reaction</td>
<td>Vascular disorders</td>
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<td>erlotinib</td>
<td>L01XX34</td>
<td>Sep-05</td>
<td>Gastrointestinal perforation</td>
<td>Gastrointestinal disorders</td>
<td>3.7</td>
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<td>sirolimus</td>
<td>L04AA10</td>
<td>Mar-01</td>
<td>Bronchial anastomosis complication</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>1.9</td>
</tr>
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<td>efalizumab *</td>
<td>L04AA21</td>
<td>Sep-04</td>
<td>Progressive multifocal leukoencephalopathy</td>
<td>Nervous system disorders</td>
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<td>etanercept</td>
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Additional safety risk to exceptionally approved drugs in Europe?

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Chapter 4:
Are more safety issues identified post approval for innovative drugs?

Peter GM Mol
Arna H Arnardottir
Domenico Motola
Patrick J Vrijlandt
Ruben G Duijnhoven
Flora M Haaijer-Ruskamp
Pieter A de Graeff
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Sabine MJ Straus
Chapter 4

ABSTRACT

Background: The knowledge at the time of approval for more innovative drugs that are often first-in-class and have a new mechanism of action might not be as extensive as compared to less innovative drugs. Since pre-approval programs are inherently limited in establishing the full safety profile of any new drug, the more innovative drugs might have even more serious safety issues that are identified only post approval.

Objective: To compare the frequency and timing of serious safety issues identified during the early and later stages post-approval for more innovative drugs versus less innovative drugs.

Methods: A retrospective cohort study was performed that included all new active substances approved under the European Centralized Procedure (CP) and for which serious safety issues were identified post-approval from 1 January 1999 to 31 December 2011. Serious safety issues were defined as issues requiring a Direct Healthcare Professional Communication (DHPC) to alert individual healthcare professionals of a new serious safety issue, or a safety-related drug withdrawal. Data were retrieved from publicly available websites of the Dutch Medicines Evaluation Board and the European Medicines Agency. The level of innovation was scored using a validated algorithm, grading drugs as important (A), moderate (B) or modest (C) innovations or as pharmacological or technological (pharm/tech) innovations. The data were analyzed using appropriate descriptive statistics and Kaplan-Meier analysis, with a Mantel-Cox log-rank test, and Cox-regression models correcting for follow-up duration, to identify a possible trend in serious safety issues with an increasing level of innovation.

Results: A total of 279 new drugs were approved in our review period; 59 (21%) were graded A, 63 (23%) B, 34 (12%) C, and 123 (44%) as pharm/tech. Nine drugs were withdrawn from the market, and 53 drugs received one or more DHPC. Serious safety issues were identified for 15 (25%) drugs graded A, 13 (21%) graded B, 8 (24%) graded C, and 19 (15%) for the drugs graded as pharm/tech [p=0.12, linear-by-linear test]. The Kaplan Meyer derived probability for having a first serious safety issue was not statistically significant, log-rank (Mantel-Cox) p=0.067. In the final adjusted Cox proportional hazard model there was no statistically significant difference in occurrence of a first serious safety issue for the more innovative (A, B, and C) drugs when compared to the pharm/tech [reference] drugs; hazard ratios 1.63 (95%CI: 0.77; 3.43), 1.48 (95%CI: 0.71; 3.08], and 1.16 (95%CI: 0.48; 2.82), respectively.
Conclusion: Slightly more than half of all new drugs approved in Europe can be considered as at least modest innovations that add value to the available drug armamentarium. A higher level of innovation was not clearly related to an increased risk of serious safety issues that are identified post marketing.
INTRODUCTION

It is estimated that a third of all drugs being approved in Europe can be considered important drug innovations. (1) These important drug innovations target diseases demonstrating major benefits on clinical endpoints or established surrogate endpoints for diseases where treatment is not available, at least not for important subgroups of patients. (1,2) They are often first-in-class and act through a new mechanism of action. As a result knowledge for these drugs at the time of approval might not be as extensive as compared to less innovative drugs, for which there are already more comparable substances approved. Any pre-approval clinical development program is limited in size, targets a specific population, and is primarily focused on establishing efficacy. (3) Especially for the innovative drugs the complete benefit-risk will only be fully established post-approval. Yet, innovative drugs are eagerly awaited by society with often high pressure to speed up development with rapid approval. As these drugs offer a potential therapeutic advantage to existing alternative treatment forms they may be rapidly taken up in clinical practice early after approval.

Although serious safety issues can occur at any time throughout the lifecycle of a drug,(4) these innovative drugs may thus be at a higher risk of identification of serious safety issues early post-approval. New safety issues may be identified earlier in part due to their relative quick uptake,(5) but also because they are channelled to patient groups that are more difficult to treat, such as patients unresponsive to already available drug therapy or who cannot tolerate available therapy. These patients may be more vulnerable and experience more drug-related problems. (6) As experience grows with these drugs they will find their way to a more general patient population and any potential difference in susceptibility due to the treated population will disappear. (7) Previously, Tavassoli and Montastruc studied the relation between level of drug innovation and safety alerts as issued by the French Drug Agency, using the French National Authority for Health classification for the level of innovation, i.e. ‘improvement in actual benefit’. They found an association with these alerts and the more innovative drugs and recommended to monitor these drugs more actively after approval. However, their study had a cross-sectional design and it is therefore unclear whether this observation applies to the early stages post-approval only. (5) The aim of this study is to compare the frequency and timing of serious safety issues identified post-approval for more innovative drugs compared to less innovative drugs.
METHODS

Design

A retrospective cohort study was performed that included all new active substances approved under the European Centralized Procedure (CP) and associated serious safety issues that were identified post approval from 1 January 1999 to 31 December 2011. New active substances were defined according the limited definition of Eichler et al; i.e. excluding biosimilars. (8) In this paper the term drugs is used for new active substances. The level of innovativeness of drugs was determined using the algorithm developed by Motola by which drugs were graded as A) important, B) moderate, or C) modest innovations or as ‘Pharmacological’ / ‘Technological’ innovations [See figure 1]. (1,2) In this paper we grouped the latter, i.e. pharmacological and technological (pharm/tech) innovations, resulting in four levels of innovation (A, B, C and pharm/tech). For grading, drugs were first divided into three groups, depending on the availability of alternative treatment possibilities; group A), drugs for diseases without available therapy, group B) drugs for subsets of patients unresponsive to available therapy, and group C) drugs with effective alternative therapy available. In the latter group class C1 drugs are more effective and/or safe than available alternatives, class C2 drugs only pharmacologically different (pharmacokinetics or mechanism of action), and class C3 drugs that are only technologically different. Secondly, drugs were graded according to their demonstrated treatment effect; group A) with a major benefit on clinical endpoint, group B) with a partial benefit on disease or less robust demonstration of major benefit, and group C) with minor or temporary benefit on some aspects of the disease. The algorithm of Motola does not allow classification of vaccines and diagnostics, which for that reason were excluded from the analyses.

Drugs approved up to 2004 have previously been classified by Motola and his group according to their own classification. (2) Drugs approved after 2004 were each classified independently by two assessors of the Dutch Medicines Evaluation Board and/or co-authors of this paper [PM, PV, PdG, AHA, DM]. The level of agreement in classifying the level of innovation was evaluated for a random subset of 20 drugs and was found to be adequate (kappa = 0.57). Therefore, in cases with disagreement all classifications were resolved in a consensus meeting with a minimum of three assessors.
Scientific and regulatory information on drugs was obtained from the European Public Assessment Report (EPAR). The EPAR is published at the EMA website (http://www.emea.europa.eu) and contains a summary report of the marketing application dossier and scientific assessment.

**Figure 1** Classification of drugs

Algorithm used to assign the overall score for innovation. Available treatments: A = drugs for diseases without recognized standard treatment; B = drugs for diseases where subsets of patients are less responsive to marketed drugs and/or other medical interventions, C = drugs for diseases responsive to marketed drugs or other medical interventions (C1= more effective or safer than existing drugs; C2= mere pharmacological innovation, i.e. drugs with better kinetics or new mechanism of action; C3= mere technological innovation, i.e. a new chemical or biotechnological product with therapeutic role similar to already existing ones). Therapeutic effect: A = major benefit on clinical end-points (e.g. increased survival rate and/or quality of life) or validated surrogate end-points; B = partial benefit on the disease (on clinical or validated surrogate end-points) or limited evidence of a major benefit (inconsistent results); C = minor or temporary benefit on some aspects of the disease (e.g. only partial symptomatic relief of a serious disease).

[Figure reproduced with permission from Motola in Brit J Clin PharP 2005(2)]
**Outcome**

The primary endpoint was the identification of a first serious safety issue post approval. Serious safety issues were defined as issues requiring a Direct Healthcare Professional Communication (DHPC) to alert individual healthcare professionals to a new serious safety issue, or a safety-related drug withdrawal. DHPCs issued between 1 January 1999 and 1 January 2012 were retrieved from the Dutch Medicines Evaluation Board website. (http://www.cbg-meb.nl) Only safety-related DHPCs were included; any DHPC related to administration of the drug, the pharmaceutical quality and/or the malfunctioning of a device (used to administer the drug) were excluded. In addition, DHPCs issued to inform healthcare professionals on the lack of efficacy of a drug were excluded. Whether a drug withdrawal was safety-related was determined from the related press release and the EPAR section ‘Procedural steps taken and scientific information after approval’ as retrieved from the EMA website.

Time to the primary endpoint was defined as the time in months from the date of market approval to the date of a first DHPC or safety-related withdrawal, whichever came first.

**Key characteristics**

Drug and procedural characteristics that could be possible confounders in our analysis were retrieved. These key characteristics were chosen based on literature data that suggested an increased risk of drug safety issues that are identified post-approval; e.g. drug class,(4) and biological drugs. (9) A larger patient population exposed to a drug before or after approval, could be hypothesized to decrease respectively increase the likelihood of identifying new serious safety issues after approval. (10)[Duijnhoven, in press] The ‘channelling’ phenomenon may be different for drugs that are used by highly specialized prescribers for rare diseases (orphan drugs), for drugs approved under ‘exceptional circumstances (EC)’ or with ‘conditional approval (CA)’. (11) As of November 2005 Risk Management Plans (RMP) have become a requirement for new drug applications in Europe. This more pro-active approach in risk management could potentially result in identifying new safety issues earlier or more frequently.

This resulted in the extraction of the following drug characteristics. Drug class was classified using the anatomical main group of the Anatomical Therapeutic and Chemical code (ATC-1 level). Three classes (A, J and L) comprise more than 50% of all drugs and are separately presented, the rest of drugs are grouped in the ‘other’ category. Second, the type of
molecule, was categorised as either a biological or a small molecule, identified from the EPARs. Third, the number of drug users, determined from the Drug Information System of the Health Care Insurance Board. This database comprises drug dispensing data for reimbursed drugs in the ambulatory care setting of 26 Dutch health care insurance companies, covering nearly all 16 million of the Dutch population. ([http://www.gipdatabank.nl](http://www.gipdatabank.nl)) The number of drug users was split into tertiles, according to the median number of users per year during the period 2007 to 2011. A separate group was created for the group of drugs not covered by the database as some drugs were not reimbursed, not marketed in the Netherlands, or used solely in the hospital setting. Fourth, the size of the study population; i.e. the total number of subjects exposed to the drug for any duration in the clinical development program before approval. [Duijnhoven, in press]

Three procedural issues were identified; orphan drug status (y/n), registration type; i.e. under exceptional circumstances or receiving conditional approval, and whether the drug had been approved after Risk Management Programs (RMPs) had become a requirement.

**Analysis**

Descriptive statistics, chi-squares and Kruskal-Wallis were used to describe differences in baseline characteristics, across the four different levels of innovation and for drugs with and without a first DHPC/withdrawal. The probability of drugs at different levels of innovation to reach the primary endpoint (first DHPC/safety withdrawal) is evaluated using Kaplan Meyer analysis correcting for follow-up duration; p-value was determined using the log-rank test using a trend-analysis. In a multivariable Cox proportional hazard model (HR and 95% CI) the association between level of innovation and the primary endpoint was determined, correcting for the key characteristics. Characteristics were included in the model (model 1) if they were unevenly distributed across the different levels of innovation or with respect to the occurrence of a serious safety issue (p<0.05). Using backward stepwise regression, only those characteristics were retained in the model that contributed to the model at p<0.2 (model 2).
RESULTS

A total of 633 drugs obtained a marketing authorization between 1 January 1999 and 31 December 2011, of which 354 were excluded [figure 2]. Of the remaining 279 new drugs, 59 (21%) were graded as important (grade A), 63 (23%) as moderate (B), 34 (12%) as modest (C), or as 123 (44%) ‘pharmacological / technological innovations (pharm/tech)’ [table 1]. The number of new drugs approved between 1999 and 2011 ranged between 12 and 26 per year [figure 3].

![Flow chart of study drugs](image)

**Figure 2** Flow chart of study drugs

Number of registrations with the European Medicines Agency (EMA) through the Centralised Procedure from 1 January 1999 to 31 December 2011. Duplicates are drugs registered under different trade names, known substances are drugs approved earlier either through national approval procedures (e.g. Tobi Podhaler containing tobramycin) and/or that were approved earlier for a different indication under a different registration number (e.g. sildenafil as Viagra™ for erectile dysfunction and subsequently as Revatio™ for pulmonary hypertension), combinations with at least one new active substances were included in our study (e.g. Tredaptive™ for dyslipidaemia that contained the new active substance laropiprant in addition to the known substance nicotinic acid), but not those containing only known active substances.

In total 114 DHPCs were issued of which 25 DHPCs for 15 drugs were excluded. Nine DHPCs concerned the administration of the drug, ten concerned the pharmaceutical quality of the drug product and two concerned the malfunctioning of a device for the administration of the drug. Four DHPCs for two highly innovative drugs (drotecogin alfa, and tenofovir [n=3]) regarded concerns of demonstrated lack of efficacy and were also excluded. This resulted in
the inclusion of 53 first and 36 repeated DHPCs. Nine drugs (3.2% of all drugs approved) were withdrawn for safety-related reasons. Clear safety-related withdrawals were efalizumab, sitaxentan (both grade B), rimonabant, rosiglitazone, and valdecoxib (pharm/tech). In four cases marketing was considered no longer commercially viable, because the target population had become too limited but without the regulatory authorities actively suspending their marketing authorisation; darbepoetin alfa, epoetin delta, inhaled insulin (all pharm/tech) and becaplermin (C).

Figure 3  Level of innovation of drugs approved in Europe (1999 – 2011)
Drugs are new active substances that are approved through the centralised procedure in Europe. Classification of innovation according to Motola (2); A) important, B) moderate, C) modest or as Pharm or Tech) merely pharmacological / technological innovations.

Fifty-five first serious safety events were identified, 53 first DHPCs and two safety-related withdrawals without a prior DHPC (the epoetins). Serious safety issues were identified for 15 (25%) drugs graded A, 13 (21%) graded B, 8 (24%) graded C, and 19 (15%) for the drugs graded as pharm/tech [p=0.40, Chi-square test, p=0.12 linear-by-linear association, table 2].

The median follow-up was 7.8 years (IQR: 4.0-10.4) for drugs graded A, 4.6 years (IQR: 2.4-6.9) graded B, 4.2 years (IQR: 3.2-7.2) graded C, and 7.3 years (IQR: 2.9-10.4) for the drugs graded as pharm/tech [p=0.01, Kruskal-Wallis test]. The Kaplan Meyer derived probability
for having a first serious safety issue, correcting for duration of follow-up, did suggest a trend in safety issues with increasing level of innovation, but was not statistically significant, log-rank (Mantel-Cox) p=0.067. Except for the biologicals, all characteristics were unequally distributed across the various levels of innovation (p<0.05) and therefore included in the multivariable Cox-model. [table 1] The key characteristics were equally distributed across drugs with or without serious safety issues. For six drugs we were unable to retrieve the number of subjects studied before approval as the scientific discussion had been removed from the EMA website after withdrawal of the products from the market. For these drugs we imputed the study population based on drugs approved within the same ATC-class (interferon alfacon-1 (1197), valdecoxib (3550), dofetilide (3410), apomorphine (2764) and fomivirsen (1328). Except valdecoxib all withdrawals were for commercial reasons and thus not recorded as a primary outcome.

In the adjusted Cox proportional hazards model (model 1) there was no statistical significant difference in occurrence of a first serious safety issue across the more innovative (A, B, and C) drugs when compared to the pharm/tech [reference] drugs [table 2, figure 4]. The results remained similar in model 2 that in addition to the level of innovation, incorporated as confounders drug class, study population size and post RMP approval; with for grade A [HR 1.63 (95%CI: 0.77; 3.43)], grade B [HR 1.48 (95%CI: 0.71; 3.08)], or grade C 1.16 (95%CI: 0.48; 2.82) drugs [table 2]. Antineoplastic and immunomodulating drugs (ATC-class L), as well as the size of the study population in the clinical program were the only significant potential confounders.
### Table 1: Key characteristics across innovation level of drugs in Europe (1999-2011)

<table>
<thead>
<tr>
<th>Drug characteristics</th>
<th>All drugs N(%)*</th>
<th>Innovation level of drugs N(%)***</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug classes (ATC-1 level)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Alimentary tract and metabolism (A)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Anti-infectives for systemic use (J)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Antineoplastic and immune</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>modulating agents (L)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Other drug classes ****</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of drug users per year**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital use only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>or not reimbursed in NL</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 228</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 228 and ≤ 2.117</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt; 2.117</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Number of drug users per year**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital use only</td>
<td></td>
<td></td>
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<tr>
<td><em>or not reimbursed in NL</em></td>
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</tr>
<tr>
<td>≤ 228</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 2.117</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biologics (y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size of study population, median (IQR)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedural characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orphan drugs (y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EC and CA registrations (y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post RMP approval (y)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| * Percentages are expressed within drugs, and level of innovation (column); ** p-value based on Chi-square (categorical data) and Kruskal-Wallis (continuous data) test; *** All drugs that are not categorized on ATC-1 level as A, J or L; & Median number of users per year in the Netherlands based on 2007-2011 reimbursement data from the Drug Information System of the Health Care Insurance Board, (y) Variable is dichotomous and value represents the "yes"; IQR Interquartile range showing 25th and 75th percentiles; ¥EPARs were not available for six drugs thus the size of the study population could not be established. For the analyses values were imputed based on the mean number of patients studied for drugs with the same ATC-5 or next the same ATC-3 level. Only in the case of valdecoxib was that withdrawal safety-related; EC Exceptional Circumstances; CA Conditional Approval; RMP Risk Management Plan; this variable indicates whether drugs were approved after RMPs became a requirement for new drug applications in the European Union (Nov 2005)
Table 2: Are serious safety issues and level of innovation associated (Cox-proportional hazards analyses) for centrally approved drugs in Europe (1999-2011)

<table>
<thead>
<tr>
<th>Drug characteristics</th>
<th>All drugs</th>
<th>Serious Safety issue (N%)</th>
<th>Cox-proportional hazards analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N(%)</td>
<td>yes</td>
<td>Model 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Model 2</td>
</tr>
<tr>
<td>Total</td>
<td>279 (100)</td>
<td>55 (100)</td>
<td></td>
</tr>
<tr>
<td>Level of innovation</td>
<td>224 (100)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Important (A)</td>
<td>59 (21)</td>
<td>15 (27)</td>
<td>1.93 (0.85;4.410)</td>
</tr>
<tr>
<td>Moderate (B)</td>
<td>63 (23)</td>
<td>13 (23)</td>
<td>1.84 (0.85;3.97)</td>
</tr>
<tr>
<td>Modest (C)</td>
<td>34 (12)</td>
<td>8 (15)</td>
<td>1.37 (0.55;3.38)</td>
</tr>
<tr>
<td>Merely pharmacological or technological (pharm/tech)</td>
<td>123 (44)</td>
<td>19 (35)</td>
<td>2.06 (1.01;4.23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.13 (1.05;4.31)</td>
</tr>
</tbody>
</table>

** Drug characteristics **

<table>
<thead>
<tr>
<th>Drug classes (ATC-1 level)</th>
<th>N(%)</th>
<th>yes</th>
<th>no</th>
<th>P**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alimentary tract and metabolism (A)</td>
<td>0.23</td>
<td>121 (43)</td>
<td>101 (45)</td>
<td>1.03 (0.44;2.44)</td>
</tr>
<tr>
<td>Anti-infectives for systemic use (I)</td>
<td>1.08 (0.42;2.81)</td>
<td>53 (18)</td>
<td>44 (20)</td>
<td>1.07 (0.39;2.97)</td>
</tr>
<tr>
<td>Antineoplastic and immune modulating agents (L)</td>
<td>1.42 (0.57;3.49)</td>
<td>53 (19)</td>
<td>36 (16)</td>
<td>1.82 (0.74;4.48)</td>
</tr>
<tr>
<td>Other drug classes ***</td>
<td>127 (46)</td>
<td>20 (36)</td>
<td>107 (48)</td>
<td>2.00 (1.01;4.23)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug characteristics</th>
<th>N(%)</th>
<th>yes</th>
<th>no</th>
<th>P**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital use only</td>
<td></td>
<td>20 (36)</td>
<td>101 (45)</td>
<td>1.03 (0.44;2.44)</td>
</tr>
<tr>
<td>or not reimbursed in NL ≤ 228</td>
<td>53.18</td>
<td>1.07 (0.39;2.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 228 and ≤2.117</td>
<td>53 (19)</td>
<td>36 (16)</td>
<td>1.82 (0.74;4.48)</td>
<td></td>
</tr>
<tr>
<td>&gt; 2.117</td>
<td>52 (19)</td>
<td>43 (19)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Biologics (y)</td>
<td>53 (19)</td>
<td>18 (33)</td>
<td>65 (29)</td>
<td>0.59</td>
</tr>
<tr>
<td>Size of study population, median (IQR)</td>
<td>1272 (522-2437)</td>
<td>1308 (878-2801)</td>
<td>1218 (460-2347)</td>
<td>0.15</td>
</tr>
<tr>
<td>Procedural characteristics</td>
<td>1.00 (1.00;1.00)</td>
<td>1.00 (1.00;1.00)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Percentages are expressed within drugs, and level of innovation (column); ** p-value based on Chi-square categorical data and Kruskal-Wallis continuous data test; *** All drugs that are not categorized on ATC-1 level as A, J or L; & Median number of users per year in the Netherlands based on 2007-2011 reimbursement data from the Drug Information System of the Health Care Insurance Board; (y) Variable is dichotomous and value represents the "yes"; IQR Interquartile range showing 25th and 75th percentiles; VEPARs were not available for six drugs thus the size of the study population could not be established. For the analyses values were imputed based on the mean number of patients studied for drugs with the same ATC-5 or next the same ATC-3 level. Only in the case of valdecoxib was that withdrawal safety-related; EC Exceptional Circumstances; CA Conditional Approval; RMP Risk Management Plan; this variable indicates whether drugs were approved after RMPs became a requirement for new drug applications in the European Union (Nov 2005)
Our data indicate that of all new drug approvals 21% can be considered important innovations, while nearly half (44%) can be considered as ‘me too’ (pharmacological or technological) developments. While 19% (53/273) of all centrally approved drugs received one or more DHPCs for a serious safety issue, only nine (3%) drugs were withdrawn. In contrast to our hypothesis, the level of innovation of drugs is not clearly correlated with serious safety issues that are identified post approval.

**DISCUSSION**

Our data indicate that of all new drug approvals 21% can be considered important innovations, while nearly half (44%) can be considered as ‘me too’ (pharmacological or technological) developments. While 19% (53/273) of all centrally approved drugs received one or more DHPCs for a serious safety issue, only nine (3%) drugs were withdrawn. In contrast to our hypothesis, the level of innovation of drugs is not clearly correlated with serious safety issues that are identified post approval.
Are more safety issues identified post approval for innovative drugs?

Serious safety issues have been suggested to be more common with biological agents versus small molecules, (9) while fewer issues were identified with orphan drugs. (11) A review of Canadian drug approvals indicated that priority review may increase the risk of serious safety issues being identified only until after approval. (12) In contrast, we showed earlier that drugs approved through EC or CA procedures that are aimed to facilitate drug approval for the same type of drugs in Europe did not show an increased risk. (13) The difference may be that in Europe the review period for this type of drugs is not necessarily shorter, allowing a robust assessment procedure. Our current findings indicate that also the level of innovation is not clearly related to the identification of serious safety issues post-approval. Possibly, this could be explained by the observed lower use of the more innovative drugs in ambulatory care. Nevertheless, in our adjusted analyses the level of use in clinical practice did not affect the risk of identifying serious safety issues. Therefore, the rapid uptake seems a less likely driver of an increased risk of identifying serious safety issues post approval. Also, channeling may not have played an important role, as neither the ECCA procedure -approval under exceptional circumstances or conditionally approved- nor orphan drug designation affected the model. These drugs are less likely to be channeled to higher risk populations post-approval than the patient population they were evaluated in pre-approval, as they are often used and reimbursed for very specific patients in highly specialized treatment centers only. Although, we were not able to prove our hypothesis our data suggest a slight trend, based on trend analyses (linear-by-linear association, and Mantel-Cox log-rank test) and incremental hazard ratios in model 2. The numbers in our study were necessary limited, due to the total number of drugs approved in our study period. Repeating this study in e.g. five years from now could result in that trend becoming statistically significant. Therefore, grading of level of innovation could be considered as a possible additional tool to guide problem-based risk management for new drugs that is currently done on a case-by-case basis.

Only two of the studied characteristics were true confounders in the association of innovative drugs and a serious safety event. Not surprising, for antineoplastic and immunomodulating drugs we observed a doubling of the risk of a serious safety issue post approval that was independent of the level of innovation. These drugs have been shown to be more commonly associated with safety-related regulatory actions. (4)(14) Still, accelerated approval of cancer drugs was considered safe, since only few drugs were withdrawn. (14) More surprising was that a larger size of the pre-approval study population
was associated with an increased risk of a serious safety issue. The numbers studied pre-approval were larger for the drugs graded as pharm/tech innovations, with only small differences between the other levels. The ‘me-too’ products are developed to get a share of large drug markets and can therefore easily include more patients in the clinical development program without really contributing to new drug safety knowledge. Our finding suggests that increasing the number of study patients pre-approval should be done with clinical judgment and is not necessarily predictive for identifying important but rare adverse drug events.

Over time there was no apparent pattern of more innovative drugs being approved, although it may be of some concern that the overall proportion of innovative drugs is lower than that reported in 2006. (1) This finding fits in the debate about the declining efficiency in drug development, drug approval success rates and lack of truly novel drug products and warrants further consideration. (8,15,16) Although, for approximately a fifth of all drugs a new serious safety issue was identified post-approval, this only resulted occasionally in the drug being withdrawn from the market. The lowest tolerance was possibly for the less innovative drugs that made up six of the nine withdrawals.

**Limitations**

Our study was limited to centralised products in Europa, which does not - especially in the earlier period - cover all important new drug approvals across the various European countries. This is however, unlikely to have affected our primary analysis as there seems to be a random variation in the level of innovation across the study years. We studied the duration from time of approval to the first serious safety issue. Therefore, as the total follow-up period, i.e. until the end of the study period, was similar (six to seven years) for both highly innovative and all other drugs this should allow for a proper analysis of time to event. The power of the study to detect differences may have been limited. However, we based our analysis on the total number of approved products in Europe, almost from the inception of the EMA in 1996. We argue that if a difference cannot be observed after 13 years of follow-up this difference may be less relevant.

Any assessment has an inherent level of subjectivity to it. The classification used by us is no exception. We performed independent assessments for each drug and resolved any discrepancies in consensus. A further shortcoming is the retrospective nature of assessing
the level of innovation. However, the EMA keeps the EPARs of the original market application at its website which we used for assessing innovativity at time of the initial approval. Whereas healthcare technology assessment agencies overseeing national reimbursement of drugs have their own grading system of a drug’s innovativity or added value there is no system adopted by EMA or one European accepted classification procedure. It may be worthwhile to come to a single European procedure that may be useful for both problem-based risk management and as a comparative indicator for reimbursement decisions. Finally, we used a national drug use database, based on reimbursement claims, in ambulatory care as a proxy for exposure. This is not representative for the whole of Europa or for world-wide uptake. In addition, some drugs are limited to use in hospital, but their use may be considerable.

Conclusion
Although, our study showed that fewer drugs represent important drug innovations than in 2006, more than half of all new drugs approved in Europe can be considered at least modest innovations that add value to the available drug armamentarium. Contrary to our hypothesis, a higher level of innovation was not clearly related to an increased risk of serious safety issues that are identified post marketing. Innovation does not go together a priori with an increased risk of serious safety issues identified post marketing.
LIST OF REFERENCES:


(3) Califf RM. Benefit assessment of therapeutic products: the Centers for Education and Research on Therapeutics.


(5) Tavassoli N, Montastruc J. Is there any relationship between actual benefit and added value of drugs and pharmacovigilance alerts?


Are more safety issues identified post approval for innovative drugs?

**APPENDIX TABLE: LIST OF DRUGS WITH OR WITHOUT SERIOUS SAFETY ISSUES AND CLASSIFICATION OF LEVEL OF INNOVATION**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>With serious safety issue</th>
<th>Without serious safety issue</th>
</tr>
</thead>
<tbody>
<tr>
<td>miglustat, voriconazole, tipranavir, abacavir, tenofovir, natalizumab, imatinib, sunitinib, natalizumab, etanercept, infliximab, verteporfin, palifermin, rimonabant, tigecycline, entecavir, telbivudine, etravirine, bevacizumab, erlotinib, bortezomib, efalizumab, lenalidomide, ranibizumab, deferasirox, dexrazoxane, methylnaltrexone, dabigatran, romiplostim, becaplermin, panitumumab, panitumumab, pemetrexed, cabazitaxel, ipilimumab, bexarotene, arsenic trioxide, eribulin, abiraterone, tumor necrosis factor alpha-1a (tasonermin), daclizumab, belatacept, canakinumab, rilonacept, pirfenidone, botulinum toxin type B, collagenase clostridium histolyticum, tufinamide, onalumab</td>
<td>Important (A) n=15</td>
<td>Important (A) n=44</td>
</tr>
<tr>
<td>methylnaltrexone, dabigatran, romiplostim, becaplermin, panitumumab, temsirolimus, adalimumab, tocilizumab, insulin human (inhalation), rosiglitazone, pioglitazone, eptifibatide, prasugrel, epsilon delta, darbepoetin alfa, dornedraone, sitaxentan, sitaxentan, sirolimus, eflornithide, anakinra, valdecoix, parecoxib, zoledronic acid, dibotefron alfa, strontium ranelate, aripiprazole, carbamyl chloride, agalsidase alfa, protein C, agalsidase beta, alglucosidase alfa, sodium phenylbutyrate, nitrosine, drotrecogin alfa, protein C, caspofungin, lipibawin, amipenavir, lopinavir/ritonavir, fosamprenavir, darunavir, telaprevir, boceprevir, efavirenz, efavirenz, alifibavir, mercuric, peramivir, repentrex, dofaribine, vinflunine, cabazitaxel, ipilimumab, bexarotene, arsenic trioxide, eribulin, abiraterone, tumor necrosis factor alpha-1a (tasonermin), daclizumab, belatacept, canakinumab, rilonacept, pirfenidone, botulinum toxin type B, collagenase clostridium histolyticum, tufinamide, onalumab</td>
<td>Merely pharmacological or technological innovations n=13</td>
<td>Merely pharmacological or technological innovations n=19</td>
</tr>
<tr>
<td>tocolizumab, insulin human (inhalation), rosiglitazone, pioglitazone, eptifibatide, prasugrel, epsilon delta, darbepoetin alfa, dornedraone, sitaxentan, sitaxentan, sirolimus, eflornithide, anakinra, valdecoix, parecoxib, zoledronic acid, dibotefron alfa, strontium ranelate, aripiprazole, carbamyl chloride, agalsidase alfa, protein C, agalsidase beta, alglucosidase alfa, sodium phenylbutyrate, nitrosine, drotrecogin alfa, protein C, caspofungin, lipibawin, amipenavir, lopinavir/ritonavir, fosamprenavir, darunavir, telaprevir, boceprevir, efavirenz, efavirenz, alifibavir, mercuric, peramivir, repentrex, dofaribine, vinflunine, cabazitaxel, ipilimumab, bexarotene, arsenic trioxide, eribulin, abiraterone, tumor necrosis factor alpha-1a (tasonermin), daclizumab, belatacept, canakinumab, rilonacept, pirfenidone, botulinum toxin type B, collagenase clostridium histolyticum, tufinamide, onalumab</td>
<td>Merely pharmacological or technological innovations n=8</td>
<td>Merely pharmacological or technological innovations n=19</td>
</tr>
<tr>
<td>tocilizumab, insulin human (inhalation), rosiglitazone, pioglitazone, eptifibatide, prasugrel, epsilon delta, darbepoetin alfa, dornedraone, sitaxentan, sitaxentan, sirolimus, eflornithide, anakinra, valdecoix, parecoxib, zoledronic acid, dibotefron alfa, strontium ranelate, aripiprazole, carbamyl chloride, agalsidase alfa, protein C, agalsidase beta, alglucosidase alfa, sodium phenylbutyrate, nitrosine, drotrecogin alfa, protein C, caspofungin, lipibawin, amipenavir, lopinavir/ritonavir, fosamprenavir, darunavir, telaprevir, boceprevir, efavirenz, efavirenz, alifibavir, mercuric, peramivir, repentrex, dofaribine, vinflunine, cabazitaxel, ipilimumab, bexarotene, arsenic trioxide, eribulin, abiraterone, tumor necrosis factor alpha-1a (tasonermin), daclizumab, belatacept, canakinumab, rilonacept, pirfenidone, botulinum toxin type B, collagenase clostridium histolyticum, tufinamide, onalumab</td>
<td>Merely pharmacological or technological innovations n=8</td>
<td>Merely pharmacological or technological innovations n=19</td>
</tr>
</tbody>
</table>

*n= number of drugs*
### APPENDIX TABLE (Cont): LIST OF DRUGS WITH OR WITHOUT SERIOUS SAFETY ISSUES AND CLASSIFICATION OF LEVEL OF INNOVATION

<table>
<thead>
<tr>
<th>Level of Innovation (grade)</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate (B) n=50</td>
<td>prucalopride, aprepitant, tocopherosan, laronidase, idursulfase, sapropterin, antithrombin alfa, ticagrelor, C1 inhibitor human, eltrombopag, conestat alfa, dorfetilde, ivabradine, icatibant, tolvaptan, retapumulin, atosiban, mecasermin, aztreonam, palivizumab, nelarabine, azactidine, catumaxomab, ofatumumab, 5-aminolevulinic acid, temoporfin, sorafenib, nilotinib, everolimus, pazopanib, mitotane, eculizumab, fingolimod, ustekinumab, epototermin alfa, zicatizone, levetiracetam, duloxetine, varenicline, amifampridine, fampridin, roflumilast, nitric oxide, fomiviren, brinzolamide, bivalirudin, rivaroxaban, ranolazine, cinacalcet, doripenem, temozolomide, trabectedin, cetuximab, porfimer, gefitinib, lapatinib, alitretinoin, anagrelide, mifamurtide, plerixafor, abatacept, belimumab, febuxostat, denosumab, stiripentol, memantine, sodium oxybate, tafamidis</td>
</tr>
<tr>
<td>Modest (C) n=26</td>
<td>betaine, galsulfase, zinc acetate, bivalirudin, rivaroxaban, ranolazine, cinacalcet, doripenem, temozolomide, trabectedin, cetuximab, porfimer, gefitinib, lapatinib, alitretinoin, anagrelide, mifamurtide, plerixafor, abatacept, belimumab, febuxostat, denosumab, stiripentol, memantine, sodium oxybate, tafamidis</td>
</tr>
<tr>
<td>Merely pharmacological or technological innovations n=104</td>
<td>palonosetron, fosaprepitant dimeglumine, insulin human (fast acting), insulin lispro, insulin aspart, insulin glulisine, insulin human (intermedia acting), insulin aspart novomix, insulin glargine, insulin detemir, sitagliptin, vildagliptin, saxagliptin, linagliptin, nateglinide, exenatide, liraglutide, velaglucerase alfa, iloprost, prasugrel, tenecteplase, apixaban, fondaparinux, human fibrinogen / human thrombin, morococog alfa, octocog alfa, human coagulation factor IX, epoetin theta, methoxy polyethylene glycol-epoetin beta, vernakalant, bosentan, ambrisentan, azilsartan, aliskiren, nicotinic acid / laropiprant, efllornithine, ethynylestradiol and norelgestromin, ulipristal, lutropin alfa, choriogonadotrophine alfa, corffollotropin alfa, bazedoxifene, lasofoxifene, oxybutynin, darifenacin, fesoterodine, apomorphine, tadalaflil, vardenafil, silodosin, somatropin, ganirelix, cetorexil, teriparadine, parathyroid hormone, ertapenem, telithromycin, fexidamicin, posaconazole, micafungin, anidulafungin, oseltamivir, human normal immunoglobulin, busulfan, cladribine, cytarabine, capcitabine, tegafur/gimeracil/oteracil, doxorubicin, degarelix, pegfilgrastim, interferon alfa-2b, interferon alfacon-1, peginterferon alfa-2a, peginterferon alfa-2b, certolizumab pegol, golimumab, characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins (ChondroCelect), capsacaricin, zonisamide, pregabalin, lacosamide, retigabine, rotigotine, rasagiline, asenapine, paliperidone, zaleplon, dexmedetomidine, agomelatime, memantine, dihydroartemisinin / piperaquine, fluticasone furoate, indacaterol, desloratadine, nepafenac, bromfenac, travoprost, emedastine, olopatadine, sugammadex, sevelamer, rasburicase</td>
</tr>
</tbody>
</table>
Part II

Importance of drug effects as perceived by regulators, doctors and patients
Regulators base their decision to approve new drugs on an assessment of benefit risk balance at the population level as determined in clinical trials. Doctors and patients make their decisions at the individual level. Doctors base their decisions to a large part on evidence based guidelines, applying these to individual patients, while patients have to integrate drugs in their daily life. Some regulatory decisions have been criticised as the conclusion on a drug’s benefit/risk balance are not always shared by doctors, patients or society at large. Demonstration of different views raises doubts whether regulators are sufficiently in touch with the clinical reality of doctors and patients. Are their different views the result of making decisions at the population level instead of the individual patient level or do regulators genuinely value benefits and risks of drugs differently from other stakeholders? We therefore wanted to study the (dis)agreement in values that regulators attach to different drug effects in comparison to doctors and patients, at the level of an individual patient. To do so we performed a discrete choice survey where regulators, doctors and patients were asked which of two hypothetical OADs with varying drug effects they preferred for a typical patient with type 2 diabetes.
Chapter 5:

Selecting drug effects for a discrete choice study
INTRODUCTION

Discrete choice models is a widely used method to elicit preferences. (1) Discrete choice models consist of providing respondents a choice between two or more options. In this study these options were drugs that were described in scenarios with relevant attributes, i.e. drug effects. Every attribute (drug effect) is varied at different levels and shown to respondents in a set of different scenarios. Respondents are given these scenarios in pairs from which to choose the scenario they prefer most. The strength of the method is that it provides information on the relative importance of the attributes. It is therefore a valuable approach to understand how trade-offs are made when weighing benefits and risks of drugs by the different stakeholder involved; regulators, doctors and patients. The relevance of the results of such discrete choice models is determined by the relevance of the selection of relevant attributes and the corresponding levels of these attributes. These should reflect actual important decision criteria of the respondents. (1,2)

In this chapter we describe how we selected the attributes and levels used in our discrete choice surveys. As in this case the benefit risk balance is the central issue, the attributes refer to drug effects, effectiveness and safety.

Regulators base their decision to approve new drugs on an assessment of benefit risk balance at the population level as determined in clinical trials. Doctors and patients make their decisions at the individual level. Doctors base their decisions to a large part on evidence based guidelines, applying these to individual patients, while patients have to integrate drugs in their daily life. In order to provide a common ground for decision, we described a hypothetical patient that we ask the respondents to keep in mind while making their decisions. In this chapter we also describe how we formulated this hypothetical patient.

The aim of this part of the study is to identify relevant decision criteria, and the corresponding levels to include in the model. In addition we describe the development of the patient hypothetical which is constant for all choices.
METHODS

We used a qualitative approach, combining literature review with in-depth interviews of relevant stakeholders.

Literature search

A search was done in Medline for studies using the discrete choice methodology to assess preferences for oral anti-diabetes drugs, spanning the years 2000 to 2011. From the studies found we determined which drug effects and characteristics had previously been used as attributes in discrete choice surveys regarding drug treatment in diabetes.

Review of regulatory documents

The regulatory guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus was reviewed for the requirements of demonstrating minimal efficacy and possible side effects. Results from the interviews also prompted a review of the relevant guidelines for weight reducing agents. The Summary of Product Characteristics for anti-hyperglycaemic drugs on the Dutch and European market were reviewed and main benefits and harms extracted.

Qualitative study, using in-depth interviews

Open interviews, using a topic guide, were performed with a purposeful sample of individuals that are representatives of stakeholder groups in diabetes care; patients with type 2 diabetes, nurses involved with diabetes care, general practitioners (GPs), internists involved in diabetes care and specialists involved with assessment of diabetes drugs from the Dutch Medicines Evaluation Board. The interviews took place at the participant’s home, at their place of work or in a meeting facility at the researchers’ workplace. Participants were interviewed independently by MMS (7) or SP (13) both observed by AHA. One participant was interviewed by AHA alone. The study is based on grounded theory (3) and the topic guide thus re-evaluated and amended after each interview to reflect new topics arising in each interview. Respondents were included until no new information was provided by the interview.

Respondents were asked open questions on how they value each drug effect for the treatment of type two diabetes mellitus. The interviewer used a list of topics that were
identified from literature(4-9) and in theory would be considered important and probed for the respondents’ views on those topics.

The topic guide consisted of the following themes: efficacy, safety, ease of use, costs and the role of the regulator. (see appendix A,B and C).

The interviews were recorded using a digital voice recorder, transcribed per verbatim and analysed using the “three-step” method: First the transcripts were read to familiarize with the content, secondly statements were coded and thirdly themes were identified from the coding.

**Compiling the attribute list**

A list of possible attributes, i.e. drug effects was compiled from the results of the literature search, review of regulatory documents and the interviews. The list was then narrowed down to 6 attributes during a discussion within the project team as generally, 6-7 attributes are advised, with no more than 3-5 levels each. (1)

**Creating the hypothetical patient**

The hypothetical patient is constructed based on the ‘average’ DM2 patient. This was based on data from the Groningen Initiative to Analyse Type 2 diabetes Treatment (GIANTT). GIANTT includes over 20,000 patients with type 2 diabetes in GP practices in the northern part of the Netherlands and collects from electronic health records.

**RESULTS AND DISCUSSION**

**Literature search**

We found four studies using a discrete choice design for eliciting preferences in diabetes treatment (table 1). All four studies included glycated haemoglobin (HbA1c) value, nausea or stomach upset and incidence of hypoglycaemias in their list of drug effects. Overall 14 drug attributes were used in these four studies. All studies included changes in HbA1c, frequency of hypoglycaemias and gastro-intestinal (GI) problems. (10-13) Three studies included changes in weight (10,11,13) and two studies included mode of administration, frequency of
Table 1: Attributes used in previous discrete choice surveys regarding diabetes

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year of publication</th>
<th>Attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hauber et.al (10)</td>
<td>2009</td>
<td>HbA1c change, Number of ‘hypos’ per month, Water retention, Weight gain in first 6 months, Mild stomach upset, Chance of a heart attack within 1 year</td>
</tr>
<tr>
<td>Jendle et.al (11)</td>
<td>2010</td>
<td>Mode of administration, Blood glucose monitoring, Payment per month, Number of hypoglycaemic events, HbA1c, Weight, Nausea, Antihypertensive treatment, Blood pressure, Heart function</td>
</tr>
<tr>
<td>Polster et.al (12)</td>
<td>2010</td>
<td>Dosing, Control of glucose levels, Incidence of nausea, Incidence of hypoglycaemia</td>
</tr>
<tr>
<td>Bogelund et.al (13)</td>
<td>2011</td>
<td>Mode of administration, Blood glucose monitoring, Payment per month, Number of hypoglycaemic events, HbA1c, Weight, Transient nausea, Anti-hypertensive treatment, Blood pressure, Heart function, Driver’s licence</td>
</tr>
</tbody>
</table>
血糖检测，患者每月支付，抗高血压药物，血糖和心功能在改善的距离患者能行走的距离，(11,13) 水肿，(10)，增加心脏病的风险(10)，服药频率(12)和保持驾照的能力(13)被包括在一个研究中。
Review of regulatory documents

The regulatory guideline directly relating to clinical development of anti-hyperglycaemic (14) is the guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus. According to the guideline, the main efficacy parameter to be determined for registration of oral anti-diabetes drugs (OAD) is the effect on blood glucose control in terms of decrease in HbA1c. Hypoglycaemia is considered an important safety parameter and is also discussed specifically in the guideline, as well as cardiovascular (CV) risk. (14)

The regulatory guideline directly relating to clinical development of weight reducing agents is the guideline on clinical evaluation of medicinal products used in weight control. According to the guideline, weight loss is the primary endpoint and drugs that are to be registered as weight reducing agents need to demonstrate at least a weight loss of 10% of the baseline weight (and at least 5% greater than a placebo) in a 12 month period. (15)

The review of summary of product characteristics of OADs and insulin resulted in a summary of the mechanism of action, the main advantages and main disadvantages of each drug group [table 2]. The main adverse drug reactions of the groups are symptomatic, such as GI complications, hypoglycaemia and weight gain, although some drug groups did have uncommon serious adverse drug effects listed, such as lactic acidosis, bladder cancer and hypersensitivity. Only one drug, metformin, has shown to reduce the risk of experiencing cardiovascular events. (16)

Qualitative study, using in-depth interviews

A total of 22 interviews were performed, involving three specialists from the Dutch Medicines Evaluation Board (MEB), four practicing internists (all male, 5 to 24 years of experience), five practicing General Practitioners (GPs) (20% female, 1 to 34 years of experience), two diabetes nurses and one specialized GP assistant (67% female, 9 to 16 years of experience), one pharmacist (male, 11 years of experience) and six patients with type II diabetes (50% female, age range 56 – 85 years).

Table 3 provides a summary of the most relevant criteria mentioned by the respondents, illustrated by quotes from the different groups.
With regards to efficacy the respondents mostly mentioned expectation of glucose control and weight loss (Table 3). Expectations of stopping disease progression and long term effect were also expressed, as well as expectations of effect on complications.

With regards to safety the respondents mostly mentioned that safety and efficacy should be balanced. Healthcare professionals and regulators acknowledged that there is an aspect of uncertainty regarding safety of drugs and some expressed reluctance to use a drug due to lack of knowledge of (long term) safety and efficacy. Symptomatic ADEs were considered to be manageable by respondents from all groups, for example by dose-adjustments or switching to another medicine.

Some respondents expressed the wish to avoid hypoglycaemias. Risk awareness of drugs new to the market clearly differed with some respondents expressing high risk awareness, while others, notably some of the patients, did not.

With regard to ease of use the respondents mostly mentioned that fewer administrations per day were preferred. When probed further most respondents had positive opinions on fixed combination products, although negative opinions were also expressed. Respondents found that dosing frequency was very important and that taking drugs should not interfere with a patients’ daily life. Regulators indicated that other drug effects have a higher priority than issues of ease of use, although one regulator shared with other stakeholders the view that a drug should not interfere with daily life.

Aspects regarding costs were not discussed if not prompted. When asked some respondents found that patient participation in costs would be a hindrance to using the drug, while others did not see that as a problem.

An additional topic arose in the interviews and was added to the topic guide, stakeholder’s attitude towards patient registries as a method for post-marketing surveillance. When asked, most stakeholders had a positive view of introducing patient registries as a requirement for prescriptions of new OADs, provided that it would not take too much time and provided that the information could not be traced to individual patients.
### Table 3: Examples of respondent remarks.

<table>
<thead>
<tr>
<th><strong>Drug related properties (efficacy)</strong></th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expectations of glucose control</td>
<td>Well, mainly that it needs to bring the HbA1c down, as an example [internist]</td>
</tr>
<tr>
<td></td>
<td>... the applicant should show that HbA1c is going down, to well, at least 0.5%, for a large population [Assessor]</td>
</tr>
<tr>
<td>Expectations of effect on complications</td>
<td>... you would like to know that something is known on [the impact on] secondary endpoints in the sense of micro- and macro-vascular complications [GP]</td>
</tr>
<tr>
<td>Expectations of long term effect</td>
<td>You don’t only want to know what it does now, but also what the effect is after 10 years [GP]</td>
</tr>
<tr>
<td>Expectations of stopping progression</td>
<td>... that the drug will be able to stop the deterioration of the beta cell function, what causes the progression of the disease and causes patients needing to take always more tablets [internist]</td>
</tr>
<tr>
<td>Expectations (desire) of weight loss due to drug</td>
<td>...because of the fact that I lose weight using it, and that has always been a problem for me [Patient]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Drug related properties (safety)</strong></th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety and efficacy need to be balanced</td>
<td>... if quite a lot of patients experience, diarrhoea or something...and then if the efficacy is only minor, well that might influence then the decision for approval or not [Assessor]</td>
</tr>
<tr>
<td>Symptomatic ADEs manageable</td>
<td>Maybe I would be satisfied with a drug that is less effective, as long as it has fewer adverse effects [GP]</td>
</tr>
<tr>
<td>Adjusting dose or changing medication to avoid ADEs</td>
<td>... when you see that with GLP1 [drugs] at first all adverse effects such as diarrhoea and those kind of things occur, but knows that these disappear after some time, then – you can still sell that your patients [Internist]</td>
</tr>
<tr>
<td>Avoidance of hypo's</td>
<td>Of course you also want to avoid complaints of hypoglycaemia [GP]</td>
</tr>
<tr>
<td>Reluctance due to lack of (long term) knowledge (safety and efficacy)</td>
<td>You know what you have, but not what you are getting [Nurse]</td>
</tr>
<tr>
<td>Acknowledgement of uncertainty</td>
<td>... you don’t want to stop development of new drugs...But on the other hand you don’t want to expose your patients to risks that might have been discovered if they had analyzed better [GP]</td>
</tr>
<tr>
<td>New drugs are not risky</td>
<td>Earlier we also started using metformine even if we did not know if it was useful in the long term. We started using SU derivatives, not knowing if they were useful... [SU derivatives] even seemed harmful and yet we prescribed them [Internist]</td>
</tr>
<tr>
<td>New drugs are/can be risky</td>
<td>No, I did not think it was risky (starting to use a drug that was new to the market) [Patient]</td>
</tr>
<tr>
<td></td>
<td>[Asked if prescribing new drugs is risky] Yes! [GP]</td>
</tr>
<tr>
<td></td>
<td>[Asked if a new drug to the market carries risks] Of course! [Assessor]</td>
</tr>
</tbody>
</table>
### Drug related properties (ease of use)

<table>
<thead>
<tr>
<th>Positive view of combinations</th>
<th>That both drugs can be in one tablet, that would be nice [Patient]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I think that generally in well controlled patients, with a chronic</td>
</tr>
<tr>
<td></td>
<td>disease, there certainly is room for [FDCs] [GP]</td>
</tr>
<tr>
<td>Negative view of combinations</td>
<td>I never prescribe Fixed Dose Combinations (FDCs)! [GP]</td>
</tr>
<tr>
<td>Fewer dosings per day preferred</td>
<td>...then you might have to swallow a lesser amount with the same effect [Patient]</td>
</tr>
<tr>
<td>Dosing routine is important</td>
<td>It is easier for your routine to take one pill a day, than to take one pill a week. I can imagine that you would forget your once weekly pill [GP]</td>
</tr>
<tr>
<td>Drugs should not interfere with daily life</td>
<td>... if patients are using insulin, then, they have to control themselves so many times a day... the patients should live ... without controlling himself every moment [Assessor]</td>
</tr>
<tr>
<td></td>
<td>...Sometimes you have to take your medicine in the presence of someone else [due to circumstances], I always try to do that a bit sneaky and now I don’t have to because I take it only once a day [Patient]</td>
</tr>
</tbody>
</table>

### Drug related properties (costs)

| Patient payments a hindrance  | Only financially it is just not feasible for me [to pay the drug myself] [Patient] |
| Patient payments not a hindrance | But it could also be that people say “yes but I do not want to wait any longer, I want to start already.” Okay, you can, but you must pay for it yourself first [Nurse] |

### Compiling the attribute list

After consideration of the interviews and results from the literature search, we compiled a list of possible attributes to include to depict a glucose lowering drug. This list comprised of 13 attributes; Change in HbA1c, effect on complications, effect on CV risk, mechanism of action, positive adverse effects, transient adverse events, persistent adverse events, uncertainty about safety of newly marketed drugs, extent of clinical trials performed, plans for post-marketing follow-up, dosing frequency, method of administration, ease of use and costs.

Thirteen attributes is too much to include in any discrete choice model. With 13 attributes, respondents would not be able to make decisions based on all of them and would revert to excluding some of them or decide not to participate. Generally, 6-7 attributes are advised, with no more than 3-5 levels each. (1) We therefore needed to narrow our selection down to 6 attributes. The attributes selected should be relevant in the registration setting, as well as...
for doctors and patients. The levels chosen for each attribute should be based on what has been seen for diabetes drugs or the requirements needed for registration.

Inclusion criteria were that different stakeholders would at least have adequate background knowledge to weigh the different drug effects. We excluded attributes that a priori would be expected to be very different between different stakeholders.

We decided to exclude attributes that are not considered in the regulatory setting, and therefore excluded attributes related to costs, dosing frequency, and ease of use (including method of administration).

Although plans for post-marketing follow-up studies, the mechanism of action and the size of clinical trials are of considerable importance in the regulatory process, for patients and doctors these issues are difficult to understand, specifically in the context of a discrete choice experiment, and were excluded.

We excluded effects on complications, because healthcare professionals in our interviews indicated that treatment of many complications, such as foot-ulcers and neuropathy, has improved considerably in recent years. Additionally, patients did not mention effects on complications in the interviews.

Although many respondents mentioned that they would like more certainty in the knowledge of the safety of drugs, we found that it would be difficult to include uncertainty as a measure that would be understood by patients. When looking at the other possible attributes, we found that including the (un)certainty of a specific adverse event might introduce the possibility that patients might understand that attribute differently from regulators or doctors. We therefore decided to exclude it from the list.

The final lists comprises of efficacy and safety parameters. Firstly there is the efficacy parameter of reducing HbA1c. The CV risk characteristic is on both efficacy and safety parameter levels, as a reduction in CV risk is considered efficacious, while an increase in CV risk is an ADR. Effect on weight is likewise on both efficacy and safety parameter levels, as a reduction in weight is considered a positive side effect and an increase in weight a negative side effect. Hypoglycaemia, gastrointestinal complications and risk of bladder cancer were all included as safety parameters, with both transient/infrequent levels and persistent/frequent levels. The final attribute and level list is provided in table 4.
At the time of development of this discrete choice model, the safety of pioglitazone was heavily debated, as it had been associated with the risk of bladder cancer. (17-21). Because of the actuality of this issue, We decided to include risk of bladder cancer in our final attribute list. The levels chosen are based on the baseline risk of bladder cancer in the diabetes population and the 50% relative risk increase associated with pioglitazone.

Control of diabetes in terms of improved HbA1c levels was included as an attribute, as it is the efficacy parameter used in trials for market authorisation applications. Additionally it was mentioned by several responders in our interviews and has been seen as an important characteristic in earlier studies. (10-13,22). The levels chosen reflect changes that are small (HbA1c remains too high), intermediate (HbA1c might be acceptable, but is still not optimal) and large (HbA1c goal of less than 7.0% is reached) (23,24) The levels of blood glucose lowering presented is based on actual effects. Guidelines recommend that patients with an HbA1c of 8.5% should receive anti-hyperglycaemic therapy in addition to life style advice. (24) In clinical registration trials usually patients have a baseline HbA1c in the range of 7.5 to 10 % and reductions are achieved in the range from 0.5 to 1.5% after 24 weeks of treatment. (25) The largest reduction described here is not usually seen after the administration of a single OAD, but was added as it provides a change that results in reaching the 7% treatment target. (24)

OADs are approved to the market based on demonstration of lowering of blood glucose. It is assumed that lowering of blood glucose results in lowering the long term risk of CV events, although only metformin has been shown to lower CV risk. (16) However, as rosiglitazone has been shown to increase the risk of CV events, we found a potential detrimental effect on CV events an important drug effect. Therefore, both lowering and increasing the risk of CV events were included, as well as no change in CV risk. (26) The levels of changes in CV risk presented are based on actual observed effects. In the high risk ACCORD population CV risk was approximately 2 % per year. (29) We used a lower baseline risk – 3% per two years - that is more appropriate for a more general T2DM population that comprises patient with and without previous cardiovascular events. In view of the increased 1.4 risk of myocardial infarction as described by Nissen and Wolski we set the increased risk at 4%. (26)

In our interviews, both a capacity to lose weight (considered an added value) as well as weight gain (considered as an ADR) were mentioned as being important drug characteristics.
Selecting drug effects for a discrete choice study

Table 4: Drug characteristics and levels used as attributes

<table>
<thead>
<tr>
<th>Drug attribute</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>Decreases from 8.5% to 8.0% (too high)</td>
</tr>
<tr>
<td></td>
<td>Decreases from 8.5% to 7.5% (suboptimal)</td>
</tr>
<tr>
<td></td>
<td>Decreases from 8.5% to 6.9% (optimal)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>An increased (4%) risk; 4 instead of 3 out of 100 patients.</td>
</tr>
<tr>
<td></td>
<td>Unchanged (3%) risk; 3 out of 100 patients.</td>
</tr>
<tr>
<td></td>
<td>A decreased (2%) risk; 2 instead of 3 out of 100 patients.</td>
</tr>
<tr>
<td>Effect on weight</td>
<td>5% (4.5 kg) weight gain. 5% weight gain.</td>
</tr>
<tr>
<td></td>
<td>No influence on weight 10% (9 kg) weight loss.</td>
</tr>
<tr>
<td>Mild nausea, vomiting or diarrhoea</td>
<td>Throughout the use of the drug (persistent)</td>
</tr>
<tr>
<td></td>
<td>During the first two weeks of use of the drug (transient)</td>
</tr>
<tr>
<td></td>
<td>No stomach complaints</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>More than 2 per month (more frequent)</td>
</tr>
<tr>
<td></td>
<td>1-2 per month (less frequent)</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Risk of cancer</td>
<td>Increased (0.06%) risk; 6 instead of 4 out of 10,000 patients.</td>
</tr>
<tr>
<td></td>
<td>Unchanged (0.04%) risk; 4 out of 10,000 patients.</td>
</tr>
</tbody>
</table>

HbA1c: glycated haemoglobin

Additionally, earlier studies reported impact on weight to be important to patients. (10,11,13,22) The levels chosen are according to the weight increase seen for insulin therapy (27) and the regulatory guideline for weight reducing agents. (15)

Gastrointestinal (GI) complaints and risk of hypoglycaemia are both common ADRs of various OADs. In our interviews these attributes were considered important, as well as in earlier studies. (10,12,13) The levels were chosen to represent a transient or not frequent event on one hand and persistent or more frequent on the other, in addition to no risk of the event.
Creating the hypothetical patient

The average age of the GIANTT population in 2007 was 67 years, with an average duration of diabetes of 5.8 years and an average BMI of 30 kg/m². Fifty-two percent of the population were female. Glucose-regulating medication was used by 83%, blood-pressure regulating medication by 76% and lipid-regulating medication by 72% of the population. (28)

We therefore described the hypothetical patient as a 67 year old man, who weighs 90kg, has diagnosis of type 2 diabetes and high blood-pressure that is well controlled with an ACE-inhibitor and is using a statin. He has no other chronic conditions and is not using any other medication.

To demonstrate that the patient needs additional treatment we included in the description that the patient is currently using the maximum dose of metformin that he tolerates but still has had an elevated HbA1c (8.5%) for the past 6 months, which is considered to be too high in the Dutch clinical guideline for the treatment of type 2 diabetes. (24)

Acknowledgements

I would like to thank Margje Monster-Simons and Sigrid Piening for interviewing the stakeholders and the respondents for giving us their time for answering the questions.
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APPENDIX A: TOPIC GUIDE FROM QUALITATIVE INTERVIEWS - PATIENTS

Introduction

We are performing research on the expectation of patients towards new drugs coming to the market – specifically drugs to treat type II diabetes.

We interview a number of patients to select the appropriate questions to ask in a more quantitative survey.

First I will be asking a few general questions about your experience with your diabetes and your medication to get the general picture of the process and thereafter more specifically into requirements and expectations for new diabetes drugs.

Demographic aspects

- How old are you?
- Do you live alone or do you have a partner?
- What kind of work do you do/have you done?
- For how long have you been diagnosed with diabetes?
- Who is the physician that handles your diabetes? Your GP or a doctor in the hospital?
  - Are you happy with your treatment?
- Are there any other healthcare professionals involved in your treatment? (nurses/home care/pharmacists)
- Do you have other illnesses apart from the diabetes
- What are the drugs that you are using at the moment?
- Do you know what these drugs are for?

Experience with diabetes and glucose lowering drugs

Disease related experience

- Have you had complications of you diabetes?
- Have you had problems with too low blood sugar (hypoglycaemia)?
- Do you monitor your blood glucose yourself? Do you go the lab for blood glucose measurements?
  - Does the term HbA1c mean anything to you?
  - Are you informed of your values from your 3-monthly tests? Do you know what they mean?

Medication related experience

- What is your experience with your diabetes medication?
  - Is your blood glucose well controlled using these drugs?
Have you had any problems with your diabetes medication?

- Do you feel that your drugs affect your quality of life?
- Do you think your medication is user friendly?
  - How many times per day do you need to take your medication?

- Have you had side effects of your diabetes medication?
  - If yes; which ones?
  - If yes; did you report it and to whom?
  - If yes; how did your doctor handle that?

- Has your diabetes medication ever been changed?
  - How?
  - Why?
- Are there any medicines that you would rather not take?
  - If yes; which ones?
  - If yes; why?

- Do you have an idea of how your drugs can help you?
  - If yes; how?
  - Do you have an idea of how your medicines work? Do you also know what you might expect in the long term?

- Do you worry about taking diabetes medication?
  - If yes; how?

- Does your doctor involve you in the decision of which drugs to choose for your therapy?
  - If yes; do you like that?

**Information regarding medication**

**Information for patients**

- Who explains your medicine to you?
  - How?
- Do you read the information sheet that comes with the drug (patient information leaflet)
  - Do you think it is easy to understand?
- If you want to know more about drugs, how do you seek that information?
New drugs on the market

Efficacy
- What kind of expectations do you have to new diabetes medication with regards to efficacy?
- In what way do you feel that a new drug should differ from the existing drugs with regards to efficacy? What do you think is the most important?
- What do you want to know about the efficacy of a new drug before you agree to use it?

Safety
- What kind of expectations do you have to new diabetes medication with regards to safety?
- In what way do you feel that a new drug should differ from the existing drugs with regards to safety? What do you think is the most important?
- What do you want to know about the safety of a new drug before you agree to use it?
- Do you think it is risky to take a drug that is new to the market?
  - What are those risks?
- How much risk are you willing to accept?
  - What if the risks are not known? (short/long term)

Ease of use
- Would you accept a new drug if you only need to take it once a day? Do you think that would be better for you than your current dosing schedule?
- If a new product contains two known drugs combined in one tablet, would that appeal to you? Do you think that would be better for you than your current medication?
- Would you be willing to use a new drug if it could be administered with a once three-monthly injection instead of a daily oral medication? Do you think that would be better for you than your current medication?
- Would you be willing to use a new drug that require you to have your checkups more often, but would make your daily routine easier? Do you think that would be better for you than your current medication?

Costs
- Would it be a problem for you if your insurance company does not pay for your medication (at all or partly)?
Chapter 5

The role of the authorities

• What do you know about development and registration of new drugs?
  o E.g. number of patients in trials, how efficacy is evaluated etc. (make this more open...)
  o What is your opinion of the current system of allowing marketing of new medications?

• If a new drug comes to the market, the manufacturer is obliged to monitor if the drug works as well in daily practice as it did in clinical trials and if it is as safe. There are several different ways to conduct this monitoring. One of those is a user registry system, where all new users of the drug must be registered in the system and all relevant information regarding the drug use and disease progression are monitored by the system.
  o Would you object to being enlisted in such a system?
  o What kind of questions would you be willing to answer if you were?
  o How much time could it cost you?

Do you have any questions or remarks regarding the subject of the interview?
APPENDIX B: TOPIC GUIDE FROM QUALITATIVE INTERVIEWS – HEALTHCARE PROFESSIONALS

Introduction
We are performing research on the expectation of doctors/nurses towards new drugs coming to the market – specifically drugs to treat type II diabetes.
We interview a number of doctors/nurses to select the appropriate questions to ask in a more quantitative survey.
First I will be asking a few general questions about your work as a doctor to get the general picture of how diabetes care is organized in your practice and thereafter more specifically into requirements and expectations for new diabetes drugs.

Demographic aspects
• How long have you worked as a doctor/specialist/nurse?
• How long have you worked in this practice?
• How many patients does your practice service?
• How does the patient population look like (e.g., old/young)?
• Can you estimate how many of your patients have diabetes type 2?
  o Can you estimate their average age?

Diabetes care in the practice
• How is diabetes care organized in your practice (monitoring)?
• Do you have a specialized diabetes nurse or assistant involved in the diabetes care?
  o If yes; how is the care divided?
• When you diagnose diabetes type II, what are the drugs you prescribe as first therapy?
  o How do you make your choice?
• Do you generally follow clinical guidelines in your diabetes care?
• Do you encounter instances where the guidelines are not sufficient?
  o What do you do then?
• Is the diabetes of your patients in general well controlled?
• Do you think your patients know what HbA1c is?
• Do you think you patients know what their HbA1c levels mean (regardless of whether they know the term)?

Experience with diabetes and glucose lowering drugs

Disease related experience
• Have you had patients that suffer from diabetes related complications?
Chapter 5

Medication related experience

• Have you had patients that suffer from (diabetes) medication related complications?
• Do you take the quality of life of patients into account when you choose their medication?
  o If yes; in what way?
• Do you think the quality of life of patients is important?
• Have you treated patients that reported side effects of their diabetes medication?
  o If yes; has that change the way you prescribe those medications?
  o If no; do you think that would change the way you prescribe those medications?
  o If yes; serious/non serious?
  o If yes; frequent/infrequent?
• Are there any medicines that you prescribe more than others?
  o Why?
  o Why not?
• Are there any medicines that you would rather not prescribe?
  o If yes; which ones?
  o If yes; why??
• Do you involve your patients in the choice of which drug to prescribe?
  o If yes; why?
  o If yes; do you think that leads to better control of the blood glucose?
  o If no; why not?
• Does the effect a medicine has on weight influence the medication choices?
  o If yes; how?
• Do you consider a delay in insulin use to be a measure of effectiveness of a drug?

Information regarding medication

Information for patients

• Do you provide information regarding the prescribed drugs to your patients? (agreement with pharmacies)?
  o If yes, how? When?
  o If no; why not?
• Do you expect your patient to read the patient information leaflet?

Information for healthcare professionals

• How do you access information regarding drugs that are new to the market?
  o Do you trust your information?
New drugs on the market

Efficacy

- What kind of expectations do you have to new diabetes medication with regards to efficacy?
- In what way do you feel that a new drug should differ from the existing drugs with regards to efficacy (soft / hard endpoints)? What do you think is the most important? (choose one aspect that is important to you)
- What do you want to know about the efficacy of a new drug before you prescribe it?

Safety

- What kind of expectations do you have to new diabetes medication with regards to safety?
- In what way do you feel that a new drug should differ from the existing drugs with regards to safety (soft / hard endpoints)? What do you think is the most important? (choose one aspect that is important to you)
- What do you want to know about the safety of a new drug before you prescribe it?
- Do you think it is risky to prescribe a drug that is new to the market?
  - What are those risks?
- How much risk are you willing to accept?
  - What if the risks are not known? (short/long term)

Ease of use

- Would you prescribe a new drug if the patient only needs to take it once a day instead of an alternative that needs to be taken multiple times a day?
- If a new product contains two known drugs combined in one tablet, would you transfer patients from the two pills to the combination tablet?
- Would you be willing to prescribe a new drug if it could be administered with a once three-monthly injection instead of a daily oral medication?
- Would you be willing to prescribe a new drug that requires you to monitor the patient more often, but would make the patients daily routine easier?

Costs

- Would it affect your prescription of a new drug if the patients would need to pay partly or fully the costs of the drug?

The role of the authorities

- What is your opinion of the current system of allowing marketing of new medications?
- What do you think of using user registries to monitor new drugs?

Do you have any questions or remarks regarding the subject of the interview?
APPENDIX C: TOPIC GUIDE FROM QUALITATIVE INTERVIEWS - REGULATORS

Introduction
We are performing research on the expectation of different stakeholders towards new drugs coming to the market – specifically drugs to treat type II diabetes.
We interview doctors, patients and assessors to select the appropriate questions to ask in a more quantitative survey.
First I will be asking a few general questions about your work as an assessor to get the general picture of the process and thereafter more specifically into requirements and expectations for new diabetes drugs.

Demographic aspects
- How long have you worked as an assessor?
- How long have you worked in the assessment of diabetes drugs?

Assessment of diabetes drugs
- How does the assessment procedure for diabetes drugs work?
- What do you keep in mind when you assess diabetes drugs?

Experience with diabetes and glucose lowering drugs

Medication related experience
- Have you ever assessed a drug that, after some time on the market, appeared to have a safety issue?
  - If yes; does that change how you regard applications for new drugs?
  - If no; do you think that would change how you regard applications for new drugs?
- Do you think of quality of life of patients when you review a new diabetes drug?
  - If yes; How?
  - A drug can have different influence on a patient’s quality of life for various reasons. How does that affect the evaluation of the drug?
- Are there certain diabetes drugs you find should be prescribed most often?
  - If yes; which ones?
  - If yes; why?
  - If not: Why not?
- Are there certain diabetes drugs you find should be used less that other drugs?
  - If yes; Which ones?
  - If yes; Why?
Selecting drug effects for a discrete choice study

• Do you think patients should be involved in deciding if a drug should be prescribed to them?
  o If yes; Why?
  o If no; Why not?

• Do you think patients should be involved in deciding if a drug should be allowed to the market?
  o If yes; Why?
  o If no; Why not?

**Information regarding medication**

**Information for patients**

• Do you expect patients to read the patient information leaflet of their drugs?
• How do you expect patients receive their information on their diabetes drugs?
  o Do you think the information they receive is trustworthy?

**Information for doctors**

• How do you think doctors get their information on new diabetes medication?
  o Do you think the information they receive is trustworthy?

**Information for assessors**

• How do you keep up to date with what is in the pipeline for diabetes drugs?
  o Do you trust the information?
  o Do you think information you receive before the process starts could influence how you assess the application?

**New drugs on the market**

**Efficacy**

• What do you require the applicant to demonstrate for their drug in the context of efficacy before you recommend granting marketing authorization?
• In what single aspect do you feel a new drug should be different from the drugs currently on the market when it comes to efficacy?

**Safety**

• What do you require the applicant to demonstrate for their drug in the context of safety before you recommend granting marketing authorization?
• In what single aspect do you feel a new drug should be different from the drugs currently on the market when it comes to safety?
• Would you think a drug that is new to the market poses some risk?
  o How much risk would you accept?
Chapter 5

Ease of use

- If a drug could be administered once daily in stead of multiple times a day, would that be a reason to recommend marketing authorization?
- Would you recommend marketing authorization to a combination preparation of two known glucose lowering drugs?
- If a drug could be administered with a once three-monthly injection in stead of a daily oral medication, would that be a reason to recommend marketing authorization?
- If a drug would be easier for patients with regards to ease of use but would require extra monitoring, would that be a reason to recommend marketing authorization?

Costs

- Does the cost of medication play any role in the decision to recommend marketing authorisation?

The role of the authorities

- What is your opinion of the current regulatory system?
- What do you think of using user registries to monitor new drugs?

Do you have any questions or remarks regarding the subject of the interview?
Chapter 6:
Benefit and risk preferences of patients for oral anti-diabetes drugs

Arna H Arnardottir
Petra Denig
Sabine MJ Straus
Pieter A de Graeff
Flora M. Haaijer-Ruskamp
Paul FM Krabbe
Peter GM Mol
**Abstract**

**Objective:** To evaluate the importance that patients with diabetes attach to glucose regulating and cardiovascular benefits of oral anti-diabetes drugs (OAD) relative to symptomatic adverse drug reactions (ADRs) and serious ADRs when choosing an OAD.

**Research Design and Methods:** A discrete choice survey was administered to 315 patients with type 2 diabetes, aged 60 to 75. Eighteen choice sets of two hypothetical drugs were created varying in their drug effects: level of HbA1c control, risk of cardiovascular disease, weight, gastro-intestinal symptoms, and hypoglycaemic episodes. Additionally, all hypothetical drugs had either a baseline or increased level risk of bladder cancer. Patients were presented with six choice sets each and asked to indicate which of the two they preferred. Analysis was done using conditional multinomial logit modelling.

**Results:** Response was 72%, of the patients with mean age 67 (SD: 4.5) years and 48% women. Patients preferred drugs that reduced CV risk (OR: 1.74, p = 0.028) and avoided drugs that had the following drug effects: persistent GI problems (OR: 0.16, p < 0.001); frequent hypoglycaemia (OR: 0.24, p < 0.001); weight increase (OR: 0.39, p < 0.001); CV risk increase (OR: 0.47, p = 0.004), and less frequent hypoglycaemia (OR: 0.50, p = 0.020). HbA1c control, risk of bladder cancer, and other levels of drug effects did not statistically affect a patient’s choice for a hypothetical drug given its other drug effects.

**Conclusion:** Patients weigh heavily ADRs that influence their daily life. Control of glucose and a small increased risk of cancer are not as important for the drug choice.
INTRODUCTION

Currently a patient-centred approach in health care is being adopted, in particular in chronic diseases, where the focus is on how patients can be (more) actively involved in treatment decisions and self-management (1). For treatment of diabetes, many pharmaceutical options are available, varying in mechanism of action, impact on clinical outcome and profile of adverse drug reactions (ADR) (2,3). All of these anti-diabetes drugs have shown to lower blood glucose levels, but evidence of long term benefit may be uncertain (3). Safety concerns range from common, often symptomatic ADRs, such as gastrointestinal (GI) upset and hypoglycaemia, to more unusual, long term ADRs like a possible increased risk of cardiovascular events or cancer (2-4). Therefore, the benefits and risks between may vary with patients and physicians differing in their treatment goals and preferences (5,6). Although clinical guidelines are available on how best to treat patients with diabetes, these are more physician oriented and do not take into account patient preferences that need to be considered when determining an optimal treatment plan.

Several studies have assessed treatment preferences of patients with diabetes (7-12). In general, patients value clinical outcomes, such as glycaemic control and ADRs, more than convenience of the medication, including dosing schedules and administration forms. When considering these clinical outcomes, avoiding side effects, especially GI effects, and weight gain as well as improving HbA1c levels, appears to be more important for patients than avoiding hypoglycaemic events (6,7,11). The relative ranking, however, depends on the extent or frequency of these positive or negative outcomes. Patients may differ in their preferences (7-11). One study included long term benefits, showing that these were considered more important than convenience of the treatment regime (8). Another study included possible serious safety outcomes, indicating that these can be at least as important to patients with diabetes as the short term benefits and risks (10). None of these studies, however, combined the full range of clinical outcomes, including short term and long term benefits as well as common and serious ADRs.

The aim of this study is to evaluate the importance to diabetes patients of short term glucose regulating and long term cardiovascular benefits of OADs relative to symptomatic ADRs (gastrointestinal problems, change in weight, hypoglycaemia) and serious ADRs (cardiovascular, cancer). A secondary aim is to explore whether the importance patients attach to these drug effects is affected by their current status of glucose control or weight or by prior experience with ADRs.
**Methods**

**Study design**

We conducted a cross-sectional survey of patients with type 2 diabetes in the Netherlands. We used a discrete-choice experimental design to estimate the relative importance of different drug effects. Patients were asked to choose between pairs of hypothetical oral anti-diabetes drugs which vary in their drug effects. An example is depicted in Figure 1. The method incorporates a trade-off to elicit patients’ willingness to accept certain risks in exchange for a certain amount of benefit (13). Subsequently, the collected responses were used in a statistical model to estimate the relative importance of different drug effects. A waiver was obtained from the medical ethical committee of the University Medical Centre Groningen for this survey.

**Selection of drug characteristics and levels**

The drug effects selected to create the hypothetical OADs were based on 22 in-depth interviews; 6 patients, 3 nurses, 9 doctors, 3 regulators and a pharmacist, and an informal review of the literature, regulatory requirements and product labelling of OADs. The drug effects chosen were [Table 1]:

- Control of diabetes in terms of improved glycated haemoglobin (HbA1c) levels. This is an important in earlier studies and in our interviews and a major efficacy parameter in trials for market authorisation applications (6,7,10-12).

- Impact on cardiovascular outcomes. One of the major reasons for controlling blood glucose levels is ultimately to reduce cardiovascular (CV) risk but some OADs may even increase CV events as shown with rosiglitazone (14).

- Impact on weight. This has been reported to be important to patients with diabetes (6,7,10,11), both as a capacity to lose weight (considered an added value) as well as to gain weight (considered as an ADR).

- Gastrointestinal (GI) complaints and risk of hypoglycaemia. These are both common ADRs of various OADs, which have been shown to be important to patients in earlier studies and our interviews (7,10,12).

- Risk of bladder cancer, a serious but rare ADR that has led to debate about the safety of another OAD, pioglitazone (15-19).
The hypothetical drugs varied on these drug effects [Table 1]. We selected levels of variation that were considered to be plausible and representative of current OAD therapy.

**Table 1** Drug characteristics and levels included in the hypothetical drugs

<table>
<thead>
<tr>
<th>Drug attribute</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>Decreases from 8.5% to 8.0% (small)</td>
</tr>
<tr>
<td></td>
<td>Decreases from 8.5% to 7.5% (medium)</td>
</tr>
<tr>
<td></td>
<td>Decreases from 8.5% to 6.9% (large)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>An increased (4%) risk; 4 instead of 3 out of 100 patients</td>
</tr>
<tr>
<td></td>
<td>Unchanged (3%) risk; 3 out of 100 patients</td>
</tr>
<tr>
<td></td>
<td>A decreased (2%) risk; 2 instead of 3 out of 100 patients</td>
</tr>
<tr>
<td>Effect on weight</td>
<td>5% (4,5 kg) weight gain</td>
</tr>
<tr>
<td></td>
<td>No influence on weight</td>
</tr>
<tr>
<td></td>
<td>10% (9 kg) weight loss</td>
</tr>
<tr>
<td>Mild nausea, vomiting or diarrhea</td>
<td>Throughout the use of the drug</td>
</tr>
<tr>
<td></td>
<td>During the first two weeks of use of the drug</td>
</tr>
<tr>
<td></td>
<td>No stomach complaints</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>More than 2 per month</td>
</tr>
<tr>
<td></td>
<td>1-2 per month</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Risk of cancer</td>
<td>Increased (0,06%) risk; 6 instead of 4 out of 10.000 patients</td>
</tr>
<tr>
<td></td>
<td>Unchanged (0,04%) risk; 4 out of 10.000 patients</td>
</tr>
</tbody>
</table>

HbA1c: glycated haemoglobin

**Choice tasks**

Patients were asked to choose between several sets of hypothetical OADs. An orthogonal algorithm (Orthoplan, SPSS) was used to select the minimum number of choice sets needed to facilitate the estimation of all main effects. The final selection comprised 18 choice sets with two OADs each. At least two drug effects differed in level between the two OADs within each choice set. To reduce the burden in time on respondents, three versions of the survey were created containing a random set of six choice sets each.

At the start, a description of a hypothetical diabetes patient was presented. This patient was a 67 years old man, weighing 90 kilos, and using metformin, as well as medication to control his high blood pressure and a statin. His blood glucose was poorly controlled and he needed another drug in addition to his metformin. Responders were asked to indicate which of the OADs they preferred, imagining being this patient. The patient description was repeated above each choice set.
### Chapter 6

<table>
<thead>
<tr>
<th>Medicine A</th>
<th>Medicine B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c</strong></td>
<td>Decreases from 8.5% to 7.5%</td>
</tr>
<tr>
<td><strong>Cardiovascular disease</strong></td>
<td>Unchanged (3%) risk; 3 out of 100 patients</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>5% (4.5 kg) weight gain</td>
</tr>
<tr>
<td><strong>Mild nausea, vomiting or diarrhoea</strong></td>
<td>During the first two weeks of use</td>
</tr>
<tr>
<td><strong>Hypoglycaemia “hypo's”</strong></td>
<td>1-2 per month</td>
</tr>
<tr>
<td><strong>Bladder cancer</strong></td>
<td>Unchanged (0.04%) risk; 4 out of 10,000 patients</td>
</tr>
</tbody>
</table>

My preference goes to:

- Medicine A □
- Medicine B □

**Figure 1** Example of a discrete-choice task

**Patient population**

Patients between the age of 60 and 75 years, receiving at least one prescription of an anti-diabetes drug (non-insulin) in the preceding four months were identified from pharmacies in the northern part of the Netherlands. The age limit was selected to include patients that could relate to our hypothetical patient. Pharmacy interns at the pharmacies contacted the identified patients by telephone and asked permission to send the patients the questionnaire. In case no response was obtained two weeks after the questionnaire was sent, the patient was contacted again as a reminder.
**Patient characteristics**

At the end of the survey, patients were asked to fill in their gender, age, and highest completed education. In addition, they were asked for the year they were diagnosed with diabetes, and to report their current height and weight, as well as the HbA1c value from their last 3-monthly check-up. These data were used to estimate the patients’ diabetes duration, body mass index (BMI), and to whether their blood glucose was under control or not (HbA1c < 7% or ≥ 7%). Finally, the patients were asked if they had experienced any side effects of their diabetes medication in the last year.

**Analyses**

For the modelling of the data collected in the discrete choice experiments multinomial statistical models were used, in which one of the levels for each drug effect is set as reference level. The following levels were chosen as reference: a small decrease in HbA1c level, no change in CV risk, no effect on weight, no stomach complaints, no hypoglycemies, and no change in risk of bladder cancer. We applied a multinomial conditional logit model (asclogit, Stata). The main effect model included 11 dummy variables, since five of the drug effects varied on three levels and one drug effect on two levels.

**Subgroup analyses**

Subgroup analyses were performed to examine whether benefit and risk preferences were different for patients with different levels of (< 30 and ≥ 30 kg/m²), HbA1c control (<7% and ≥7%), or previous experience with ADRs (yes or no). Patients with BMI over 30 kg/m² were compared with patients with BMI under 30 kg/m² regarding their preferences for changes in weight, patients reporting an HbA1c of 7% or more were compared to those reporting HbA1c under 7% regarding their preferences for HbA1c control, and patients reporting experience with ADRs were compared to those reporting no such experiences regarding their preferences for avoiding hypoglycaemias and GI problems.
**Table 2:** Demographic and clinical characteristics of respondents

<table>
<thead>
<tr>
<th>Demographics and clinical characteristics</th>
<th>Number (% ) or mean (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender [female; n (%)]</strong></td>
<td>108 (47.8%)</td>
</tr>
<tr>
<td><strong>Age [years; mean (sd)]</strong></td>
<td>67 (4.5)</td>
</tr>
<tr>
<td><strong>Highest education</strong></td>
<td></td>
</tr>
<tr>
<td>High school diploma or less [n (%)]</td>
<td>151 (67.1%)</td>
</tr>
<tr>
<td>More than high school diploma [n (%)]</td>
<td>74 (32.9%)</td>
</tr>
<tr>
<td><strong>Weight [kg]</strong></td>
<td>86 (14.8)</td>
</tr>
<tr>
<td><strong>BMI [mean (sd)]</strong></td>
<td>29 (5.2)</td>
</tr>
<tr>
<td>Non-obese [BMI &lt; 30; n (%)]</td>
<td>130 (59.4%)</td>
</tr>
<tr>
<td>Obese [BMI ≥ 30; n (%)]</td>
<td>89 (40.6%)</td>
</tr>
<tr>
<td><strong>Duration of diabetes [years; mean (sd)]</strong></td>
<td>9 (8.8)</td>
</tr>
<tr>
<td><strong>Last HbA1c value [mean (sd)]</strong></td>
<td>6.8 (1.1)</td>
</tr>
<tr>
<td>&lt; 7% [n (%)]</td>
<td>91 (54.8%)</td>
</tr>
<tr>
<td>≥ 7% [n (%)]</td>
<td>75 (45.2%)</td>
</tr>
<tr>
<td><strong>Self-reported ADRs experienced [yes; n (%)]</strong></td>
<td>51 (22.8%)</td>
</tr>
</tbody>
</table>

sd: standard deviation, BMI: Body Mass Index; HbA1c: Glycosylated haemoglobin

**Table 3:** Perceived importance of drug characteristics for specific subgroups

<table>
<thead>
<tr>
<th></th>
<th>Patients with HbA1c under 7%</th>
<th>Patients with HbA1c over 7%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>HbA1c small change</td>
<td>1.49</td>
<td>0.57 - 3.88</td>
</tr>
<tr>
<td>HbA1c large change</td>
<td>1.89</td>
<td>0.49 - 7.38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Patients with BMI under 30</th>
<th>Patients with BMI over 30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Weight increase</td>
<td>0.39</td>
<td>0.23 - 0.68</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>0.85</td>
<td>0.55 - 1.31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Patients without ADR experience</th>
<th>Patients with ADR experience</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Long term GI</td>
<td>0.19</td>
<td>0.11 - 0.32</td>
</tr>
<tr>
<td>Short term GI</td>
<td>0.84</td>
<td>0.50 - 1.41</td>
</tr>
<tr>
<td>Frequent hypos</td>
<td>0.30</td>
<td>0.13 - 0.70</td>
</tr>
<tr>
<td>Infrequent hypos</td>
<td>0.62</td>
<td>0.32 - 1.21</td>
</tr>
</tbody>
</table>

HbA1c: Glycosylated haemoglobin; OR: odds ratio; CI: confidence interval; BMI: Body Mass Index; ADR: Adverse Drug Reaction; GI: Gastro-intestinal
**RESULTS**

**Response**

Of the 315 patients that received the survey, 226 responded (72%), with mean age 67 (sd: 4.5) years and 48% were women. The mean self-reported HbA1c was 6.8% (sd: 1.1), the reported mean duration of diabetes was 9 years (sd: 8.8), and the mean BMI was 29 kg/m$^2$ (sd: 5.2). Fifty-one (23%) of patients reported to have experienced adverse drug reactions (ADRs) from their current OADs in the previous year. [Table 2]

**Preferences**

Patients preferred drugs that had as one of their drug effects that they reduced CV risk (OR: 1.74, p = 0.028) [Figure 2]. Patients were less inclined to choose drugs that had the following drug effects: persistent GI problems (OR: 0.16, p < 0.001); more than 2 episodes of hypoglycaemia per month (OR: 0.24, p < 0.001); weight increase (OR: 0.39, p < 0.001); CV risk increase (OR: 0.47, p = 0.004), or 1-2 episodes of hypoglycaemia per month (OR: 0.50, p = 0.020). HbA1c, the risk of bladder cancer and other levels of drug effects did not statistically affect a patient’s choice for a hypothetical drug given its other drug effects.

**Subgroup analyses**

A large decrease in HbA1c level was valued higher by patients with inadequate control of HbA1c than by patients with good glucose control, while both groups had similar values for smaller changes in HbA1c. Patients that had experienced ADRs were less inclined to choose OADs with persistent GI problems than those who had not, but they did not differ in their preference regarding transient GI problems or hypoglycaemias. [Table 3]

Obese patients valued increase in weight and weight loss similarly to patients that were not obese.

**DISCUSSION**

Our results show that long term cardiovascular benefit and risk and persistent symptomatic ADRs influence patients’ preferences for a specific OAD more than glucose regulating benefits or an increase in small cancer risk. These preferences were in part affected by previous or current experiences of the patient, especially regarding HbA1c control and ADRs.
Figure 2 Perceived importance of drug characteristics by patients (Log of Odds Ratios and 95% Confidence Intervals)

An OR>1 indicates that patients are more inclined to choose a drug with a specific characteristic and level. Vice versa, patients are less inclined to choose drug characteristics and levels with an OR<1.
As could be expected patients preferred OADs that decrease their CV risk and avoided drugs increasing their CV risk, which is in line with a similar study (10). In our study this long term benefit had a greater weight than short term changes in HbA1c but smaller than of ADRs experienced; i.e. persistent GI problems and frequent hypoglycaemias. Patients are less likely to adhere to drug treatments that have intangible benefits, especially when ADRs are experienced (10,20). Our results underline the need to take into account patients’ concerns about ADRs and to discuss with them not only the long term benefits of OADs but also the possible negative effects and how to manage them (21).

We saw very little effect of changes in HbA1c on patient preferences, except in those patients whose HbA1c was uncontrolled (higher than 7%). Previously, a large decrease in HbA1c was reported to be the largest influence on patient preferences (10). This difference may be explained by the levels of the HbA1c selected by other researchers where their largest decrease was from 10.5% to 6.5%. This change is very large and is unlikely to be achieved by one drug (2). However, others have reported changes in HbA1c being important to patient preferences, although not always as the most important drug effect (6,7,11,12). These studies did include a younger study population than is presented here. In a study in the elderly glucose control did have a lower importance to patients than diet and exercise and the more vulnerable patients did have an even lower preference for intense glucose control than non-vulnerable patients (22).

Patients preferred to avoid persistent GI problems while they did not seem particularly worried about transient GI problems. This is in line with earlier results that showed that persistent stomach problems are considered important, in contrast to transient stomach problems (7,10). On a similar note, patient find it more important to avoid drugs with more than two hypoglycaemias per month than drugs with one or two hypoglycaemia attacks per month, suggesting that they find the magnitude of the problem relevant. Patient preferences regarding transient ADRs and frequency of recurrent ADRs underline the importance of improving understanding of the time course and frequencies of ADRs (7,10,11,23,24). Routine collection of data about the time course of ADRs (e.g., when an ADR can be expected, how frequently it occurs and how long it will last with or without stopping therapy) is usually not performed in clinical drug trials (25,26) and not addressed in the
drugs’ patient information leaflet or the summary of product characteristics (27). Given our results of patients discriminating between ADRs with short or long duration, this information should be investigated more thoroughly and be available to patients.

Additionally, patients having experienced ADRs were even less inclined to choose hypothetical drugs that caused persistent GI problems than patients that did not report having experienced ADRs. These results, coupled with the results of patients that have uncontrolled HbA1c, suggest that patients that have had difficulties with their treatment, have different preferences for drug effects. However, patients that have experienced ADRs did not differ with regard to avoiding hypoglycaemia as found in earlier studies. (10,11) Therefore, we cannot extrapolate these findings to all ADRs.

Patients tried to avoid increase in weight as an ADR, while a possible benefit of weight loss did not seem to affect their preferences. The former is in line with what has been seen previously (6,7,10,11,28), while the non-effect of weight loss seems contradictory to results from similar studies, where preferences for weight loss were high (6,7,11). Additionally, presence of obesity has been shown to influence patient preferences for OADs that may give weight loss while our results show no differences between obese patients and those who are not obese (6,7,11). The overall difference in weight loss preferences is unlikely to be a result of the levels/scale used by the researchers, as the weight loss presented in our study was higher than in the previous studies. Also it cannot be attributed to lack of statistical power in our sub-population analysis as the odds ratios for weight increase were statistically significant for both sub-groups. A more likely explanation is that the study population in the previous studies was much younger than the population in this study, while they did not differ in gender ratio and might therefore have a stronger preference for weight loss, particularly for the young obese (6,7,11).

The apparent lack of effect of at 50% increased risk of bladder cancer seems surprising in view of the concerns raised in response to the association with pioglitazone use. This could have two possible explanations. One is that the baseline risk of bladder cancer in the diabetes population is very small and small risks are difficult to grasp for the studied patients (29). The other is that patients actually have understood the risk but identified more common risks as being more relevant to them.
Limitations/ strengths:

The results of the discrete-choice method is subjective to the drug effects and levels chosen. As discussed earlier, when larger differences in levels are given, more effect on patient preferences may result. (30) We tried to minimize this effect by selecting levels that are plausible and representative of what is known about the OADs already on the market.

In presenting the drug scenarios to patients, some of the drug effects were depicted only with text and numbers, while others were depicted with coloured pictures, hence being more noticeable on paper. The design of the scale figure used to describe changes in HbA$_1c$ is based on a previous discrete choice study (10). The design of the ‘smiley-face’ matrix used to describe changes in risk of CV events was intended to make the proportions presented more understandable to patients (31,32). The results show that most value was attached to two of the drug effects presented with text and numbers, indicating that this difference in presentation did not lead patients to disregard those drug effects.

The population was selected from pharmacies in the northern part of the Netherlands and might not necessarily represent patients with diabetes from outside the Netherlands. The patients selected for the study were ranging from 60 to 75 years of age and might differ in their preferences or values from those older or younger. However, this age group consisted of a large group of users of OADs in the Netherlands (43% of total OAD users in 2009 (33)) and with a response rate of more than 70% we may assume that the responders are representative of Dutch diabetes type 2 patients. Finally, the subgroup analysis of patient characteristics was based on self-reported values. We did not have access to the patients’ medical files and could not verify that those values were accurate.

Implications for practice:

Diabetes patients have clear preferences about treatment options, which are partly driven by their own experiences. Patients value CV risk reduction, one of the main goals of diabetes treatment, but also prefer drugs more that do not lead to persistent symptomatic ADRs. This calls for a dialogue between prescriber and patient to ascertain that the OAD chosen is appropriate for each patient. Following prescription, active monitoring for and management of ADRs by both patient and prescriber is necessary. Symptomatic ADRs affecting patients’ quality of life and CV risk are indicated as being more important to patients than other drug effects, including a small realistic risk of bladder cancer.
LIST OF REFERENCES:


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Chapter 7:

Do regulators value benefits and risks of oral anti-diabetes drugs in the same way as doctors and patients?

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Paul FM Krabbe
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Pieter A de Graeff
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Petra Denig
Peter GM Mol
ABSTRACT

Regulatory decisions are criticised for not always reflecting the benefit/risk assessment as made by doctors and patients. We investigated whether the value regulators attach to benefits and risks of oral anti-diabetes drugs (OAD) is in agreement with these stakeholders. We administered a discrete choice survey to 79 regulators, 845 doctors and 315 patients with type 2 diabetes. Eighteen choice sets were made comparing two hypothetical OADs with varying drug effects on glycated haemoglobin (HbA1c), cardiovascular (CV) risk, weight, duration of gastrointestinal (GI) complaints, frequency of hypoglycemia, and bladder cancer risk. Responders were asked each time which OAD they preferred. Multinomial conditional logit analyses were conducted. CV risk reduction was valued by regulators positively, whereas drug choices were negatively affected by persistent GI problems and CV risk increase in the same way as doctors and patients. This shows that they can support regulators in making decisions at an individual patient level.
INTRODUCTION

Regulators base their decision to approve new drugs on an assessment of the balance between their benefit and risks at a population level as determined in clinical trials. Doctors and patients make their decisions at the individual level. In their decision making, doctors rely to a large part on evidence based guidelines, applying these to individual patients, while patients may value benefits and risk from the perspective of having to integrate drugs in their daily life based on the information that they receive from their physician and other information sources, including the patient leaflet. As in clinical practice, where patient participation in decision-making has been accepted as an integral part of the management of chronic diseases, (1) also regulators acknowledge a growing role of the patient in the drug approval process. The European Medicines Agency (EMA) has formalised collaboration with patient organisations in the Patients’ and Consumers’ Working Party and in the USA, the Food and Drug Administration (FDA) did the same in the Patient Representative Program. (2,3) Nevertheless, to date the patient role in the scientific discussions and decision making regarding the approval of drugs has been very limited. (2)

Occasionally, regulatory decisions have attracted the attention or even opposition from doctors and patients. Clear examples were in the field of HIV/AIDS and vaccines. For instance, there has been strong opposition from certain consumer groups to the approval and subsequent use of human papilloma virus vaccine and the combined measles, mumps and rubella vaccine. (4-8) On the other hand, patients with HIV/AIDS have pressured regulators to approve new drugs faster. Recently, natalizumab, a drug to treat multiple sclerosis (MS), was taken off the market by the FDA because it could cause progressive multifocal leukoencephalopathy (PML). However, when patient benefit risk perception was made explicit, and the risk of PML was found to be acceptable to the individual MS patient, natalizumab was re-introduced to the market. (9,10)

Cases like these raise doubt whether regulator decisions sufficiently reflect the clinical needs and reality of doctors and patients. Their different views could be the result of making decisions at the population level instead of the individual patient level but it could also be that regulators genuinely value benefits and risks of drugs different than other stakeholders. Several studies have evaluated how patients and doctors value drug benefits and risks, for example in the field of diabetes, (11-15) but not in relation to regulators’ assessments.
The field of diabetes provides a good case to assess whether values that regulators attach to different drug effects are in agreement to the values of doctors and patients. In this field, several oral anti-diabetes drugs (OADs) from different pharmacological classes are available that all provide some level of glucose control but have different immediate and long term risks. To compare the values underlying drug decisions at the level of an individual patient, we conducted a ‘discrete choice’ survey where regulators, doctors and patients were asked which of two hypothetical OADs with varying drug effects they preferred for a typical patient with type 2 diabetes.

**METHODS**

We performed a survey to estimate the relative value that regulators, doctors and patients with type 2 diabetes assign to different drug effects. A discrete-choice experimental design was used where responders were asked to choose between several pairs of hypothetical OADs. The method incorporates a trade-off to elicit responders’ willingness to accept certain risks in exchange for a certain amount of benefit. (43) A waiver was obtained from the medical ethical committee of the University Medical Center Groningen for this survey.

**Study participants and recruitment**

All 65 clinical and pharmacovigilance assessors and 14 members of the Board identified from the internal telephone directory of the Dutch Medicines Evaluation Board (MEB) were sent an e-mail containing a link to the survey website and unique log-in information. Two and three months later an e-mail reminder was sent to non-responders.

Doctors included were general practitioners and internists practicing in diabetes care. A randomly selected list of 593 general practitioners was obtained from the Dutch institute of research in healthcare (NIVEL). A list of 252 internists practicing in diabetes care was compiled from the websites of all Dutch hospitals. These doctors were sent a paper-based questionnaire including an option to respond electronically through a secure website. Two months later non-responders were reminded to fill in the questionnaire.
Patients between the age of 60 and 75 years, receiving at least one prescription of an OAD in the preceding four months, were identified from pharmacies in the northern part of the Netherlands. Pharmacy interns contacted these patients by telephone and requested permission to send a questionnaire. Two weeks after the questionnaire was sent, the interns phoned again to follow up on non-responders.

**Table 1: Drug effects and levels as used for the hypothetical drugs**

<table>
<thead>
<tr>
<th>Drug effect</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>Small decrease from 8.5% to 8.0% (too small)</td>
</tr>
<tr>
<td></td>
<td>Intermediate decrease from 8.5% to 7.5% (suboptimal)</td>
</tr>
<tr>
<td></td>
<td>Large decrease from 8.5% to 6.9% (optimal)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>An increased (4%) risk; 4 instead of 3 out of 100 patients.</td>
</tr>
<tr>
<td></td>
<td>Unchanged (3%) risk; 3 out of 100 patients.</td>
</tr>
<tr>
<td></td>
<td>A decreased (2%) risk; 2 instead of 3 out of 100 patients.</td>
</tr>
<tr>
<td>Effect on weight</td>
<td>5% (4.5 kg) weight gain.</td>
</tr>
<tr>
<td></td>
<td>No influence on weight</td>
</tr>
<tr>
<td></td>
<td>10% (9 kg) weight loss.</td>
</tr>
<tr>
<td>Mild nausea, vomiting or diarrhea</td>
<td>Throughout the use of the drug</td>
</tr>
<tr>
<td></td>
<td>During the first two weeks of use of the drug</td>
</tr>
<tr>
<td></td>
<td>No stomach complaints</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>More than 2 times per month</td>
</tr>
<tr>
<td></td>
<td>1-2 times per month</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Risk of cancer</td>
<td>Increased (0.06%) risk; 6 instead of 4 out of 10,000 patients.</td>
</tr>
<tr>
<td></td>
<td>Unchanged (0.04%) risk; 4 out of 10,000 patients.</td>
</tr>
</tbody>
</table>

HbA1c: glycated haemoglobin
**Selection of drug effects and levels presented**

The drug effects selected to create the hypothetical OADs were based on 22 in-depth interviews (with 6 patients, 3 nurses, 9 doctors, 3 regulators and a pharmacist), and an informal review of the literature, regulatory requirements and product labelling of OADs. The effects selected were [Table 1]:

- Control of diabetes in terms of improvement in the HbA1c levels. This is the efficacy parameter used in trials for market authorisation applications and earlier studies have shown it to be an important drug effect. (11-15)
- Impact on cardiovascular outcomes. Controlling blood glucose levels should ultimately lead to a decreased cardiovascular (CV) risk. However, an increase in this risk can also occur, as shown by the OAD rosiglitazone. (20)
- Impact on weight. In our interviews, both weight loss (considered an added value) as well as weight gain (considered as an ADR) were seen as being important. Others have found it to be important to patients. (11-13,15)
- Duration of GI complaints and risk of hypoglycaemia. Both are common ADRs of various OADs and have been shown to be important to patients in earlier studies as well as our interviews. (11,13,14)
- Risk of bladder cancer. A serious but rare ADR that has led to debate about the safety of pioglitazone. (44-48)

The hypothetical drugs varied on these drug effects [Table 1]. We selected levels of variation that were considered to be plausible and representative of existing OADs.

**Choice tasks**

Responders were presented several sets of two hypothetical OADs and asked each time to choose between the two OADs. Each set differed on at least two drug effects. An orthogonal algorithm (Orthoplan, SPSS v.19) was used to select the minimum number of choice sets needed to facilitate the estimation of all main effects. The final selection comprised 18 choice sets and regulators received all choice sets. To minimize the time burden on patients and doctors, three versions of the survey were created containing a random set of six choice sets each. [Figure 1]
Do regulators value benefits and risks of drugs in the same way as doctors and patients?

<table>
<thead>
<tr>
<th></th>
<th>Medicine A</th>
<th>Medicine B</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>Decreases from 8.5% to 7.5%</td>
<td>Decreases from 8.5% to 7.5%</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Unchanged (3%) risk; 3 out of 100 patients</td>
<td>An increased (4%) risk; 4 instead of 3 out of 100 patients</td>
</tr>
<tr>
<td>Weight</td>
<td>5% (4.5 kg) weight gain</td>
<td>No influence on weight</td>
</tr>
<tr>
<td>Mild nausea, vomiting or diarrhoea</td>
<td>During the first two weeks of use</td>
<td>No stomach complaints</td>
</tr>
<tr>
<td>Hypoglycaemia “hypo's”</td>
<td>1-2 per month</td>
<td>None</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>Unchanged (0.04%) risk; 4 out of 10.000 patients</td>
<td>Increased (0.06%) risk; 6 instead of 4 out of 10.000 patients</td>
</tr>
</tbody>
</table>

My preference goes to:

- Medicine A □
- Medicine B □

**Figure 1** Example of a discrete-choice task

At the start of the survey, the participants were presented with a description of a hypothetical diabetes patient; the patient vignette. This patient was a 67 years old male, weighing 90 kilos, and using metformin, antihypertensive medication, and a statin. His blood glucose was poorly controlled and he was in need in need for a second drug in addition to the metformin. The regulators were asked to indicate which of the two OADs they felt was more appropriate for the patient. Doctors were asked to imagine that they were treating this patient and base their choices on their treatment preferences for that patient. The patients
were asked to imagine being this patient and to indicate which drug they preferred based on their own preference. The patient vignette was repeated above each choice question.

**Additional data collection**

At the end of the survey, a number of general questions were included. Regulators were asked their gender and how many years they had worked for the Dutch MEB. Doctors were asked their gender, whether they were GPs or specialists, and how many years they had been registered as practitioners. Patients were asked their gender, age, highest completed education, and the year they were diagnosed having diabetes.

**Analyses**

Separate analyses were performed for each stakeholder group. For the modelling of the data collected in the discrete choice experiments multinomial statistical models were used, in which one of the levels for each drug effect is set as reference level. (43,49) The following levels were chosen as reference: a small decrease in HbA1c level, no change in CV risk, no effect on weight, no stomach complaints, no hypoglycaemias, and no change in risk of bladder cancer. The main effect model included 11 dummy variables, since five of the drug effects varied on three levels and one drug effect on two levels.

To detect whether regulator responses differed significantly from the responses of doctors or patients, we performed separate analyses. In these analyses, not the three groups of interest, but only two groups of interest (regulators vs. doctors; regulators vs. patients) were analysed. A dummy variable was created to indicate the membership of the 2 groups to assess whether being a regulator lead to significantly different drug choices.

**RESULTS**

**Respondents**

The survey using hypothetical drug scenarios to elicit what values regulators’, doctors’ and patients’ attach to OAD benefits and risks was returned by 52 (66%) regulators, 175 (21%) medical doctors and 226 (72%) patients. The regulators had a median work experience of 5 years (interquartile range (IQR) 3 – 11 years) and comprised a mixture of clinical and pharmacovigilance assessors as well as seven independent members of the Dutch Medicines Evaluation Board (MEB). The doctors comprised a group of 130 GPs and 45 internists of
whom 49% had more than 20 years’ experience in clinical practice. The median age of the patients was 67 years (IQR 64 - 71); 48% were women and they had a median disease duration of 7.5 years (IQR: 3 – 13). [Table 2]

Table 2: Demographic characteristics of responders

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Number (%)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regulators (n=52)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender [female; n (%)]</td>
<td>24 (48%)</td>
<td></td>
</tr>
<tr>
<td>Experience at the MEB [years; median (IQR)]</td>
<td>5 (3 – 11)</td>
<td></td>
</tr>
<tr>
<td><strong>Doctors (n=175)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender [female, n (%)]</td>
<td>69 (39%)</td>
<td></td>
</tr>
<tr>
<td>GPs [n (%)]</td>
<td>130 (73%)</td>
<td></td>
</tr>
<tr>
<td>Years of experience [n (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>3 (2%)</td>
<td></td>
</tr>
<tr>
<td>1-5 years</td>
<td>12 (7%)</td>
<td></td>
</tr>
<tr>
<td>5-10 years</td>
<td>24 (14%)</td>
<td></td>
</tr>
<tr>
<td>10-20 years</td>
<td>50 (28%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 20 years</td>
<td>87 (49%)</td>
<td></td>
</tr>
<tr>
<td><strong>Patients (n=226)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender [female; n (%)]</td>
<td>108 (47.8%)</td>
<td></td>
</tr>
<tr>
<td>Age [years; median (IQR)]</td>
<td>67 (64 – 71)</td>
<td></td>
</tr>
<tr>
<td>Duration of diabetes [years; median (IQR)]</td>
<td>7.5 (3 – 13)</td>
<td></td>
</tr>
</tbody>
</table>

MEB = Dutch Medicines Evaluation Board, GP = General Practitioner, BMI: Body Mass Index; HbA1c: Glycosylated haemoglobin, IQR: interquartile range

Values attached to drug effects by regulators

Regulators received 18 choice sets of two hypothetical drugs as depicted in figure 1, which differed on six drug effects, i.e impact on; glycat ed haemoglobin (HbA1c) levels, associated cardiovascular (CV) risk, weight change, presence and duration of gastro-intestinal (GI) complaints, frequency of hypoglycemia, and potential risk of bladder cancer [Table 2]). A reduction in CV risk was the drug effect that positively affected the regulator’s choice (Odds Ratio (OR) 1.98, 95% Confidence Interval (CI) 1.11 - 3.53). Persistent GI problems (OR 0.24, 95% CI 0.14 - 0.41) and CV risk increase (OR 0.49, 95% CI 0.27 - 0.87) were considered as significant negative drug effects. A 5% weight gain was considered a negative drug effect,
but was marginally significant (OR 0.64, 95% CI 0.41 – 1.00). Risk of bladder cancer and decrease in HbA1c did not significantly affect the choices made by the regulators. [Figure 2]. These data indicate that in the context of the studied drug effects, the regulators preferred OADs that reduced CV risk (OR>1) and avoided OADs that had persistent GI problems, increased CV risk or resulted in weight gain (OR<1).

Agreement with doctors and patients

When comparing the results of the analyses for each group of respondents, there was a clear difference in the value attached to frequency of hypoglycaemias [Figure 2]. Regulators’ choices were not significantly affected by any level of frequency of hypoglycaemias, frequent (> 2 episodes per month) versus less frequent (1-2 episodes per month) or no hypoglycaemias, [OR 0.46, 95% CI 0.19 – 1.11, OR 1.30, 95% CI 0.64-2.62, for frequent and less frequent respectively], whereas doctors’ choices were affected by frequent hypoglycaemias [OR 0.16, 95% CI 0.07 - 0.37] and patients’ choices were affected by both levels [OR 0.24, 95% CI 0.11 - 0.51, OR 0.50, 95% CI 0.28 - 0.90, for frequent and less frequent respectively].

While weight gain as a negative drug effect was only marginally significant for the regulators’ choices (OR 0.64, 95% CI 0.41 – 1.00), it had a similar but significant value for doctors (OR 0.62, 95% CI 0.41 - 0.94) and a more pronounced significant value for patients (OR 0.39, 95% CI 0.26 - 0.59).

Regulators were in agreement with doctors and patients regarding the value of changes in CV risk and persistent GI problems for the drug choice, and the lack of importance of changes in risk of bladder cancer. [Figure 2]

Regarding HbA1c, minor differences were seen. While there was no significant impact of either intermediate or large decreases in HbA1c for the regulators’ or patients’ choices, doctors did prefer OADs with a large decrease in HbA1c levels (OR 3.24, 95% CI 1.25 - 8.43).

In additional analyses in which regulators were compared with doctors, respectively patients, no statistically significant differences were observed regarding the specific drug choices they made (p=0.13 and p=0.19, respectively).
Figure 2: Perceived value of drug effects by regulators, doctors and patients (Log of Odds Ratios and 95% Confidence Intervals) An OR>1 indicates that responders are more inclined to choose a drug with a specific drug effect and level. Vice versa, responders are less inclined to choose drug effects and levels with an OR<1.
**DISCUSSION**

Our results indicate that regulators value drug effects of OADs similar to doctors and patients when a benefit risk assessment is made at an individual patient level. Regulators valued the presented long term cardiovascular benefits and symptomatic adverse drug reactions (ADR) as more important for the drug choice than the other drug effects including an increase in bladder cancer risk, which was in agreement with both doctors and patients.

*Values attached to drug effects by regulators*

Regulators did not value reduction in HbA1c level significantly when taking into account the other drug effects of the hypothetical drugs included in our study despite the fact that the European Medicines Agency guidelines acknowledge HbA1c as the surrogate outcome measure on which new OADs can be approved. Although our data suggest that regulators may be inclined to prefer hypothetical drugs causing increasing levels of glucose control, this observation did not reach statistical significance. This could be due to recent evidence that more aggressive strategies to control glucose levels have not always translated in better long term patient outcomes; i.e micro and/or macrovascular benefit. (16,17) Also, we simultaneously presented the effect of our hypothetical drugs on CV risk, while the scenario read that all drugs had a similar impact on microvascular outcomes. Therefore, the impact on the long term patient outcome appears to have dominated the regulator’s choice, an effect that is usually not known when the drug receives market approval. (18)

It is in line with the increasing regulatory perception of the relevance of improved clinical outcome measures, especially since rosiglitazone was shown to increase the risk of cardiovascular disease and heart failure despite a significant glucose lowering effect. Ultimately its marketing authorisation in the EU was suspended in the EU and the guideline on clinical investigations for anti-diabetes drugs amended to include a more systematic collection of data on CV safety in the clinical studies before authorisation. (18-21) In the USA, similar measure were taken by the Food and Drug Administration (FDA) with a restriction to the use of rosiglitazone in a small subset of patients. (22,23)

Concerning other effects, regulators avoided choosing drugs causing persistent GI problems whereas transient GI problems had little influence on their choices. These types of problems are usually considered in the context of overall occurrence of symptomatic ADRs or discontinuations due to ADRs and not unusual. (18) More surprising was the fact that
regulators did not attach much value to drugs causing hypoglycemic events. The EMA diabetes guideline (18) specifies detailed analyses of occurrence and severity of hypoglycaemias, but it might be that regulators regard hypoglycaemia as an inevitable ADR that is linked to the working mechanism of the drug. Our finding that persistent ADRs are seen as more important than transient ADRs, is in line with other studies. (11,13)

Regulators valued weight gain as an effect of OADs negatively, albeit only marginally significant whereas weight loss did not affect the choices made by regulators. Although it is possible to use a clinically meaningful reduction in weight as a measure for metabolic control in clinical trials, regulators might be wary of any claims on effects on weight loss as the extent to which weight loss contributes to the CV benefit is not unequivocally established and an effect on weight is easily misused in a marketing context. (18,24) Inversely, some increase in weight might be considered a less serious ADR, partly cosmetic and therefore might have less weight in the assessment of the benefit-risk balance than e.g. persistent GI upset.

The lack of a significant effect of an increased risk of bladder cancer in our study is in line with the position taken by the Dutch MEB and the EMA that considered the absolute increase in risk of bladder cancer too small to remove pioglitazone from the market. (25,26) While the FDA and EMA decided that the benefit-risk balance for pioglitazone was still positive in a limited population, the French and German authorities suspended its use. (25,27-29) The increase was displayed in absolute terms, and not as a relative risk, giving a more accurate picture of the clinical relevance attached to this drug effect and this may have contributed to its interpretation. (30)

**Agreement with doctors and patients**

Regulators did agree with doctors and patients on the value of changes in CV risk. This agreement suggests that all groups value what is considered to be one of the most important aims of OAD treatment, even though only metformin has actually shown to reduce CV events in patients with type 2 diabetes. (31) Additionally, regulators placed similar values on persistent GI complications as doctors and patients, acknowledging the disruptive effect persistent symptomatic ADRs can have on the patients quality of life and, most likely, treatment compliance. Regulators, doctors and patients also agreed in the value they
attached to changes in weight, although patients were even less inclined to choose drugs that resulted in weight gain. This may be explained by the fact that regulators look at weight as an indicator of metabolic control while patients may have already struggled with losing weight as means to control their diabetes or because of social pressure to be thin. (32) Finally, an interesting observation was that also the doctors and patients agreed in the lack of value they attached to an increased risk of bladder cancer. It seems that they also interpreted that risk as less relevant in view of its low absolute risk.

On two drug effects regulators differed from patients and doctors. Frequent hypoglycaemic events significantly affected drug choice by patients and doctors, but not by regulators. The regulators may be more willing to accept hypoglycemia as a pharmacologically inevitable ADR of some OADs. Patients and doctors may have actual experience with hypoglycemia and its effects on quality of life and hence put more value on this ADR. (11,12,33) Finally, regulators and patients both did not place a significant weight on changes in HbA1c in relation to the other included drug effects, while doctors did. Doctors are nowadays faced with benchmarking and quality indicators that may explain the higher value they attach to achieving control on a surrogate measure. (34) A previous study showed that patients also considered HbA1c an important drug effect but in that study an effect on HbA1c was not shown in the context of a beneficial effect on CV risk. (11) Patients may therefore in our study have valued an improvement on CV risk more relevant, similar to the regulators.

**Limitations:**

The results of a discrete-choice method are inherently subjective to the drug effects and levels chosen. When larger differences in levels are presented, different effects on preferences may result. (35) To minimize this effect we selected levels that are plausible and representative of what is known about real OADs. By focusing on OADs, we could include a range of different drug effects. However, for other drug classes with other drug effect profiles the results might have been different.

Drug scenarios were presented in various ways. Some of the effects were depicted only with text and numbers, while others with coloured pictures, hence being more noticeable. The design of the scale figure used to describe changes in HbA1c is based on a previous discrete choice study. (11) The design of the ‘smiley-face’ matrix used to describe changes in risk of CV events was intended to make the proportions presented understandable to all groups of
Do regulators value benefits and risks of drugs in the same way as doctors and patients?

respondents. (36,37) The results show that most value was attached to a drug effect (persistent GI problems) that were presented with text only, indicating that this difference in presentation did not lead respondents to disregard those drug effects.

We used a typical 67 year old diabetes patient for which a drug choice had to be made. A different patient vignette, e.g. an elderly patient, might have changed the responses. Gastroenterologists valued ADRs less important when presented a vignette of an elderly patient than of a younger patient. (38) However, the aim of this study was to assess differences between groups when presented with the same patient.

The patient population was selected from pharmacies in the northern part of the Netherlands and might not necessarily represent patients from outside the Netherlands. The patients selected for the study were 60 to 75 years of age and might differ in their preferences or values from those older or younger. However, this age group represents the largest user group of OADs in the Netherlands (43% of total OAD users in 2009 (39)) and, with a response rate of more than 70%, we assume that the responders are fairly representative of Dutch diabetes type 2 patients. Likewise the doctors and regulators selected for this study were working in the Netherlands and could have different values than those working in other countries. The low response rate of doctors is a limitation, but respondents were representative in terms of gender (40) and location in the Netherlands. (41) A low response by doctors has been more often reported and we cannot exclude that it may have biased our results in a sense that doctors that are especially interested in diabetes treatment may be overrepresented. There is no indication, however, that more interested doctors would value drug effects differently.

**Implications for policy and practice:**

In conclusion, our results indicate that regulators may value major benefits and risks of drugs in the same way as doctors and patients. As such, the input of these other stakeholders in the regulatory process could support regulators in making decisions that are not that straightforward and may provoke debate, such as regarding the impact of small risks for serious adverse effects or of certain benefits. Specifically, doctors and patients could influence the benefit/risk discussion by expressing their views at an individual patient level instead of a population level that is often the basis for regulatory decision making. So far, selected patients and doctors are being involved in selected regulatory activities in Europe, such as by participation in scientific advisory groups, but their role needs further strengthening as suggested elsewhere. (42)
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Chapter 8:

General discussion and summary
The costs of developing new drugs is increasing and the drug regulatory requirements are becoming stricter. At the same time the number of new drug registrations is decreasing. (1) At the same time for already marketed drugs new safety concerns are identified that lead to warnings being issued or even withdrawals. (2,3) Finding safety issues post marketing is not surprising as clinical trials have limited power to detect safety issues that are not directly linked to a drug’s pharmacology. (4) However, others have criticised the regulators for not evaluating thoroughly enough potential known safety issues, e.g. through knowledge of the safety profile of similar drugs. (5) Therefore, striking a balance of regulatory requirements, safety ascertainment and stimulating drug innovation is complex, but essential. Over-regulation could prevent important therapeutic options from reaching patients, while insufficient post-marketing surveillance might leave harmful effects of drugs undetected. (4) For diseases with unmet medical need, regulators have responded with specific registration procedures that allow for less data to be collected pre-marketing. (6-8)

In the first part of this thesis I focused on the ability of the regulatory process to safeguard that new drugs entering the market are sufficiently safe and whether regulators learn from earlier experience with related drugs. I explored the relationship between knowledge at market approval and the risk of safety issues arising post-marketing.

In Chapter 2 we focused on regulatory learning by evaluating the extent to which regulators and industry have addressed the risk of safety issues focusing on the example of HIV drugs based on experience with other drugs in the same class. We focused on HIV drugs as for these more often than for any other drug class new safety issues were identified post approval. We evaluated whether the regulators and industry considered earlier identified safety concerns in the development and assessment of new drug class from the same class. Safety issues were identified from Direct Healthcare Professional Communication (DHPC) letters issued for HIV drugs. We reviewed the European Public Assessment Reports (EPARs) of drugs to assess whether the safety issues had been considered during the drug development and approval. In addition, we reviewed whether this knowledge led to appropriate changes in the Summary of Product Characteristics (SmPC). We found that regulatory learning was appropriate as in most cases class-related safety issues were taken into account in the approval process of new drugs. How this was done varied and was mostly determined by the nature of the safety issue. For drugs already on the market, the majority of the safety issues were addressed in the drug label.
In chapter 2 we also explored whether increasing regulatory requirements have an impact on the development times of new HIV drugs by assessing clinical development time, using time from first patent application to market authorization as proxy. We compared the clinical development times between drugs with a safety issue and drugs receiving market authorisation after issuance of the DHPCs. We found that although regulators and industry addressed class-related safety issues in the new drug development and approval process, this did not seem to have had an impact the duration of the pre-approval clinical programme.

In chapter 3 we looked at the association between knowledge at time of approval and safety issues from a reverse angle compared to chapter 2. We reviewed EPARs of all new drugs registered in Europe in an 11 year period and DHPCS in the same period. The aim was to determine whether for drugs registered with special procedures (Exceptional Circumstances (EC) or Conditional Approval (CA)), allowing for less information to be present at approval, are at more risk of having a safety issue identified after marketing. Drugs that are registered with these special procedures usually meet an unmet medical need or are technically difficult to evaluate in a clinical trial. We found that despite allowing less data in the clinical development program, these procedures were not associated with a higher probability of DHPCs as 16% of regularly approved drugs and 15% of drugs registered with EC or CA received a DHPC. When correcting for time, the difference between the registration procedures remained insignificant, suggesting that registration with procedures allowing for a smaller clinical data package does not lead to an earlier nor later discovery of serious safety issues. We concluded that our results do not support the view that early drug approval increases the risk of serious safety issues emerging after market approval for drugs meeting the requirements of an exceptional circumstances or conditional approval procedure.

The method used in chapter 3 was repeated in chapter 4, but extended with an analysis of innovativeness of drugs. We assessed the innovativeness of drugs using a decision matrix that takes into account the seriousness of the disease the drug is intended to treat, whether therapy to treat the disease is already available and how much of an improvement the drug is from the available therapy and finally how effective the drug is in the treatment of the disease. (9) We hypothesized that highly innovative drugs may find their way quickly into daily practice as they are considered an important addition to the available therapeutic armamentarium. They mays also be used in a more diseased population, where other drugs
may have failed but where the drug may have been less researched. This is the so-called ‘channelling’ phenomenon. This pattern of use may therefore lead to identifying hitherto unknown safety issues. The focus of our study was to compare the frequency and timing of serious safety issues identified post-approval for more innovative drugs versus less innovative drugs. We found that grading of innovativeness is not significantly associated with the likelihood of receiving a DHPC, in contrast with our hypothesis. We concluded that more than half of all new drugs approved in Europe can be considered at least modest innovations that add value to the available drug armamentarium. In spite of our hypothesis, a higher level of innovation was not clearly related to an increased risk of serious safety issues that are identified only after the drug being marketed.

In the second part of this thesis I determined the values stakeholders in drug regulation and drug use attach to benefits and risks of drugs. In management of chronic diseases, patient self-management and participation in treatment decisions is an integral part. (10) Regulators have acknowledged that patients are a valuable source of information and can contribute to work within the regulatory agencies. (11,12) However, patient involvement has to date been of an advisory nature and not as active participants in the decision making before allowing drugs on the market. With increasing patient involvement in the activities of the European Medicines Agency, the Agency believes their scientific committees are encouraged to reflect about the real-life implications of regulatory decisions. (11) Whether that is the case has not yet been established and it is unclear if regulators share the same values of benefits and risks as patients. Additionally, formal assessment of patient preferences has to date not been a part of the regulatory decision making.

There are cases where regulatory decisions have been criticised by healthcare professionals, patients or society at large. Pressure was put on regulators to approve drugs to treat HIV infection when little was known about their mechanism of action, while opposition has been voiced against the approval or continued use of human papilloma virus vaccine and the combined measles, mumps and rubella vaccine. (13-17) The decision of the FDA to remove natalizumab from the market was met with great opposition from patients with multiple sclerosis, ultimately resulting in the re-introduction of the drug to the market. (18,19)

There is an essential difference in perspective between regulators on one hand and doctors and patients on the other when they are assessing the benefits and risks of any new drug. Regulators base their decision to approve new drugs on an assessment of their benefit risk balance at the population level while doctors and patients make their decisions on the individual level. Whether this different perspective explains why regulators sometimes
make decisions that meet opposition, or whether there is a genuine difference in the values regulators attach to drug benefit and risks in comparison to doctors and patients is hitherto unexplored.

To this extent we set up discrete choice surveys studies that consist of providing respondents a choice between two or more options. In our studies these options were drugs that were described in scenarios with relevant attributes, i.e. drug effects. Every attribute (drug effect) is varied at different levels and shown to respondents in a set of different scenarios. Respondents are given these scenarios in pairs from which to choose the scenario they prefer most. The strength of the method is that it provides information on the relative importance of the attributes. It is therefore a valuable approach to understand how trade-offs are made when weighing benefits and risks of drugs by the different stakeholder involved. The relevance of the results of such discrete choice models is determined by the relevance of the selection of relevant attributes and the corresponding levels of these attributes. These should reflect actual important decision criteria of the respondents. (20,21)

In Chapter 5 we explained how we selected drug effects to develop the hypothetical drugs that were used the discrete choice surveys. To identify drug effect candidates we used a combination of methods, comprising a public literature review, a review of regulatory EMA guidelines and qualitative interviews with stakeholders in drug regulation and diabetes care. These interviews were performed to elicit potentially overlooked and/or possibly non rational drug effects that were considered important by these stakeholders. Based on these activities we selected the following drug effects; HbA1c control, cardiovascular effects both detrimental as well as beneficial, effect on weight, the potential to cause gastrointestinal side effects and hypoglycaemia as well as a potential risk to cause bladder cancer. All these effects were identified from the three different methods we used. Interestingly during the interviews ease of use (once versus multiple times per day, injectables versus oral administration) or costs were not spontaneously introduced. A few other issues came up during the discussions and from the review, but were not included in the stated choice models as they were either considered less relevant (dosing frequency and administration schedule, costs) or considered too complex a task (uncertainty at time of approval and possibility to postpone further studies till after approval). Finally, we added the risk of bladder cancer as at time of designing the study there was a major controversy between European regulators whether the benefit/risk of pioglitazone could still be considered positive after another the risk of bladder cancer was added to its long list of important
safety concerns. In at least two European countries the marketing of the product was suspended.

In **Chapter 6** we then evaluated separately the values patients with type 2 diabetes attach to these different drug benefits and risks using the discrete choice survey design. The aim of this study was to identify what value patients attach to short-term and long-term benefits relative to symptomatic adverse drug reactions (ADR) and serious ADRs. In our discrete choice survey on the patients were asked to choose between sets of hypothetical oral anti-diabetes drugs. The drugs in the choice sets were created with varying levels of the drug effects described in chapter 5. We found that the long-term efficacy parameter of cardiovascular risk was considered more important than the surrogate efficacy parameter of changes in HbA1c level. However, the patients did find it more important to avoid persistent or frequent symptomatic ADRs than a large increase in the small risk of bladder cancer, indicating that patients weigh more heavily ADRs that influence their quality of life on a daily basis. Our results further demonstrated that experience with the drug therapy affects the preferences of patients, as a large decrease in HbA1c was valued higher by patients that had inadequate control of their HbA1c and patients that had experienced ADRs were less inclined to choose OADs with persistent GI problems than those who had not.

In **Chapter 7**, the discrete choice survey of chapter 6 was extended to regulators working for the Dutch Medicines Evaluation Board and doctors treating type 2 diabetes. The aim of this study was primarily to compare the values regulators attach to benefits and risks of new drugs when compared to doctors and patients, when presented with the same trade-offs between short-term and long-term benefits relative to symptomatic ADRs and serious ADRs for an individual patient. In the survey, we asked regulators to base their decisions for an individual hypothetical patient with type 2 diabetes, in order to put them at par with the doctor and patient. Thereby avoiding that the regulators’ usual focus on a population level would obscure the values they attach to the investigated benefits and risks as presented in our scenarios. We found that regulators considered a lowering of CV risk more important than lowering of HbA1c and saw persistent GI problems and increase of CV risk as important negative drug effects. Regulators also considered weight increase as a negative drug effect, but those results were barely significant. Overall, we saw no significant differences between regulators and doctors nor regulators and patients. Looking descriptively at the separate analyses of each group we did see a difference in the value of frequent hypoglycaemia, where regulators did not place a significant value on frequent hypoglycaemia while both doctors and patients considered that significantly as a negative drug effect. Slight differences were also seen between regulators and doctors regarding a large decrease in
HbA1c, where only doctors significantly valued it as a positive drug effect. Patients also regarded an increase in weight more strongly as a negative drug effect than both regulators and doctors. Based on our results we concluded that regulators value drug effects of oral anti-diabetes drugs similar to doctors and patients when a trade-off between benefits and risks is made at the patient level.

**METHODODOLOGICAL CONSIDERATIONS**

**Design**

The studies included in part I in this thesis have a retrospective cohort design, using data collected from the websites of the European Medicines Agency (EMA) and the Dutch Medicines Evaluation board (MEB). The studies in part II are cross-sectional surveys using the discrete choice method, which is a form of conjoint analysis. Subsequently the strengths and limitations of the methods used in this thesis are discussed.

**Information reliability in retrospective studies**

Retrospective studies have usually the disadvantage of retrospectively not being able to measure some key statistics and biases that may affect the selection of controls. In our case we are not measuring disease state or biological changes in living subjects, but procedural and technical aspects of drug licensing. Most relevant data was recorded at the time of drug licensing and needed to be collected from the websites of the appropriate agencies. However, there are issues with reliability as we have had to trust that the information currently presented on the websites is as it was at the time of approval of each drug or at the time of issuance of the DHPCs. Particularly with regards to the scientific discussion of the EPARs this results in some uncertainty, as before 2005 these were regularly updated so it proved difficult to define what information was available at time of approval and what became known at a later stage. Other aspects of the information we collected are susceptible to change. Orphan designation of drugs can also change over time and it is possible that some drugs that had an orphan designation at time of marketing are classified as non-orphan drugs in our studies. Also the EPARs do not include data that applicant and regulator found confidential and we might therefore not be able to detect possible biases that could be found in the confidential material. However, one may assume that all relevant clinical efficacy and safety data are present in the EPARs; the available data should therefore be sufficient to draw conclusions. Data that is considered confidential mostly concerns data on the quality of the medicinal product (the drug formulation, manufacturing methods,
The EMA has taken a turn towards making data of marketing application dossiers available to the public. This will greatly facilitate the research presented in the first part of the thesis. However, it should be realised that the magnitude of the data, and its granularity will need skilled researchers that conscientiously review the available data to be able to present a balanced and reliable interpretation.

In assessing the innovativeness of drugs, we had to look retrospectively and grade according to the situation at the time the drug was approved. Most EPARs did have an introduction discussing the nature of the disease the drug was intended to treat and the availability of treatment. This discussion was usually very short and limited, often requiring us to look up other treatment options and assess whether or not they were available at the time of licensing of the drug we were assessing. It is possible that we might have missed other treatment options or overestimated what was available. Additionally, the criterion for assessing innovativeness requires an estimation of whether the drug for assessment is better than available treatment, either with regards to efficacy or safety. Most EPARs did not include any head-to-head comparison of treatments, but included comparison with placebo. This required the assessors to look up the safety and efficacy of the available treatments. Therefore, the classification was performed by at least two independent reviewers, where all cases of disagreement were resolved by discussing these cases with a third reviewer. This was done using the validated scoring method developed by one of the co-authors Domenico Motola. (9)

**Complexity of discrete choice studies.**

Discrete choice methods have the distinct advantage that they recognize that people are willing to make trade-offs between the different attributes (in our case drug effects) of a product. In our studies we measure the importance of a drug effect in relation to other drug effects that are presented. Each time the responder is asked to make a choice between two drugs he is implicitly asked to make a trade-off between all those drug effects. With enough observations and enough different choice sets we can estimate the weight our group of responders place on individual drug effects in their trade-offs. However, this method has limitations.

Firstly, we had to make a choice on which drug effects to include in creating our hypothetical drugs. We tried to make a list of drug effects that was relevant to today’s treatment of diabetes, but we had to drop several possible attributes. We could only measure what we present to the responders and might therefore miss drug effects that
could have been important to some of the responders. However, if we had included more
drug effects or other drug characteristics we would have run into a power problem or had to
ask the responders to make too many trade-offs at the same time. More attributes require
more observations to be able to run the analysis. This issue poses a risk of researcher bias
that we cannot leave without discussion. In our selection criteria, we excluded attributes
that are not of great consideration in the regulatory setting, such as costs and ease of use.
These attributes might have been of importance to doctors and patients, which could have
demonstrated a larger difference in choices made by regulators on one hand and doctors
and patients on the other. Though in our explorative interviews this was not the case.
Likewise we excluded attributes that we expected could be difficult to grasp for patients but
may have be significant to the regulators, e.g. the size of clinical trials and to what extent
stakeholders accept further evaluation of drug benefits and risks post approval. Our
selection of attributes, focusing on drug effects, may have caused an underestimation of
differences between regulators on one hand and doctors and patients on the other.
However, these issues are difficult to translate to the individual patient level and were
somewhat aside of our main research question. They would have asked the doctor and
patient to take the perspective of the regulator, which may be an interesting question for
further study.

Secondly, the responses are inherently linked to the levels of the drug effects chosen. When
larger differences in levels are given, more effect on patient preferences may result and vice
versa for smaller differences in levels. As with selecting the drug effects to be included, the
levels were selected by the researchers and are subjective to researcher bias. We tried to
minimize this effect by selecting levels that are plausible and representative of what is
known about the OADs already on the market or recently taken off the market. It is
therefore important to perform these studies with realistic estimation.

**Generalizability**

Generalizability of results is always a potential limitation of any study. The studies in part I
focused on drugs registered with the European Centralized Procedure. In the early years of
the Centralized Procedure only drugs that fulfilled certain requirements were allowed to be
licenced using the procedure. Gradually these requirements have changed and currently the
procedure is mandatory for drugs to treat HIV/AIDS, cancer, diabetes, neurodegenerative
diseases, auto-immune and other immune dysfunctions and viral diseases as well as drugs
derived from biotechnology processes and orphan medicines. Other new active substances
are allowed to be licensed using the Centralized Procedure, but can go through national
procedures, mutual recognition procedures or de-centralized procedure. Therefore we
cannot claim that our results are generalizable to drugs approved before our study period or using other procedures than the Centralized Procedure. Although experience teaches us that currently only few new important active substances do not go through the Centralised Procedure in Europe. Therefore, the clinical relevance for daily practice will grow over time. Chapter 2 particularly focused on HIV drugs, which do have significantly higher likelihood of receiving a DHPC than other drug classes, and cannot be extrapolated to other types of drugs. However, European regulatory guidelines do acknowledge class-related drug effects and similar requirements as those on the guideline for clinical development of HIV drugs have been taken up for other disease areas.

In part II we used the example of type 2 diabetes to examine the values regulators, doctors and patients attach to drug benefits and risks and what trade-offs they make. The regulators that participated in our study were all working for the Dutch Medicines Evaluation Board and might not be representative of regulators working for other competent authorities. Particularly when looking at the differences in reactions to the cancer risk linked with pioglitazone, we might expect different results should this study be repeated with regulators from countries that removed pioglitazone from the market. Similarly, the doctors participating in our study were also practising in the Netherlands and might not be representative of doctors practicing in other areas in Europe. Although the doctors responding to our survey were representative of Dutch doctors in terms of gender and location in the Netherlands, we did have a low response rate that may have biased our results in a sense that doctors that are especially interested in diabetes treatment may be overrepresented. Finally, the patient population resides in the northern part of the Netherlands and might not necessarily represent patients from outside the Netherlands. The patients selected for the study were ranging from 60 to 75 years of age and might differ in their preferences or values from those older or younger. However, this age group is the largest users of OADs in the Netherlands (43% of total OAD users in 2009 (22)) and with a response rate of more than 70% we may assume that the responders are representative of Dutch diabetes type 2 patients.
IMPLICATION FOR REGULATORY POLICY AND PRACTICE

So what are then the implications of the research presented in this thesis, considering our findings and the limitations as described.

Limited knowledge at time of approval

Highly innovative drugs are likely to be registered through EC and CA procedures and are often first-in-class drugs. As first-in-class drugs have no class experience to base on, and EC and CA approved drugs have limited clinical data, we assume that there is even more limited knowledge on these drugs at the time of approval than for ‘me-too’ drugs registered with the regular central procedure. Because of this, regulators usually require even stricter risk management plans for EC and CA approved drugs. (6,7) In chapter 3 we demonstrated that drugs registered with EC and CA procedures were not more likely to be subject to DHPCs or safety related withdrawals, despite the limited clinical data and more rigorous risk management plans. Likewise in chapter 4 for the drugs with various levels of innovation we found that a higher level of innovation was not clearly related to an increased risk of serious safety issues that are identified only after the drug being marketed. It is possible that the population exposed to EC and CA drugs and many highly innovative drugs might not be sufficiently large to detect less common ADRs. We did try to address the influence of drug use in chapter 4, but saw no indication that higher use resulted in more safety alerts. Although safety issues of highly innovative drugs might be detected earlier because doctors might be more prone to report issues with drugs that are not familiar to them or are first-in-class drugs, we did not find a correlation. (24) The message is thus that for the specific group of drugs meeting the requirements of an exceptional circumstance or conditional approval procedure, or are graded important innovations, this can be considered to provide an acceptable trade-off between knowledge required at time of approval and long-term safe and effective use in clinical practice. For both sets of drugs pro-active pharmacovigilance seems indicated and we suggest that the effectiveness of these measures should be monitored. Finally, none of both types of drugs were removed from the market because of safety concerns, thereby indicating that appropriate monitoring post approval may suffice and where DHPCs may contribute to optimizing safe and effective drug use in clinical practice.
The option of patient registries and adaptive licensing

In this thesis I have focused on the drug approval process, but before a new drug becomes available on the market it has pass another hurdle that of the health technology assessment (HTA). The HTA is basis for re-imbursement decisions, that is whether the drug will be paid for by the health insurance. These decisions are made on national basis and although collaboration has been set up with the European Network of Health Technology Assessment (EUnetHTA), HTA must be performed taking into account individual national priorities and systems. (25) Payers may not agree with regulators that sufficient demonstration of efficacy and safety has been demonstrated with the EC and CA procedures. (26) A recent proposal of adaptive licensing procedure (AL) suggests a method of continuous assessment that would include a dialogue between study sponsors, regulators and payers. Although for drugs registered with EC or CA procedures further data collection is required post marketing to maintain the marketing approval, how this should be done is not pre-defined in the legislation. The AL procedure would require that a pre-defined protocol should be followed, allowing only patients that comply with a “label-scenario” to receive the drug and ensuring that prescription controls and support are in place for the prescribing doctors. (26) The current requirements of the European Centralized Procedure include a submission of a risk management plan that address all known and possible risks associated with the drug. (27) In special cases this may include educational material for patients and doctors or the set-up of a patient registry, where only those registered can receive or prescribe the drug.

While conducting our interviews in chapter 5, the topic of patient registries arose. The general consensus of the participants was that a patient registry for the first few years after market approval would be an attractive strategy in the view of a number of respondents. Since patient dossiers are mostly electronic and filled out by the physicians or nurses during the consultation, it would not add considerable burden to the healthcare provider. In our interviews the patient did not oppose the idea of their dossiers being linked securely to a central patient registry for this purpose, provided it would be anonymised.

In the context of the proposed adaptive licensing procedure, or even the current EC and CA procedures, mandatory patient registries seem opportune. Well-designed registries might not only detect safety issues sooner, it might also shed light on effectiveness of the drug in wider patient groups or where surrogate endpoints were used as determinants for efficacy. The collaboration of regulators and payers proposed in the adaptive licensing procedure could ensure that the drugs would be paid for by the payers if the patient conforms with the “label-scenario” and is registered in the system and only doctors linked to the system would be allowed to prescribe the drug. Data handling and analysis would be in the hands of the national pharmacovigilance centers and the financing of the system could, at least in part,
be from fees collected from the pharmaceutical industry. Whether this approach could also mean as for the EC and CA approved drugs that some of the establishment of safety knowledge can be relegated to post approval is an interesting consideration supported by our findings in chapter 3.

**Patient and healthcare professional participation in regulatory decision making**

Although standardization of regulatory decision making has been proposed (28) it still remains that the decisions are made by regulators who individually attach values to drug effects and other drug characteristics. How these values are attached may differ between cultures, countries and individuals, although guidance is provided with guidelines and regulations. Personal experience can play a role in attributing these values, as we demonstrated in chapter 6, where it seems that patients that have experienced difficulties with their diabetes treatment have different preferences relating for the particular drug effect, usually adverse drug effect. The regulators take on drug effects is also affected by the, national authority’s policies, which may vary due to legal, cultural and other differences. (29) It is evident that regulators from different national authorities do not always agree on decisions to grant or suspend market approval. Some drugs are allowed to the market based on a majority vote of the CHMP, not consensus, and different responses have been seen with regards to serious safety issues, such as the bladder cancer risk associated with pioglitazone. While the FDA and EMA decided that the benefit-risk balance for pioglitazone was still positive in a limited population, the French and German authorities suspended its use. (30-33)

In chapter 7 we demonstrated that regulators value drug effects similar to doctors and patients when a benefit risk assessment is made at the individual patient level. In cases such as that of pioglitazone and bladder cancer risk, the decisions made by regulators are not always straightforward and the input of healthcare professionals and patients may be of value in the debate. Shared decision making has become an integral part of management of chronic diseases, where dialogue between the patient and healthcare provider allows for patient participation in decisions made regarding their treatment. (10) A path towards patient and healthcare professional participation in regulatory decision making has been laid out by including selected individuals in regulatory activities. (11) EMA has formalised collaboration with patient organisations in the Patients’ and Consumers’ Working Party. In the USA, the Food and Drug Administration (FDA) did the same in the Patient Representative Program. (11,12) However, patients and healthcare professionals have a limited contribution to the scientific discussion, as they are not allowed to take part in active discussions on the application and can only give their expert opinion. (11) In regulatory
policy, the public has the option to comment and give recommendation on guidelines under development, although it has been claimed that not enough is done to promote the involvement of healthcare professionals and patients. (34) Our studies suggest that regulators value major benefits and risks of drugs similar as doctors and patients. As such, the input of doctors and patients in the regulatory process can support regulators in making decisions which are not that straightforward and may provoke debate, such as regarding the impact of small risks of serious adverse effects. Furthermore, we see some slight differences in valuing less serious adverse effects, which should be addressed further when involving other parties in the regulatory decision process. Steps have been taken in that direction, but further strengthening of the patient and healthcare professionals’ voice is needed. This could in our view comprise the option of mapping the opinion of a larger group of patients and healthcare professionals on the benefit risk balance in ambivalent situations related to new drugs or new drug information.

**IMPLICATIONS FOR FUTURE RESEARCH**

*Regulatory learning*

While we have shown for the class of HIV drugs that regulators had addressed previously identified class-related safety issues when assessing new drugs, another study within the Escher project has found that this may not always be the case. (5) When reviewing the EPARs and SmPC of several pairs of first-in-class and me-too drugs it was noted that safety learning occurred for nearly half of the ADRs reported for each drug. Although at first sight our results might be at odds, there are methodological differences that explain these opposite findings. Firstly, we investigated different drug groups. While the study finding regulatory learning lacking investigated drugs from several different drug groups, we look closely at the development and registration of HIV drugs only in chapter 2. It is possible that HIV drugs are treated differently by regulators, where regulators better responded to previous findings, i.e. they showed ‘regulatory learning’. Secondly we differed in the proxy used for safety issues. In our case we focused on safety issues, resulting in DHPCs or safety related withdrawals. These safety issues were generally more serious than the ADRs included in the other study, where all ADRs mentioned in the drugs’ SmPCs were included. It is logical to assume that more serious issues would be more likely to be taken up, thus supporting regulatory learning. Without stating which method of assessing is correct, as both methods have their merits, it remains clear that further studies on regulatory learning are necessary. These studies should include a critical assessment of the validity of
recommendations in the many regulatory guidelines on disease specific drug development as well as how these recommendations have been followed in new dossiers. These studies should expand on the knowledge already acquired by the Esher project.

**Patient and healthcare professional involvement in regulatory decision making**

We have discussed the merits of including healthcare professionals and patients in regulatory decision making. Although there are different ways to do so, research in the area is still lacking. The feasibility of including discrete choice experiments in the context of contentious market approval applications needs to be viewed critically. Such studies should when performed be executed by independent researchers that are neither biased towards the industry or the regulators position. Direct participation of healthcare professionals and patients has already started and the participants experience in the process has been researched. (11) More research on that experience is still needed and estimates of how an increased involvement would affect the regulatory process need to be made. Other methods of patient and healthcare professional involvement need to be proposed and discussed. Although from our study there seems to be no major disconnect between regulators and these other stakeholders on how to value benefits and risks of new drugs.

Regulatory science is relatively new and with the Escher project it has reached new heights. The experience of the Escher project needs to be built upon, making regulatory science an integral part in public health discussions.
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Nederlandse samenvatting
De kosten van het ontwikkelen van nieuwe geneesmiddelen nemen toe, mede door de toegenomen eisen van de geneesmiddelautoriteiten. Tegelijkertijd neemt het aantal nieuw geregistreerde geneesmiddelen af en zien we dat voor al geregistreerde geneesmiddelen nieuwe veiligheidsproblemen worden geïdentificeerd, die er toe hebben geleid dat autoriteiten urgent waarschuwingen naar zorgverleners hebben moeten sturen of zelfs het geneesmiddel van de markt hebben moeten halen. Het vinden van veiligheidsproblemen nadat een geneesmiddel eenmaal is geregistreerd is overigens niet verwonderlijk, omdat preregistratie klinische studies maar een beperkte statistische power hebben om bijwerkingen die niet rechtstreeks gekoppeld zijn aan de farmacologie van een geneesmiddel op te sporen. Echter, verschillende belanghebbenden hebben de registratieautoriteiten bekritiseerd dat zij niet voldoende gedegen potentiële voorspelbare veiligheidsproblemen al voor registratie in kaart hadden gebracht, bijvoorbeeld door de kennis die zij hebben over soortgelijke geneesmiddelen voldoende mee te wegen. Het vinden van een goede balans tussen aan de ene kant adequate regelgeving, met name wat betreft het vaststellen van geneesmiddelrisico’s, en aan de andere kant het stimuleren van geneesmiddelinnovatie is complex, maar van essentieel belang. Overregulering zou er toe kunnen leiden dat patiënten belangrijke therapeutische vernieuwingen worden onthouden, terwijl onvoldoende post-marketing surveillance er toe zou kunnen leiden dat schadelijke effecten van geneesmiddelen onopgemerkt blijven. Om de registratie van nieuwe geneesmiddelen te faciliteren voor ziekten waar onvoldoende of geen adequate behandelingstrategieën beschikbaar zijn – die voorzien in een ‘onvervulde medische behoefte’ - hebben de registratieautoriteiten specifieke registratie-procedures ingesteld die minder onderzoek voor registratie vereisen.

In het eerste deel van dit proefschrift onderzocht ik het vermogen van het huidige registratiesysteem om te waarborgen dat nieuwe geregistreerde geneesmiddelen voldoende veilig zijn en of de registratieauthoriteiten leren van eerdere ervaringen met verwante geneesmiddelen. Ik onderzocht daarnaast of de mate van kennis ten tijde van registratie geassocieerd is met het optreden van ernstige bijwerkingen na registratie.

In hoofdstuk 2 hebben we ons gericht op het lerend vermogen van de registratieautoriteiten. We evalueerden hoe industrie en registratieautoriteiten het risico van veiligheidsproblemen die bekend waren van oudere middelen hebben meegenomen bij het ontwikkelen,
respectievelijk beoordelen van nieuwe gerelateerde geneesmiddelen (uit dezelfde geneesmiddelklasse). Wij keken specifiek naar HIV-medicijnen, omdat bij deze middelen vaker dan voor enige andere klasse van geneesmiddelen ernstige nieuwe veiligheidsproblemen werden geïdentificeerd na registratie. Veiligheidsproblemen werden geïdentificeerd aan de hand van Direct Healthcare Professional Communication (DHPC) brieven afgegeven voor HIV medicijnen. Deze DHPCs worden door de industrie na afstemming met de registratieautoriteiten naar zorgverleners gestuurd om hen te informeren over een nieuw geïdentificeerd ernstig geneesmiddelprobleem. We zochten in de publiek toegankelijke beoordelingsrapporten, European Public Assessment Reports (EPAR's), van geneesmiddelen naar informatie over hoe de veiligheid van het HIV-middel was onderzocht en of er aandacht was besteed tijdens de beoordeling door de registratieautoriteit aan een al bekend geneesmiddelrisico van gerelateerde geneesmiddelen. Daarnaast hebben we beoordeeld of deze kennis heeft geleid tot relevante wijzigingen in de samenvatting van de productkenmerken (Summary of Product Characteristics SPC). We vonden dat de registratieautoriteiten een adequaat lerend vermogen hadden. In de meeste gevallen werden al bekende klasse-gerelateerde veiligheidsproblemen in aanmerking genomen tijdens de beoordeling van nieuwe geneesmiddelen. Hoe dit gedaan werd varieerde en hing af van de aard van het veiligheidsprobleem. Voor geneesmiddelen die al op de markt waren, werd het merendeel van de veiligheidsproblemen behandeld in de SPC.

In hoofdstuk 2 onderzochten we ook of toenemende regelgeving van invloed is op de ontwikkelingsduur van nieuwe hiv-medicijnen. Hiervoor hebben we gekeken naar de duur van het klinische geneesmiddelonderzoeksprogramma. We gebruikten hiervoor als proxy de tijd die verstrekken was sinds de eerste octrooiaanvraag tot de datum waarop het geneesmiddel werd geregistreerd. We vergeleken de duur van het klinische onderzoeksprogramma voor geneesmiddelen, die geregistreerd werden voordat een klasse-gerelateerd veiligheidsprobleem was geïdentificeerd met die middelen die werden geregistreerd nadat een DHPC voor een klasse-gerelateerd geneesmiddel was verzonden. We vonden dat, ondanks dat de industrie en registratieautoriteiten aandacht hadden besteed aan deze klasse-gerelateerde problemen in het ontwikkelingsprogramma en het beoordelingsproces, dit geen invloed lijkte te hebben gehad op de duur van het klinische onderzoeksprogramma inclusief de beoordelingstijd.
In hoofdstuk 3 keken we naar de relatie tussen kennis over een geneesmiddel op het moment van registratie en veiligheid vanuit eentegenovergesteld perspectief ten opzichte van hoofdstuk 2. Wij beoordeelden EPAR’s van alle nieuwe geneesmiddelen die geregistreerd werden gedurende een periode van 11 jaar in Europa en naar de verstuurde DHPCs voor deze middelen in dezelfde periode. Het doel was om te bepalen of voor geneesmiddelen die geregistreerd werden via speciale procedures; de ‘uitzonderlijke omstandigheden’ (Exceptional Circumstances, EC) of ‘voorwaardelijke goedkeuring’ (Conditional Approval, CA)) procedures. Bij deze EC of CA procedures is het mogelijk geneesmiddelen te registreren op basis van minder pre-registratie onderzoek. Deze speciale procedures zijn toegankelijk voor geneesmiddelen die in een ‘onvervulde medische behoeft’ voorzien of waar het technisch niet haalbaar is om in klinisch onderzoek doorslaggevend de klinische effectiviteit aan te tonen. Het doel van ons onderzoek was om te kijken of deze middelen een groter risico lopen op het vinden van veiligheidsproblemen na registratie. We vonden dat ondanks dat registratie voor deze middelen mogelijk was met minder gegevens in de klinische ontwikkelingsprogramma’s, deze procedures niet waren geassocieerd met een hogere kans op een DHPC na registratie. Uiteindelijk kregen 16% van de geneesmiddelen die werden geregistreerd via de reguliere procedure en 15% van de geneesmiddelen geregistreerd bij EC of CA ontving een DHPC. Dit verschil bleef niet statistisch significant wanneer gecorrigeerd werd voor de follow-up duur, hetgeen suggereert dat deze registratieprocedures met kleinere klinische ontwikkelingsprogramma’s niet tot eerdere (of latere) ontdekking van ernstige veiligheidskwesties leidt. Hieruit concludeerden wij dat een eerdere goedkeuring van dit soort geneesmiddelen, die voldoen aan de voorwaarden voor een EC of CA procedure, het risico op ernstige bijwerkingen na registratie niet verhogen.

We pasten de methode die in hoofdstuk 3 werd gebruikt opnieuw toe in hoofdstuk 4, waarbij we keken naar de relatie tussen post-registratie veiligheidsproblemen en de mate van innovativiteit van een geneesmiddel. Wij beoordeelden de mate van innovativiteit van nieuwe geneesmiddelen op het moment van registratie, waarbij we gebruik maakten van een algoritme dat was ontwikkeld door de groep van Motola in Italië. Het algoritme houdt rekening met de ernst van de ziekte waarvoor het geneesmiddel bedoeld is, of er voor de behandeling van de ziekte al effectieve alternatieve therapiën zijn en tenslotte hoe groot de effectiviteit van het geneesmiddel was voor de behandeling van de ziekte. De hypothese was dat innovatierende geneesmiddelen kunnen hun weg snel vinden naar de patiënt in de dagelijkse praktijk, omdat ze worden beschouwd als een belangrijke aanvulling op het
beschikbare therapeutische arsenaal. Ze worden mogelijk ook gebruikt in een ziekere patiëntenpopulatie waar andere geneesmiddelen niet effectief waren, maar waar het geneesmiddel mogelijk niet specifiek is onderzocht. Dit is het zogenaamde "channeling" fenomeen. Dit soort van gebruik kan dus mogelijk leiden tot het identificeren van tot dan toe onbekende bijwerkingen. Het doel onze studie was om de frequentie en timing van post-registratie ernstige veiligheidsproblemen te vergelijken van innovatieve geneesmiddelen versus niet innovatieve geneesmiddelen. We vonden dat de mate van innovativiteit niet significant geassocieerd was met de kans op een DHPC. We concludeerden dat meer dan de helft van alle nieuwe geneesmiddelen die werden goedgekeurd in Europa in onze studieperiode op zijn minst konden worden geklassificeerd als bescheiden innovaties, die waarde toevoegen aan het beschikbare geneesmiddelarsenaal. Dus in tegenstelling tot onze hypoteese was een hoger niveau van innovatie niet duidelijk geassocieerd met een verhoogd risico op ernstige veiligheidsproblemen, die pas nadat het geneesmiddel op de markt werd gebracht werden gevonden.

In het tweede deel van dit proefschrift onderzocht ik de waarde die belanghebbenden; registratieautoriteiten, voorschrijvers en patiënten, hechten aan de baten en risico's van geneesmiddelen. Participatie van de patiënt in behandelbeslissingen en het management van zijn/haar chronische ziekten, is tegenwoordig steeds meer de norm. De registratieautoriteiten erkennen dat patiënten een waardevolle bron van informatie kunnen zijn en dat zij kunnen bijdragen aan verschillende activiteiten van deze autoriteiten. Echter, het betrekken van patiënten bij het registratieproces is meer in de vorm van het geven van advies, maar gaat niet zover dat zij als actieve deelnemers betrokken zijn in het besluitvormingsproces over registratie van een geneesmiddel. Met de toenemende betrokkenheid van de patiënt bij de activiteiten van het Europese geneesmiddelen agentschap (European Medicines Agency, EMA), verwacht het agentschap dat haar wetenschappelijke comités worden aangespoord om meer rekening te houden met de gevolgen van hun regulatorie beslissingen voor de dagelijkse praktijk. Of dit ook werkelijk het geval is, is nog niet vastgesteld en het is onduidelijk of geneesmiddelenbeoordelaars dezelfde waarden hechten aan baten en risico's (van geneesmiddelen) als patiënten. Tot op heden is een formele evaluatie van de voorkeuren van patiënten, met betrekking tot verschillende baten en risico's van geneesmiddelen, geen onderdeel van het besluitvormingsproces.
Verschillende door de registratieautoriteiten genomen beslissingen zijn bekritiseerd door beroepsbeoefenaren in de gezondheidszorg, patiënten of de samenleving als geheel. Er is in het verleden bijvoorbeeld grote druk uitgeoefend op de registratieautoriteiten om geneesmiddelen te registreren voor de behandeling van het humane immunodeficiëntievirus (HIV) terwijl er slechts weinig bekend was over het werkingsmechanisme van deze middelen. Daarentegen is er kritiek geuit op de registratie van het humaan papilloma virus (HPV) vaccin, of handhaving van de registratie van het gecombineerde mazelen, bof en rubella vaccin. De beslissing van de FDA om natalizumab van de markt te halen ontmoette veel weerstand van patiënten met multiple sclerose, wat er uiteindelijk toe leidde dat het geneesmiddel opnieuw werd geïntroduceerd op de markt.

Er is een essentieel verschil in het perspectief waarmee registratieautoriteiten enerzijds en artsen en patiënten anderzijds de baten en risico's van een nieuw geneesmiddel wegen. De autoriteiten baseren hun beslissing om een nieuw geneesmiddelen goed te keuren op een beoordeling van de baten-riscobalans op populatieniveau, terwijl artsen en patiënten hun afwegingen op een individueel niveau maken. Of dit andere perspectief verklaart waarom registratieautoriteiten soms beslissingen nemen die op tegenstand stuiten, of dat geneesmiddelbeoordelaars daadwerkelijk een andere waarde hechten aan baten en risico's van geneesmiddelen in vergelijking met artsen en patiënten is tot nu toe nooit onderzocht.

Om dit te onderzoeken hebben we een zogenaamd ‘discrete choice’ experiment opgezet. Dit is een vragenlijstonderzoek waarbij respondenten gevraagd wordt een keuze te maken uit twee of meer opties. In onze studies waren deze opties geneesmiddelen die werden beschreven in scenario's met relevante attributen, dat wil zeggen verschillende geneesmiddelweffecten. Elke attribuut (geneesmiddelweffect) varieert dan op verschillende niveaus en wordt getoond aan de respondenten in onze studie als een set van telkens zes attributen, dus leidend tot verschillende scenario's (= fictieve geneesmiddelen). De respondenten kregen deze scenario's telkens in paren gepresenteerd, waaruit ze dan het door hen geprefereerde scenario moesten kiezen. De kracht van deze methode is dat hieruit informatie verkregen kan worden over het relatieve belang dat de respondenten hechten aan individuele geneesmiddelweffecten (attributen) ten opzichte van de andere effecten. Deze techniek is dan ook een waardevolle methode om te begrijpen welke onderliggende keuzes de verschillende belanghebbende partijen maken bij het wegen van de baten-risico balans van een geneesmiddel. De waarde van de gevonden resultaten van dergelijke ‘discrete choice’ modellen wordt sterk bepaald door het kiezen van de meest
In hoofdstuk 5 hebben we uitgelegd waarop de selectie berust van de geneesmiddeleffecten die we in de ‘discrete choice’ studie gebruikt hebben om de fictieve geneesmiddelen (scenario’s) samen te stellen. Om mogelijk relevante geneesmiddeleffecten te identificeren voor onze studie gebruikten we een combinatie van methoden. We kozen voor ons experiment geneesmiddelen voor de behandeling van diabetes als casus. We voerden een literatuurstudie uit en extraheerden we de belangrijkste criteria uit de EMA richtlijnen waarop registratieautoriteiten hun beoordeling van een nieuw geneesmiddel voor de behandeling van diabetes baseren. Daarnaast voerden we kwalitatieve interviews met betrokkenen partijen in het geneesmiddeltoezicht en de diabeteszorg. Deze interviews werden gevoerd om mogelijk over het hoofd gezien en om eventueel niet rationale geneesmiddeleffecten die wel als belangrijk werden beschouwd door deze betrokken boven tafel te krijgen. Op basis van deze verschillende methoden hebben we de volgende geneesmiddeleffecten geselecteerd om de scenario’s op te stellen: de mate van HbA1c controle, zowel positieve als negatieve cardiovasculaire effecten, toename afname van gewicht, het meer of minder frequent optreden van gastro-intestinale bijwerkingen of hypoglykemie en een mogelijk verhoogd risico op blaaskanker. Interessant was dat tijdens de interviews gebruiksgemak (eenmaal versus meerdere keren per dag toedienen of injecteerbare versus orale toedieningsvormen) of kosten niet spontaan in de gesprekken naar voren kwamen als zijnde relevant. Deze en sommige andere mogelijke geneesmiddeleffecten kwamen tijdens literatuur/richtlijn studie en of de interviews wel naar voren, maar werden niet opgenomen in de uiteindelijke scenario’s omdat ze als minder relevant (toedieningsfrequentie en toedieningsschema, kosten) of als te complex (de onzekerheid op het moment van registratie over de baten-risico balans van een nieuw geneesmiddel en de mogelijkheid om verdere geneesmiddelonderzoek uit te stellen tot na registratie) werden beschouwd. Ten slotte hebben we nog een toegenomen risico op blaaskanker als bijwerking van een antidiabetesmiddel opgenomen. Dit effect werd geselecteerd omdat ten tijde van het ontwerpen van de ‘discrete choice’ studie er een grote controverse was ontstaan tussen Europese registratieautoriteiten of de baten-risicobalans van het betreffende antidiabetes middel, pioglitazon, nog positief was nu het risico op
blaaskanker werd toegevoegd aan de al lange lijst van belangrijke bijwerkingen. In ten minste twee Europese landen werd het gebruik van pioglitazon opgeschort.

In hoofdstuk 6 hebben we vervolgens de daadwerkelijk 'discrete choice' studie beschreven waarin we evalueerden welke waarde patiënten met type 2-diabetes hechten aan de in hoofdstuk 5 beschreven afzonderlijke positieve en negatieve geneesmiddeleffecten. Het doel van deze studie was om te bepalen hoe patiënten de verschillende korte en lange termijn baten wegen in vergelijking tot symptomatische en frequente bijwerkingen en/of ernstige maar zeldzame bijwerkingen. In onze 'discrete choice' studie werd aan patiënten gevraagd om telkens te kiezen tussen twee fictieve orale anti-diabetes geneesmiddelen met verschillende effecten, de scenario's. De geneesmiddelen beschreven in de scenario's werden samengesteld door de zes geneesmiddeleffecten te variëren op verschillende niveaus, bijvoorbeeld toe- of afname van het risico op hart- of herseninfarct en cardiovasculaire dood, zoals beschreven in hoofdstuk 5. We vonden dat voor patiënten de werkzaamheid op lange termijn, dat is het verminderen van hartinfarct en cardiovasculair voorval, belangrijker was dan een afname in HbA1C een erkende surrogaat parameter voor werkzaamheid van anti-diabetes geneesmiddelen. De patiënten vonden het belangrijker om persisterende of frequentie symptomaticus bijwerkingen indien mogelijk te vermijden dan dat zij een geneesmiddel vermeden dat een forse relatie toename gaf van een klein absoluut risico op blaaskanker. Deze laatste bevinding geeft aan dat patiënten bijwerkingen die de kwaliteit van hun leven op een dagelijkse basis negatief beïnvloeden zwaar wegen. Onze resultaten laten verder zien dat eerdere ervaringen met anti-diabetesmiddelen de voorkeuren van een patiënt beïnvloedt. Een groot effect (meer daling) op het HbA1c niveau werd meer gewaardeerd door patiënten waarbij het werkelijke HbA1c niet voldoende onder controle was. Patiënten die eerder bijwerkingen hadden ervaren waren minder geneigd om orale anti-diabetes middelen met hardnekkige gastro-intestinale problemen te kiezen dan degenen die zelf geen bijwerkingen hadden ervaren.

In Hoofdstuk 7 werd de 'discrete choice' studie uit hoofdstuk 6 uitgebreid door dezelfde vragenlijst voor te leggen aan geneesmiddelenbeoordelaars werkzaam bij het College ter Beoordeling van Geneesmiddelen en huisartsen en internist-endocrinologen. Het primaire doel van deze studie was om de waarde die geneesmiddelenbeoordelaars hechten aan baten en risicod 's van nieuwe geneesmiddelen te vergelijken met die van artsen en patiënten, wanneer zij met dezelfde scenario's te maken krijgen en een afweging gevraagd worden te
maken voor de behandeling van één individuele patiënt. Om de beoordelaars vanuit hetzelfde perspectief te laten beslissen, werd aan alle groepen dezelfde hypothetische patiënt met type 2 diabetes gepresenteerd, waarvoor aan alle groepen werd gevraagd om hun keuze te baseren met deze patiënt in gedachten. Op deze wijze wordt voorkomen dat de geneesmiddelenbeoordelaars hun keuze zouden baseren vanuit hun gebruikelijke perspectief op het populatie niveau, wat mogelijk de waarde die zij hechten aan de individuele baten en risico's zoals gepresenteerd in onze scenario's zou vertroebelen. We vonden dat ook de beoordelaars een verlaging van het cardiovasculaire risico belangrijker beschouwden dan het verlagen van HbA1c en dat zij daarnaast aanhoudende gastro-intestinale klachten en verhoging van het cardiovasculaire risico als belangrijke negatieve geneesmiddel effecten beschouwden.

De geneesmiddelenbeoordelaars beschouwden ook een gewichtstoename als een relevant negatief effect van het fictieve anti-diabetesmiddel, maar dit resultaat was maar net statistisch significant. Over het geheel genomen zagen we geen belangrijke verschillen tussen de geneesmiddelenbeoordelaars en artsen, noch tussen de beoordelaars en patiënten. Wanneer we meer beschrijvend naar de afzonderlijke analyses van de effecten binnen elke groep keken zagen we wel een verschil in de waarde die de beoordelaars hechtten aan het optreden van frequent hypoglycemie episodes. Bij de geneesmiddelenbeoordelaars was de waarde die zij aan dit effect hechten niet statistisch significant, in de context van alle andere geneesmiddel effecten, terwijl dit bij zowel de artsen als patiënten als een statistisch significant negatief geneesmiddel effect naar voren kwam. Kleine verschillen werden ook gezien in de waarde die de beoordelaars en artsen hechtten aan een door een fictief geneesmiddel veroorzaakte grote afname in HbA1c, dat alleen in de analyse in de groep artsen als een statistisch significant positief effect van het geneesmiddel naar voren kwam. Wat uiteindelijk nog opviel was dat patiënten een meer uitgesproken negatieve waarde hechten aan een toename in gewicht dan zowel de geneesmiddelenbeoordelaars en artsen.

Op basis van onze resultaten concluderen wij dat beoordelaars werkzaam bij de registratieautoriteiten effecten van orale anti-diabetes geneesmiddelen op een vergelijkbare wijze wegen als artsen en patiënten wanneer hen gevraagd wordt een keuze te maken tussen de verschillende baten en risico's van een middel voor een individuele patiënt.

In hoofdstuk 8 bespreken wij een aantal limitaties van dit onderzoek, zoals daar zijn het retrospectieve karakter van de studies in deel 1 waardoor niet alle parameters even hard
kunnen worden gedefinieerd. In het algemeen zijn de registratiedata die we gebruikt hebben in onze studies echter goed gedocumenteerd. Nochtans zijn de wetenschappelijke discussies in de EPARs meer gestructureerd na 2005. De beoordeling van de innovativiteit heeft ondanks het gebruikte algoritme enige mate van subjectiviteit, en het was soms lastig om de waarde op het moment van registratie achteraf te bepalen. We hebben gepoogd dit op te lossen door een beoordeling in consensus met minimaal 3 beoordelaren te maken. De ‘discrete choice’ studies hebben een complex ontwerp en vragen de doelgroep zich te verplaatsen naar het perspectief beschreven in de scenario’s. Het aantal geneesmiddelen dat kon worden meegenomen was beperkt, vanwege de noodzaak om hoe meer effecten te worden meegenomen er ook meer scenario’s aan de ondervraagden moeten worden voorgelegd. De keuze van de geneesmiddelen is daarom ook cruciaal en dit is de reden van ons uitgebreide vooronderzoek om deze te selecteren.

Wat uit dit proefschrift naar voren komt is dat de Europese registratie autoriteiten een lerende organisatie lijken te zijn. Het gebruik van de speciale ‘exceptional circumstances’ en ‘conditional approval’ procedures voor geneesmiddelen die in een ‘onvervulde medische behoefte’ voorzien blijkt uit ons onderzoek gerechtvaardigd. Deze procedure leidde niet tot meer onverwachte problemen na registratie dan op reguliere wijze geregistreerde middelen en dient dus te worden gecontinueerd. Geneesmiddelenbeoordelaars werkzaam bij de registratieautoriteiten hechten een vergelijkbare waarde aan baten en risico’s van geneesmiddelen als artsen en patiënten. Het betrekkend zij deze laatste groepen bij lastige beslissingen, bijvoorbeeld waar weinig voorkomende maar ernstige risico’s kunnen optreden, kan extra draagvlak creëren voor de uiteindelijke beslissing die door de autoriteiten op populatieniveau wordt genomen. Doordat op deze wijze ook het individuele perspectief op de baten-risico balans wordt meegewogen.
Samantekt á íslensku
Kostnaður við þróun nýrra lyfja eykst og færri lyf koma á markað á meðan þær kröfur sem gerðar eru til nýrra lyfja herðast. Á sama tíma koma alvarlegar aukaverkanir lyfja sem þegar eru á markaði í ljós og leiða til þess að aðvörun er gefin út eða lyfín jafnvel tekin af markaði.

Þær sem klinískar lyfjarannsóknir eru takmörkunum háðar í mati á öryggj lyfja, ætti ekki að koma á óvart að sumar alvarlegar aukaverkanir uppgótvast þegar lyfið er komið á markað. Því er mikilvægt að finna rétt jafnvægi milli þeirra skilyrða sem lyf þurfa að uppfylla við skráningu, t.d. við mat á öryggj og þess að örva þróun nýrra lyfja. Of stifar reglur gætu haldið nauðsynlegum lyfjum frá sjúklingum sem þarf þeirra, á meðan of slakt aftur aftir markaðsetningu dugar ekki til að bera kennsl á neikvæðar aukaverkanir lyfja. Í sjúkdónum þar sem meðferðarmöguleika skortir, hafa skráningarférvöld brögust við með sérstökum ferulum sem leyfa söfnun minni gagna til að skrá lyf.

Í fyrri hluta þessarar ritgerðar er áhersla lögð á getu skráningarkerfisins til að tryggja öryggi nýrra lyfja og athugað hvort skráningarférvöld læri af reynslu sinni af eldri lyfjum í sama flokki. Ég kann tengsl þeirrar þekkingar sem er til staðar þegar lyf er skráð á markað við áhættu á aukaverkanum.

Í kafla tvö er einnig kannað hvort auknar skráningarkröfur hafi áhrif á þann tíma sem tekur að próa og koma nýju HIV lyfi á markað. Áætlað er að klinísk próun hefjist þegar sótt er um einkaleyfi á lyfinu og vari þann tíma sem líður frá gerð einkaleyfaumskónar til útgáfu markaðsleyfis. Tíminn sem klinísk próun lyfja sem fengu gefnar út aðvaranir er borinn saman við tímann sem klinísk próun lyfja sem komu seinna á markað tók. Niðurstaða okkar er að þratt fyrir að lærðómur væri dreginn af alvarlegum aukaverkunum í próun og skráningu nýrri lyfja, hafði hann ekki áhrif á hversu langan tíma það tekur að próa og skrá lyfin.

Í kafla þrjú skoðum við samband þekningar við skráningu og aukaverkana eftir markaðsetningu frá öðru sjónarhorni. Við rýnum í EPAR allra nýrra lyfja skráðra í Evrópu á ellefu ára tímabili og DHPC aðvaranir gefnar út í Hollandi á sama tímakíli. Markmiðið var að ákvarða hvort lyf sem skráð eru með sérstökum ferlum (samþykki með undantekningum (Exceptional Circumstances – EC) eða skilyrt samþykki (Conditional Approval – CA)) fengu frekar DHPC eftir markaðssetningu. Þessir sérstóku ferlar gera fyrirtækjum kleift að sækja um markaðsleyfi fyrir lyf sín með takmörkuðum upplýsingum og færri rannsóknunum, og eru yfirleitt ætlaðir lyfjum til meðhöndlunar á vanræktum sjúkdómmum eða þeim sem er tæknilega erfitt að rannsaka kliníkt. Í ljós kom að þratt fyrir færri klinískar rannsóknir fyrir skráningu, voru lyf skráð með þessum sérstóku skráningarferlum ekki líklegri til að fá DHPC viðvörun, en 16% lyfja skráð með hefðbundnum ferlum og 15% EC eða CA skráðra lyfja fengu DHPC. Niðurstaða okkar styður ekki þá hugmynd að lyf skráð með takmörkuðum upplýsingum séu ekki örugg, að því gefnu að þau uppfylli skilyrdi sérstakra skráningarferla.

Aðferðin í kafla þrjú er notuð aftur í kafla fjögur, auk þess að meta hversu mikil nýjung lyfið er við skráningu. Í rannsókninni er lögð á hversu lyf, sem metin voru mikils á sérstókum nýjungarmælikvarða, væru líklegri til að fá DHPC ðöðvörun eftir markaðssetningu. Nýjungarmælikvarðinn bygdir á fylki sem tekur mið af alvarleika sjúkdómsins sem lyfinu er ætlað að meðhöndlal, hvort meðferð til að meðhöndlal sjúkdómninn er nú þegar í boði og hvort lyfið er framför miðað við það meðferð. Þá er einnig tekið mið af því hversu virkt lyfið er í meðferð sjúkdómsins. Tilgáta okkar var að nýstárleg lyf fara fyrir í netkun og læknar áðurs þeim frekar en dhrum lyfjum þar sem þau eru álitin mikilvæg viðbót við lyfjaúrvalið sem til staðar er. Einnig gæti hugsað að slikar nýjungar séru frekar notaðar í meðferð mjög veikra sjúklinga, þar sem önnur lyf hafa brugðist, en í slíkum tilfellum gæti lyfjó hafa verið rannsakað minna. Slikt notkunarmynstur gæti því leitt til þess að áður óþekktar aukaverkanir uppgötvist. Því var borin saman tíðni og tímasetning tilkynninga um alvarlegar aukaverkanir
milli mismunandi lyfja eftir því hversu miklar nýjungar lyfin eru. Í ljós kom að það hversu nýstárlegt lyf er tengist ekki likindum á að alvarlegar aukaverkanir komi fram. Niðurstöður syndu að a.m.k. helmingur nýrra skráðra lyfja í Evrópu eru að einhverju leyti nýjungar og fjölga meðferðarúrræðum.


Upp hafa komið tilfelli þar sem ákvarðanir skráningaryfirls valda hafa verið gagnrýndar af heilbrigðisstarfsfólki, sjúklingum eða öðrum einstaklingum. Þráustingi var beitt til að samþykkt yrðu lyf við HIV sýkingu þegar littið var vitað um verknarmáta þeirra. Þá hefur skráning og áframhaldandi notkun Human Papilloma Virus bóluefnisins mætt andstöðu, sem og samsett bóluefni gegn mislingum, hettusótt og rauðum hundum. Ákvörðun bandarísku lyfjastofnunarinnar um að fjarlægja natalizúmab af markaði var einnig mótmælt af MS sjúklingum sem að lokum leiddi til þess að lyfina verið áhættu veitt markaðsleyfi.

Í þessu samhengi þróuðum við spurningalista sem byggir á „conjoint analysis“ aðferðarfraeði sem nefnist „discrete choice“. Í hverri spurningu er þátttakendum boðin a.m.k. tveir valkostir og eiga að velja þann sem þeim hугнаст best. Í okkar könnun voru þessi valkostir ímynduð lyf samsett af mismunandi eiginleikum sem lýsa mismunandi verknunum eða afleiðingum af notkun lýfsins. Hver eiginleið var breytilugur og sýndur í samhengi við aðra eiginleiga lýfsins. Þátttakendur sáu hverja samsetningu við hlið annarrar sem hafði a.m.k. tvo eiginleika ólíka þeim í fyrri samsetningunni og voru boðin um að merkja við þá samsetningu sem þeim líkaði betur. Kostur þessarar aðferðar er að hún veitir upplýsningar um hlutfallslegt mikilvægi hvers eiginleiga og getur synt þær málamiðlar sem mismunandi hagsmunaaðilar eru tilbúinir að gera þegar þeir vega og meta ávinning og áhættu lýfja.

Í kafla fimm útsýrum við hvernig við völdum eiginleika lýfjanna sem notaðir voru til að setja saman lýfjasamsetninguna fyrir „discrete choice“ könnunina. Til að bera kennsl á mögulega eiginleika notuðum við mismunandi aðferðir; við rýndum fræðigreinar, reglugerðir evrópsku lýfjastofnunarrannsóknar og tókum viðtöl við hagsmunaaðila í skráningu lýfjöldu við sykursýki. Markmið viðtalanna var að bera kennsl á eiginleika lýfja sem einstaklingum gætu þótt mikilvægir, en vilja gleymast í umræðunni, eða eiginleika sem einstaklingum bykja mikilvægir en eru óræðir. Að lokum voru eftirtaldir lýfjægileikar valdir til notkunar í könnunina; stjórn HbA1c, aukning eða lækkun áhættu hjarta- og æðasjúkdóma, áhrif á þyngd, líkur á óþægindum í meltingafærum eða líkemlið af svipaðum í skráningu lýfjöldu, sem og áhættu á krabbameini í þvagblöðru.

Aþygli vakti að í viðtölunum minnst þátttakendur ekki á það að fyrira bragði að það skipti máli hversu auðvelt væri að nota lýfið, (p.e. einu sinni á dag eða oftar og í sprautuformi eða tölfluformi) eða að konstaða við lýfið skipti máli. Fleiri eginleikar fundust við að rýna í fræðirum og í viðtölum. Þeir voru aftur á móti útilokaðir frá könnuninni vegna þess að þeir þóttu ekki eins mikilvægir (t.d. skammtafjöldi á dag eða konstaður) eða þóttu of flóknir fyrir þátttakendur (t.d. óvissa um eiginleikann við markaðssetningu og möguleikinn að rannsóknun eftir markaðssetningu). Að lokum voru líkur á krabbameini í þvagblöðru bætt í hóp eginleikanna þar sem lyf var tekið af markaði í a.m.k. tveimur löndum í Evrópu vegna aukinnar áhættu á krabbameini í þvagblöðru.

Í kafla sex lögðum við áherslu á að kanna hvaða mat sjúklingar með sykursýki af típu 2 leggja á ávinning og áhættu lýfja við sykursýki. Markmið rannsóknarinnar var að skilgreina mikilvægi skammtíma og langtíma ávinnings í samhengi við alvarlegar aukaverkanir og
léttvægari en óþægilegar aukaverkanir. Í könnuninni voru sjúklingar beðnir um að velja á milli tveggja ímyndaðra lýfja við sykursýki. Þessi lýf voru samsett af mismunandi stigum þeirra lýfjægileikla sem lýst er í kafla fimn. Niðurstöður okkar benda til þess að langtímaávinningur meðferðarinnar, þ.e. minni líkur á hjarta- og æðasjúkdómum, var talinn mikilvægari en skammtímaávinningurinn sem mældur er með stjórn á blóðsykri. Aftur á móti þóttu sjúklingum skammtíma aukaverkanir, sem hafa áhrif á daglegt líf, mikilvægari en aukning á lágrí áhættu á krabbameini í þavgblöðru. Niðurstöður okkar sýndu enn fremur að reynsla sjúklinga af lýfjameðferði hefur áhrif á óskir þeirra. Sjúklingum með ófullnægjandi stjórn á blóðsykri sínun þótti til dæmis mikilvægara að stjórna blóðsykri betur, og þeir sjúklingar sem höfðu reynslu af aukaverkunum völdu síður lýfjasamsetningar með viðvarandi meltingarvandamál.

svipað mat á ávinnung og áhættu lyfja við sykursýki af típu 2 og læknar og sjúklingar þegar lyf er valið fyrir dæmigerðan sjúkling.

Í kafla átta eru teknar saman helstu takmarkanir rannsóknanna. Til dæmis eru rannsóknirnar í fyrri hluta þessarar ritgerðar afturvirkar. Þar sem gögnum er safnað afturvirk er ekki vist að hægt sé að ákvarða allar breytur á öruggan hátt. Í okkar tilfelli voru breyturnar sem notaðar voru vel skráðar á þeim tíma sem þær komu fram. Einnig var uppbyggingu vísindalegrar umræðu í opinionum skræningar og breytt árið 2005 og er nú mun aðgengilegri. Ákvörðun nýjungar nýrra lyfja er einnig mjög huglæg, þátt fyrir notkun á fyrirfram skilgreindu fylki við þá vinnu, og erfitt var að meta breyturnar í fylkinu aftur í tímann. Það vandamál var leyst með því að a.m.k. þrjár mismunandi séfræðingar mátu nýjun hvers lyfs. Aðferðin notuð í köflum sex og sjö er mjög flókin og krefst þess að þátttakendur setji sig í spor einhvers annars. Einnig varð að takmorka hversu marga eiginleika lyfs var hægt að setja fram í lýsingu lyfjanna, þar sem fleiri svarendur hefði þurft til að ná marktækri niðurstöðu og fleiri eiginleikar hefðu gert verkefnið erfiðara fyrir þátttakendurna. Því varð að vanda valið á þeim eiginleikum sem notaðir voru og því var nauðsynlegt að fara í þær forrannsóknir sem líyst er í kafla fimm.

Niðurstæða þessarar ritgerðar er að viðeigandi lærðómur er dreginn af alvarlegum aukaverkunum lyfja í evrópska skræningarferlanum, viðeigandi notkun EC og CA skræningarferlan sem nýtist áfram og að sjónarmið og álit læknar og sjúklinga sem og starfsmanna skræningarferlan geta verið gagnleg í matsferli ávinnings og áhættu lyfja.
Regulatory benefit-risk assessment
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Regulatory benefit-risk assessment
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SHARE publications

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Previous dissertations from the Research Institute SHARE:
((co-) supervisors are between brackets)

Benka J. Living with rheumatoid arthritis: do personal and social resources make a difference? (prof JW Groothoff, prof JJL van der Klink, dr JP van Dijk)

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