

Priority Medicines for Europe and the World  
"A Public Health Approach to Innovation"

Update on 2004 Background Paper

**Background Paper 8.2  
Regulatory structures  
to support pharmaceutical innovation**

**Towards a marketing authorization system that better supports pharmaceutical  
innovation and addresses priority health care needs;  
Recent developments and research priorities**

**By Michelle Putzeist <sup>1</sup>, Jean Philippe de Jong <sup>2</sup>, Pieter Stolk <sup>1</sup>**

**<sup>1</sup> WHO Collaborating Centre for Pharmaceutical Policy & Regulation, Utrecht  
University, The Netherlands**

**<sup>2</sup> Exon Consultancy, Amsterdam, The Netherlands**

## Table of Contents

<b>Preface .....</b>	<b>3</b>
<b>1. Developments in the overall marketing authorization system .....</b>	<b>7</b>
1.1 Adaptive approaches to marketing authorization .....	8
1.2 Key policy priorities from regulatory agencies .....	9
<b>2. Developments in key components of the system .....</b>	<b>10</b>
2.1 Evidence generation and requirements .....	10
2.2 Benefit-Risk assessment .....	14
2.2.1 Initiatives to improve benefit-risk assessment .....	14
2.2.2 Quantitative instruments for benefit-risk assessment .....	15
2.2.3 Opportunities of quantitative benefit-risk assessment instruments .....	16
2.2.4 Challenges for implementation .....	16
2.3 Scientific Dialogue .....	17
2.3.1 Types of interaction between pharmaceutical companies and regulatory authorities .....	18
<b>3. Development in specific regulations .....</b>	<b>22</b>
3.1. Specific disease categories: rare diseases, neglected diseases and unmet medical needs .....	22
3.1.1 Regulatory incentives for rare diseases .....	22
3.1.2 Neglected tropical diseases and collaboration with the World Health Organization .....	24
3.1.3 Diseases with unmet medical needs .....	25
3.1.4 Antimicrobials .....	26
3.1.5 Specific patient groups: paediatrics, elderly and women .....	27
3.1.6 Paediatrics .....	27
3.1.7 Elderly .....	29
3.1.8 Women .....	29
3.2 Specific products: advanced therapy medicinal products .....	30
3.2.1 The ATMP regulation: scope and objectives .....	30
<b>4. Developments in the context of the regulatory system .....</b>	<b>32</b>
4.1 Collaboration with Health Technology Assessment bodies .....	32
4.2 Globalization of regulatory requirements and decision-making .....	34
4.3 Patient involvement in regulatory decision-making .....	35
4.4 Integration with devices and diagnostics .....	35
<b>5. Conclusions and research priorities .....</b>	<b>37</b>
<b>Reference .....</b>	<b>41</b>

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

### Preface

In this Background Paper <sup>a</sup> to the 2013 Priority Medicines Report we describe developments in the system for marketing authorization of new medicines related to pharmaceutical innovation and meeting priority health care needs. In order to support the development of innovative medicines, and to properly address health care needs we propose research priorities for the regulatory system in the coming years. We consider relevant developments at four levels: (1) the overall system of marketing authorization; (2) key components of the system; (3) specific regulations within the system; and (4) broader developments surrounding the system.

The previous Priority Medicines Report was published nine years ago and mentioned a number of issues in the regulatory field, including: innovation in trial design/evidence generation, better communications between stakeholders, the role of patients and the importance of phase IV studies and post-marketing surveillance (see Box 8.2.1).

#### **Box 8.2.1: From the 2004 Priority Medicines Report**

*“All authors agreed that every aspect of the regulatory process should be re-examined and that the evidence base for regulatory practices should be critically analysed using modern methodologies. In particular, this includes preclinical regulatory ‘rituals’. For clinical research, there is a suggestion from Rawlins that alternatives to randomized controlled trials should be investigated. Under some circumstances, he suggests, historical controls could be utilized and alternative analytical statistical techniques using Bayesian statistics could be used to analyse data. A key recommendation of all the authors is the need to improve communication between industry, physicians and regulators in the regulatory process. What is particularly striking about the EMEA, Rawlins and FDA papers are two significant omissions. Apart from the industry paper, none of the three regulatory papers mention any role for patients in the regulatory process. They are referred to as beneficiaries of the process but never as contributors to the decision-making. This is surprising as patients have been very influential in the rapid authorisation of AIDS medicines and in the orphan drug movement. It is not clear how patients could be most effectively involved in promoting innovation and removing barriers but this is clearly an area for research. The second striking omission is the absence of any discussion of post-marketing surveillance as a critical component of the overall process. The FDA diagram of the stages of the medicine development process omits Phase IV from its description of all of the steps in medicine development (see Figure 8.3.1 in Background Chapter 8.3).”*

Work has been done in the past decade on the topics highlighted in the 2004 Report, shown above. Various regulatory authorities now accept the changing role of patients and that they should be involved in the regulatory process. However, more information is needed about what patients can add at the different stages of decision making (see Chapter 8.5 and the related Background Paper). With regard to post-marketing activities, the strengthening of the pharmacovigilance legislation and discussion about adaptive licensing are important drivers

---

<sup>a</sup> This background paper is partly based on the discussion paper ‘Towards appropriate levels of evidence, a regulatory science perspective on adaptive approaches to marketing authorization’ written in the context of a workshop on 6-7 December in Amsterdam, organized by the Dutch Escher Project. See also: [www.escher-projects.org](http://www.escher-projects.org)

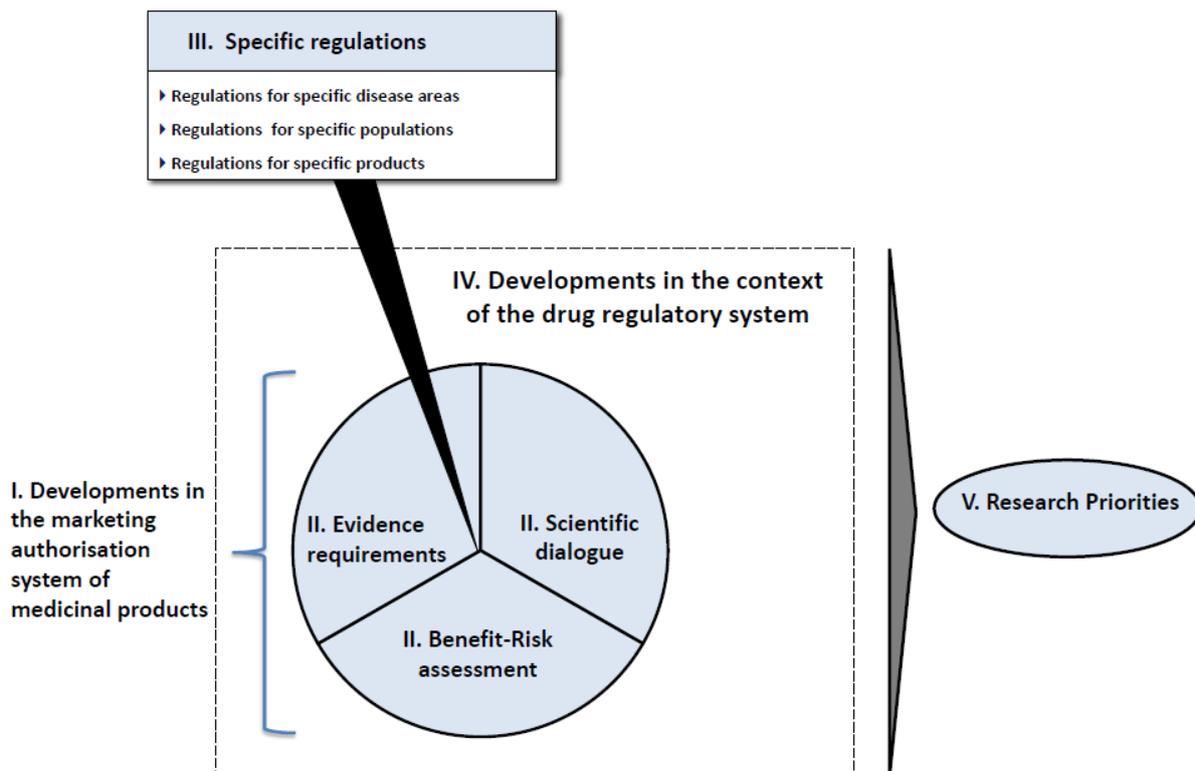
## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

for an increasing role for post-marketing studies. While 10 years ago it was not uncommon for important policy documents to exclude the post-marketing phase, today this is rarely seen, and the role of post-marketing (safety) surveillance is well entrenched.

The current background paper will revisit all of the topics from the 2004 report and will also describe completely new developments in the regulatory system. We will start out by providing a brief overview of developments in the overall marketing authorization system, such as 'adaptive licensing' (Section 1). Following this, we will describe three key components of the regulatory system (Section 2): evidence generation and requirements, decision making about the benefit and risk balance, and the dialogue between regulators and applicants. Next, we discuss regulations introduced for certain disease areas, patient populations or products (Section 3). In Section 4 we will address broader developments surrounding the system for marketing authorization, such as the interaction between health technology assessment bodies and regulatory agencies, and the integration of medicines, diagnostics and devices. In each of these sections we propose research priorities and in the final section (Section 5) we provide a number of general conclusions on research agendas for the regulatory system.

Although this paper takes the EU regulatory system as a starting point, the discussions here are relevant for developments at a global level. We will mention other regulatory arenas, such as the United States of America, where relevant, or where examples are illustrative.

Figure 8.3.1 – Overview of the sections in this background paper



## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

In this background paper to the 2013 Priority Medicines Report we aim to identify research priorities for the coming years concerning the regulatory system for marketing approval of medicines. Research priorities identified in this paper can help to shape a regulatory environment that is beneficial for pharmaceutical innovation and that addresses priority health needs.

**Section 1** gives a brief overview of developments that aim to improve the whole system of marketing authorization, amongst others proposals for adaptive approaches towards marketing authorization. These adaptive approaches propose to replace the single transition from non-approval to approval with a series of approval stages with iterative phases of evidence gathering and regulatory evaluation.

In **Section 2** we describe developments in three key components of the regulatory system: evidence generation and requirements, decision-making, and the scientific dialogue. A key challenge for the regulatory system is how to improve efficiency and quality of evidence generation in order to support the development of innovative and needed medicines. Several new methods, such as introducing innovative design features in clinical trials (e.g. adaptive study designs) and the development of surrogate endpoints have been developed that could optimize evidence generation. Piloting and validating these instruments should be a research priority. Research should also focus on assessing the added value, possibly including cost-effectiveness considerations, of existing regulatory requirements and guidelines in order to support a more flexible approach to evidence requirements

To facilitate the marketing authorization of pharmaceutical innovations, regulatory benefit-risk assessments should be consistent, transparent and predictable for applicants. Several (quantitative) frameworks have been developed that aim to structure, standardize and simplify benefit-risk assessments. Case studies of these (quantitative) benefit-risk instruments are needed to explore the opportunities and limitations for further implementation.

A timelier and more continuous scientific dialogue between companies and regulators could help to implement a more case by case approach to regulatory requirements for evidence, which could support the development of innovative and needed medicines. However, the current practice of scientific advice revolves around getting reassurance of ongoing development plans in the later stages and on interpretation of guidelines. Research priorities would be to identify opportunities and challenges for a more prospective discussion on development plans and whethermore binding agreements about clinical study programs are desirable. The initiatives for joint advice with regulatory bodies such as the U.S. Food and Drug Administration and Health Technology Assessment bodies should be evaluated and further explored.

In **Section 3** we discuss regulatory initiatives that aim to stimulate pharmaceutical innovation and better address medical needs by focusing on certain disease areas (e.g. orphan and neglected diseases), specific populations (e.g. paediatrics and the elderly), and special products (e.g. advanced therapy medicinal products). These initiatives vary from scientific guidance by specific guidelines, to free scientific advice, commercial incentives such as market exclusivity and special marketing approval pathways. The need for new incentives and the performance of current incentives has to date, not been assessed in a

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

systematic way. We have collected the scientific evidence that is currently available and recommend conducting such systematic assessments.

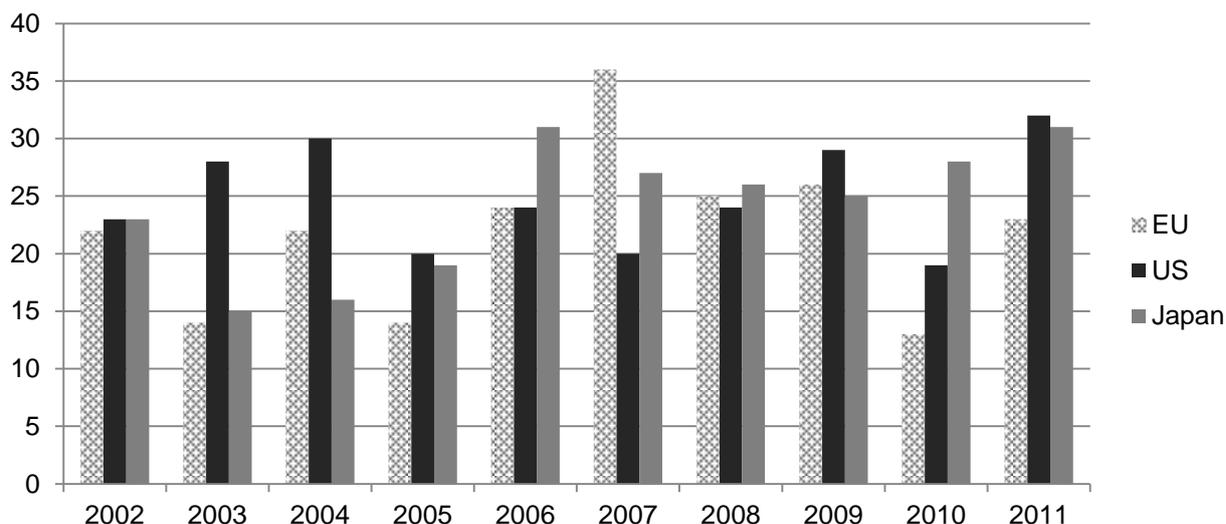
In **Section 4** we address several major developments in the context of the regulatory process for marketing authorization, such as the interaction between regulatory agencies and Health Technology Assessment bodies and the role of Notified Bodies, responsible for evaluating devices. Research efforts could focus on making better predictions about relative effectiveness during drug development, at marketing authorization and afterwards. Studying differences in marketing approval decisions between leading regulatory authorities and the practical implications of these differences is also needed. An evaluation of the regulatory procedures for combined devices and medicinal products can indicate whether these are in need of further harmonization.

In **Section 5** we present four overarching messages for the approach of regulatory studies, based on the discussion of current developments and possible research priorities in this paper: (1) continue to test and explore new methods using (pilot) studies; (2) clearly identify expectations and key performance indicators for new regulations and set up prospective studies; (3) set up constructive collaborations and dialogues with key actors and (4) invest in sharing and analysis of regulatory documents. Combining these approaches can strengthen future research agendas that aim to help the regulatory system support the development of innovative and needed medicines.

## 1. Developments in the overall marketing authorization system

Over the years, an extensive regulatory system has been constructed that covers virtually all aspects of drug development, from early stage pre-clinical development to phase III trials and post-marketing studies. This system has to take into consideration the protection of public health, while at the same time ensuring that patients have timely access to new medicines that address medical needs. Overall, the system has been successful in ensuring that many valuable medicines with a positive benefit-risk profile have reached the market. However, there are also important challenges that this system has to meet in order to ensure a continuous flow of innovative, safe, effective and good quality medicines most needed by society. For example, public trust in the system is frequently challenged by the controversies over timely access to new medicines, medicine withdrawals, and post-approval modifications to labels.<sup>1</sup> Furthermore, the price of innovation is on the rise. Figure 8.2.2 shows that the number of new active substances approved by the European Medicines Agency (EMA), U.S. Food and Drug Administration and Japanese Pharmaceutical and Medical Devices Agency (PMDA) has been relatively stable from 2002 to 2011.<sup>2</sup> However, in the same period research and development expenditures have increased substantially,<sup>3</sup> meaning that the investments per medicine that is brought to the market has also increased.

**Figure 8.2.2: Number of New Active Substances approved by major regulatory agencies by approval year in the EU (EMA), USA (FDA) and Japan (PMDA)**



Source: Centre for Innovation in Regulatory Science (CIRS). New drug approvals in ICH countries: 2002-2011.<sup>2</sup>

An even more important issue is whether the medicines that have been developed are the ones that are most needed by society.<sup>4</sup> In general, portfolio decisions of pharmaceutical companies and research and development strategies are driven by: market opportunity (competitive landscape, reimbursement environment), exploitable scientific knowledge (new targets) and developmental challenges (barriers and the investment of time and resources)<sup>5</sup>. The regulatory system plays an important role in the developmental challenges for

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

pharmaceutical innovation: amongst others, it sets the thresholds for market approval and steers the development process through its interactions with companies.

In order to function optimally the regulatory system has to find the right balance in three key areas:

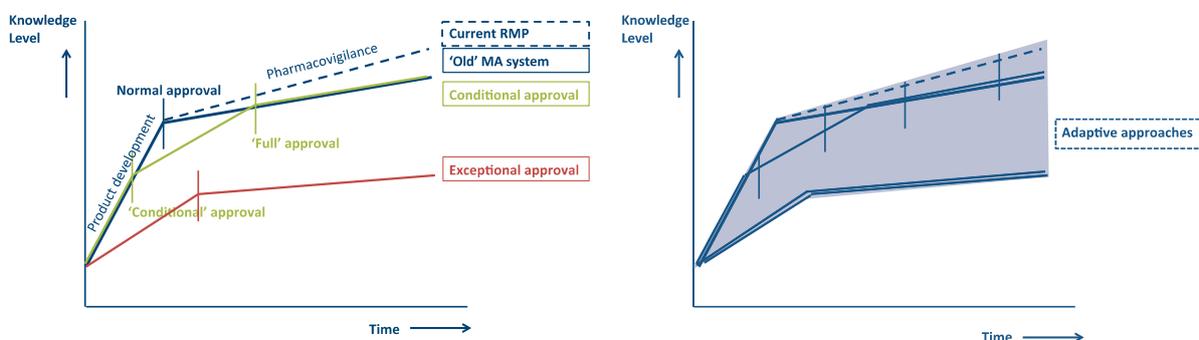
1. Cautiousness: It can be overly or insufficiently cautious (for example, by not granting marketing approval for a medicine with a favourable benefit-risk profile that could have addressed an unmet medical need, or by allowing unsafe or ineffective medicines on the market). This is especially relevant in the context of a society that is increasingly risk averse, and in which regulatory authorities have to make clear to the general public the rationale for their decisions.
2. Incentive structure: It can lack incentives for pharmaceutical innovation, or can provide incentives for innovations that do not address public health needs.
3. Comprehensiveness: It can add undue regulatory burden through redundant regulation or have regulatory gaps.

### 1.1 Adaptive approaches to marketing authorization

To find the proper balance in these areas and find ways to accelerate the flow of innovative and important medicines, in the last decade, several 'adaptive' approaches to marketing authorization have been proposed by key opinion leaders in the EU and the United States (e.g. staggered approval, managed entry, adaptive approval, progressive authorization, and adaptive licensing).

These adaptive approaches are all based on the premise that knowledge about medicines is not binary but continues to evolve over time (Figure 8.2.3). They propose to replace the single transition from non-approval to approval with a series of approval stages with iterative phases of evidence gathering and regulatory evaluation.<sup>6,7</sup> Adaptive approaches aim to facilitate early access by approving medicines early, with acknowledged uncertainty about the favourable and unfavourable effects. The appropriate level of uncertainty can be decided on a case by case basis depending on considerations about the therapeutic area, medical need and willingness of stakeholders to accept more uncertainty.

**Figure 8.2.3: Transition from existing pathways to a comprehensive vision of adaptive approaches to marketing authorization.**



Note: Current regulatory pathways (left hand side) consist of various approaches to balance the moment of market authorization with a certain level of knowledge about the product. Adaptive pathways (right hand side) approach this in a more dynamic manner and allow for more tailoring in the level of knowledge of a product required at marketing authorization.

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

Adaptive approaches, which incorporate elements of existing pathways, should be seen as a holistic vision of a possible future regulatory system, but incorporate also many elements of existing pathways. For example, in the European Union this includes the regulations/guidelines for Conditional<sup>8</sup> and Exceptional Marketing Authorization,<sup>9</sup> the introduction of Risk Management Plans and the recent pharmacovigilance legislation<sup>10</sup>. In the United States this includes the Accelerated Approval pathway<sup>11</sup> and the recent proposal for regulations concerning Special Medical Use.<sup>12</sup>

Although adaptive approaches are attractive options, they also have to confront several challenges. For example, when medicines are initially approved for a restricted population, based on specific evidence for this subpopulation, appropriately defining, targeting and learning from this population during the initial phases after approval to avoid safety issues would require systematic restrictions on prescribing, monitoring of utilization, and interventions to ensure appropriate drug use, including patient adherence. These steps would need to be strong enough to influence the behaviour of patients, physicians, pharmacists, HTA bodies, and reimbursement authorities and to provide sufficient information for policy makers.<sup>13</sup> In an adaptive approach, a medicine's regulatory status (authorization and indication) are likely to change over time. This will have implications for pricing and reimbursement decisions, especially when value-based pricing is fully implemented.

Furthermore, ensuring the appropriate conduct of post-marketing studies could be challenging.<sup>14</sup> Having proper evidence of favourable and unfavourable effects later in the life cycle of a medicine is crucial for being able to allow more uncertainty early in the life cycle. An additional critical issue here is what the regulatory action will be in the event promised studies are not (adequately) performed: restriction of the label could affect patient groups currently taking the medicine and taking no action would undermine the foundation of such an adaptive system. The introduction of the new pharmacovigilance legislation in 2012 may offer the conditions needed for the conduct of additional studies after initial approval.<sup>15</sup> Over recent years, numerous studies have been conducted on different elements of the regulatory system such as evidence generation for initial marketing approval and the benefit-risk assessment. Adaptive licensing is a strong focus of the NEW Drug Development ParaDIGmS ('NEWDIGS') program which studies more flexible, adaptive regulatory models and is launching a series of demonstration and research activities in this field.<sup>16</sup> In addition, various new trial designs and analysis techniques are being piloted. Meanwhile, other initiatives such as<sup>17</sup> CASMI<sup>18</sup> and The Escher Project<sup>19</sup> have created networks for analysis of regulatory practices and information sharing in Europe. However, a number of topics remain to be studied in detail.

### 1.2 Key policy priorities from regulatory agencies

The issues described above are reflected in the strategic priorities from various regulatory agencies.<sup>20,21,22</sup> Table 8.2.1 gives an overview of nine general strategic priorities that were identified by the authors in key policy documents from the FDA and EMA but that can also be found in strategy documents from national authorities.

These strategic priorities tackle the challenges in stimulating innovation and addressing public health needs from a policy perspective. The research topics that are proposed in this

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

background paper aim to fuel an evidence driven discussion on how these strategic priorities could best be supported and implemented.

**Table 8.2.1: Key priorities identified in strategy documents/activities from leading regulatory agencies.**

<b>Strategic priorities</b>
- Address medical needs and align basic methods to estimate an unmet medical need during drug development
- Facilitate the development of new methods for drug development and approval
- Ensure an efficient regulatory approval process
- Improve the quality of information for regulatory decision making about medicines
- Improve the quality of the regulatory decision making process for medicines
- Make regulatory decisions about medicines more transparent
- Align standards for marketing authorization and Health Technology Assessments
- Stimulate responsible use of medicines
- Strengthen post approval safety monitoring of medicines

Sources: <sup>20,21,22</sup>

## 2. Developments in key components of the system

In this section we discuss three components of the regulatory system for marketing authorization that impact pharmaceutical innovation and the addressing of health needs via a wide number of new products or applications; evidence generation and requirements, decision making about the benefit-risk balance, and the dialogue between regulators and applicants. We describe how these components have evolved in recent years and suggest research priorities.

### 2.1 Evidence generation and requirements

The amount of evidence about medicines is the result of two major forces: (1) the supply of evidence by companies through development plans, 'evidence generation'; and (2) the demand for evidence by regulators through regulations and other requirements, 'evidence requirements'. One of the challenges for the regulatory system is to find an appropriate balance between the need for (more) rapid and affordable access to new medicines and the need to ensure comprehensive evidence on benefits and risks needed for an approval decision.<sup>23</sup> This balance has shifted in the last decades towards an increase in evidence requirements for efficacy and safety and more evidence generation for marketing approval decisions. The regulatory system has therefore been criticized by some as overly cautious in the pre-marketing phase, hampering pharmaceutical innovation.<sup>24</sup> This development indicates a need to critically evaluate evidence generation over the whole lifecycle in order to achieve a more sustainable situation, which is also an important tenet of adaptive approaches to marketing authorization, as described in the first section of this paper. In this

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

section we identify opportunities from recent research to optimize evidence generation and requirements and provide research priorities for the future.

Evaluating the evidence on efficacy and safety of a medicinal product and evaluating the uncertainties surrounding this evidence is at the core of the regulatory assessment and should be based on scientific methods.<sup>25</sup> An assessment of the internal and external validity of the data (preclinical and clinical data, including statistical uncertainties) that is provided by companies constitutes the key input for aggregated information on a product's multiple favourable and unfavourable effects and quality. Subsequently, the (clinical) relevance of available information on favourable and unfavourable effects is evaluated and combined into an overall picture of the product's quality and 'benefit-risk balance'.

Re-evaluating the added value of studies for medicinal products in various phases of drug development could help optimize data generation. Although different types of studies are required for marketing authorization, regulators often do not make explicit how important a study is for the body of knowledge about a product. Obviously, refraining from conducting studies that contribute little to the body of knowledge could help to reduce upfront data generation. However, this requires insight in the added value of different types of studies at the particular point in time of the development process at which the decision is made to conduct them. For example, recent publications show that appropriate preclinical and early Phase I and II studies contribute significantly to reducing attrition rates<sup>26,27,28,29</sup> and successful marketing authorization.<sup>30</sup> On the other hand, data from animal (toxicology) studies are sometimes of limited value to detect safety issues.<sup>31</sup> Deciding to refrain from conducting studies with limited added value to the assessment of efficacy and detection of safety issues will lead to more uncertainties about a medicinal product's value. However, in order to stimulate pharmaceutical innovation, besides deciding how much uncertainty is appropriate, a major challenge will also lie in deciding which studies to forego at which moment during development or how these studies can be redesigned.

For the purpose of redesigning studies, many novel methods for trial design and statistical analysis have been introduced that could serve as ways to optimize efficiency of confirmative evidence generation.<sup>32,33,34,35</sup> However, an important point to consider in accepting new methods is that they involve a trade-off between statistical precision and validity and thereby introduce another type of uncertainty: decreased validity. In the words of the CHMP: adaptive designs could render 'confirmatory' trials to be considered merely 'exploratory'.<sup>36</sup>

The internal validity of current clinical trials is ensured by a number of design features, including randomization, blinding (of allocation, patients, treating physicians and measurements), and a thorough follow-up of all patients. Although it is possible to give up some of these design features, this can be problematic for three reasons: (1) it can lead to systematic error (of unknown source) and render results simply untrue; (2) it is unlikely to shorten or reduce the size of studies and therefore does not help early access to the market; (3) it is unethical to enrol research subjects in less rigorous studies because it can mean that their efforts will not contribute to the body of knowledge about a medicine. Nevertheless, a currently used route that sacrifices internal validity is to conduct single-arm and observational studies instead of trials. This has been the basis for the conditional marketing authorization for some cancer and orphan medicines. Still, even for orphan medicines,

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

randomized controlled trials are preferred by regulators and are in fact supplied in almost 60% of the dossiers.<sup>37</sup>

Besides the general design features of trials, the use of alternative outcome measures, so-called “surrogate outcome measures”, is also a way to optimize evidence generation. Although surrogate outcome measures can turn out to be inadequate predictors of clinical effects, they hold promise to shorten development timelines, especially for diseases with long-term outcomes.<sup>38,39</sup> The validation of surrogate outcome measures seems to be high on the research agenda of both EU and USA public-private partnerships<sup>40,41</sup> and should continue to be so in future. However, the next step is to introduce validated outcomes in regulatory practice. This will require effort from scientists, companies and regulators.

Reconsidering external validity also seems a promising avenue to optimize evidence generation. This line of thinking can be seen in a recent concept guideline by the EMA on ‘extrapolation’. Extrapolation can be done between: population subsets, diseases, animal-to humans, healthy volunteers to patients, and between medicines, within and between classes.<sup>42</sup> Studies on extrapolation within and between medicines have shown that this could be a valuable way to reduce uncertainty, without requiring additional data generation. A study that focused on medicines from the same class during marketing approval found that adverse drug reactions of *first* in class medicines were not always included in the Summaries of Product Characteristics of *second* in class medicines.<sup>43</sup> Another study showed that for HIV medicines safety issues were taken into account in the approval process of other medicines in the same class.<sup>44</sup> Improving this kind of learning could help to achieve a proper level of knowledge about a product while requiring less data to be collected preapproval.

A complementary way to achieve an ‘appropriate’ level of evidence in an efficient manner could be to use guidelines more flexibly and decide more on a case by case basis whether guideline adherence is needed for a specific medicinal product or group of medicinal products. However, a more flexible approach to evidence requirements needs to be supported by having (better) insight in the effects of existing requirements and guidelines. This is also in line with the 2002 WHO report ‘Effective Drug Regulation’ which states that “*ideally, an assessment of drug regulation should begin by studying regulatory outcomes to judge overall performance*”. The report concluded that “*outcomes are often not readily measurable*”.<sup>45</sup> However, regulatory science has made progress in this respect by providing insight into the effects of evidence requirements.<sup>46,47</sup> Recent studies show that promising instruments exist to adjust regulatory requirements, also for the case-by-case evaluations of the need for evidence as proposed by adaptive approaches to marketing authorization.<sup>48,49</sup>

The EMA acknowledges the value of evaluating the need for an ‘impact assessment’ for new guidelines.<sup>50</sup> However, currently this impact assessment results in a standard formula which does not describe a comprehensive assessment of pros and cons and the resulting ‘go/no go’ decision for the development or application of a guideline. A possible solution for this is to involve companies, academia and patients more intensively in the early stages of guideline development, which is in line with recent EMA thinking.<sup>51</sup> We would suggest that this activity is strengthened, and is combined with a comprehensive assessment of the effects of evidence requirements in regulatory practice.

One element of optimizing evidence generation that is not prominent in regulatory thinking is the costs of evidence requirements. Hardly any evidence regarding the cost-effectiveness

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

of regulatory requirements exists.<sup>52,53</sup> Recent studies show that systematically evaluating the cost-effectiveness of regulatory requirements is feasible.<sup>54,55</sup> An example is the cost-effectiveness study of guideline ICH E14 requiring QT/QTc studies for particular products which shows that this requirement in its current form is not cost-effective.<sup>54</sup> Such evaluations could become part of a comprehensive impact assessment of regulatory requirements and could support a more flexible approach to evidence requirements.

As described above, both evidence generation and evidence requirements could be optimized and tailored in order to achieve a more efficient development process towards marketing authorization. When the 2004 Report<sup>56</sup> was published, the traditional randomized controlled trial was still seen as the gold standard for measuring efficacy. In 2013, this is increasingly being challenged, based on the need to move from efficacy based on limited clinical trials to real-world effectiveness, with broadening of indications, repurposing of medicines and demands for comparative effectiveness. According to recent proposals for adaptive approaches to marketing authorization, medicines could be initially approved with more uncertainty about efficacy and safety, but only if this is adequately supported by continuous evidence generation throughout the lifecycle of medicines.<sup>57</sup> Currently, the conduct of Phase IV activities and studies to monitor and explore (un)known risks is controlled by EU risk management requirements in the 2012 pharmacovigilance legislation. Post-marketing evidence on efficacy, effectiveness and safety can for example be generated by Phase IV randomized clinical trials in therapeutic settings, but observational studies can also play a major role.<sup>57</sup> So far experience with observational studies has mainly been gained with safety studies to detect and monitor adverse effects of medicines. In line with the proposals for adaptive approaches to marketing authorization, observational studies could also contribute to reducing uncertainty about efficacy. Observational data gathering can be conducted within existing infrastructures such as electronic medical records, but might also require additional investments (see the Background Paper Chapter 8.4). Furthermore, improvements in health information technology will be needed to facilitate proper information exchange between parties.<sup>57</sup>

### **Research priorities evidence generation & requirements**

To improve efficiency and quality of evidence generation in drug development for initial marketing authorisation, research should focus on:

- Assessing the added value of existing regulatory requirements and guidelines to support a more flexible approach to evidence requirements;
- Making cost-effectiveness evaluations part of a comprehensive impact assessment of regulatory requirements;
- Piloting and validating promising instruments aimed at efficiency in drug development (e.g. surrogate outcome measures and adaptive study designs).
- Further developing methodology for post-marketing observational safety studies (e.g. linking datasets and signal detection), in particular relevant in a flexible/adaptive approach of requirements for initial marketing approval.
- Developing effectiveness studies to reduce uncertainty around efficacy and to compare the effects of medicines in real life settings.

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

In the next section we focus on another important component of the regulatory process: the benefit-risk assessment by authorities. We describe a number of initiatives that intend to make this crucial step more transparent and consistent.

### 2.2 Benefit-Risk assessment

The assessment of benefits and risks of new medicinal products is a central element of the evaluation of a marketing authorization application by regulatory authorities. Additionally, benefit-risk assessments play an important role in companies' development strategies, in reimbursement decisions by health technology assessment bodies and in decision making by research ethics committees.<sup>58,59,60,61</sup> Regulatory benefit-risk assessments should be as consistent and transparent as is reasonably possible, to increase predictability of the approval recommendations for applicants and facilitate marketing authorization of innovative medicines, and to allow for clear communication with applicants and the public about the rationale behind decisions. In recent years, improving consistency and transparency of the decision-making process by regulatory agencies is also seen as an opportunity by the EMA,<sup>62</sup> which has led to a number of initiatives that will be discussed here. Although we focus on benefit risk assessment in the context of decision-making about marketing authorization by EU regulators, much of our discussion is relevant to other decision makers and for other geographical areas.

Benefit-risk assessments consist of three ingredients: (1) data about the favourable and unfavourable effects of a product; (2) uncertainties about these effects; and (3) judgements about the clinical relevance of effects based on data and accompanying uncertainties.<sup>63</sup>

In addition, a properly conducted benefit risk assessment should have two important qualities:

1. It should be a rational process of combining objective elements (data and uncertainties) with subjective elements (clinical judgement, trust), leading to consistent decisions;
2. It should be a transparent process, making it communicable and accountable.

Although the elements identified above provide a clear structure, in 'real-world' practice, benefit-risk assessment is a complex, multi-person process that requires the evaluation of a large volume of data (up to 10Gb, when the required digital storage space is used as a measure) on multiple effects and transformation into an overall balance, usually resulting in a 'yes/no' decision.<sup>64,65</sup> In general, discussions and evaluations of a qualitative nature guide this transformation by regulatory agencies and most companies.<sup>63,64</sup>

#### 2.2.1 Initiatives to improve benefit-risk assessment

To help increase consistency and transparency of benefit-risk assessments, many organizations, including companies and regulators, have developed frameworks to structure, standardize and simplify benefit-risk assessments. Examples are the Unified Methodologies for Benefit-Risk Assessment (UMBRA) initiative of the Centre for Innovation in Regulatory Science (CIRS)<sup>66</sup>, the IMI PROTECT work package on benefit-risk integration and representation<sup>67</sup> and EMA's Benefit Risk Methodology Project. We will discuss some of these initiatives in more detail.

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

The EMA Benefit Risk Methodology Project aims to improve the transparency, consistency and communicability of marketing approval decisions of medicines by developing instruments and processes for balancing multiple benefits and risks<sup>68</sup> that can aid benefit-risk assessment by regulators. So far, the project has resulted in an improved conceptualization of 'benefit' and 'risk', replacing these words with four separate items: 1) favourable effects; 2) uncertainties about the favourable effects; 3) unfavourable effects; and 4) uncertainties about the unfavourable effects. The CHMP has incorporated this conceptualization in relevant guidance documents for assessment reports. Furthermore, the project has endorsed a descriptive ('PrOACT-URL') framework for systematically evaluating the benefit-risk profile and has proposed an 'Effects Table' for displaying a product's relevant effects and uncertainties.<sup>69</sup> The PrOACT-URL framework consists of the following steps: Problem formulation, Alternatives (options), Objectives and criteria, Consequences, Trade-offs, Uncertainty, Risk attitude, and Linked Decisions. Both PrOACT-URL framework and Effects Table are descriptive tools to structure the benefit-risk evaluation.

### 2.2.2 Quantitative instruments for benefit-risk assessment

However, many of the recent initiatives to achieve more consistent and transparent decision making involve not only descriptive tools, but also 'quantitative' instruments<sup>66,67</sup>. Although currently no regulatory authority uses them, various authors and organizations (including the EMA<sup>70</sup>), endorse these 'quantitative' instruments.<sup>71,72,,73,74,75,76</sup>

To support benefit-risk assessment quantitative instruments distinguish three steps in decision making: (1) decompose problematic situations into its constituent pieces; (2) make assessments about these pieces; and (3) recompose the pieces to a whole. The first step is descriptive (e.g. PrOACT-URL framework and Effects Table), but step 2 and 3 are 'quantified'; in step 2, input elements (effects, uncertainties and value judgments) are translated into numbers or ranks on a common scale; step 3 consists of a formal model with an algorithm for integrating different input elements into a single output.<sup>77</sup>

A commonly discussed quantitative instrument, also within the EMA, is the Multi-Criteria Decision Analysis (MCDA) instrument. Within the context of regulatory benefit risk assessment, MCDA can incorporate in a logical, coherent model, different forms of data, multiple objectives, uncertainties, and value judgements. This covers all elements of regulatory benefit risk decision making.<sup>77</sup> An additional feature of MCDA (and many other quantitative instruments) is that it can visualize how different elements contribute to the overall benefit-risk balance, comparing one product to another.

The EMA field-tested an MCDA approach with medicines that were under review at the CHMP. At five member state agencies, a one-day, facilitated 'decision conference' was organized using the EMA's PrOACT-URL framework in order to construct on-the-spot a benefit-risk model of the medicines and their comparators. Field-tests showed that a quantitative approach was feasible within the context of regulatory benefit-risk assessment of a product. Assessors especially appreciated the feedback the quantitative model gave them on the impact of uncertainty in the data and of differences of opinion about clinical relevance. Limitations of the software instruments utilized were that the instruments had limited capabilities to incorporate statistical uncertainty, an essential element of benefit risk assessment. Furthermore, building up the model through input of data and relevant criteria

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

with measurement scales was time consuming.<sup>78</sup> There are currently software tools under development that aim to address these limitations.<sup>79</sup>

Although the EMA considered the field-tests a success, recent EMA proposals for implementation of benefit-risk tools focus on purely descriptive tools such as the Effects Table.<sup>80</sup> Currently, case studies are conducted within the PROACT-URL framework to explore opportunities for implementation in regulatory practice.<sup>81</sup>

### 2.2.3 Opportunities of quantitative benefit-risk assessment instruments

Because quantitative instruments force decision makers to explicate and systematise judgements about benefits, risks and their uncertainties, and because they allow an exploration of any discrepancies between personal intuitions and computer results, quantitative instruments can increase consistency of decision making between different medicinal products, and of repeated decisions about the same (type of) product. In particular, quantitative instruments could help to (re)align judgements about clinical relevance between regulators which could contribute to consistent decision making. Furthermore, explicating these judgements about clinical relevance could help regulators to better communicate the rationale of benefit risk decisions to companies and the public and so strengthen trust in the regulatory system.

Furthermore, during the process of medicine development, regulators could use quantitative instruments to simulate scenarios and thereby explore how changes in value judgements or (uncertainty about) data could affect the overall benefit risk balance. This would allow regulators and companies to have a constructive and prospective discussion on what evidence is needed for marketing authorization. In addition, such scenario analyses could help to get insight into how robust decisions are in relation to different perspectives about clinical relevance (e.g. by patients or prescribers) and how (new) real world data would affect the balance. Having insight in the robustness of decisions could strengthen the confidence of regulators for approving medicines on the basis of adjusted evidence requirements in areas of high medical need. In collaboration with the European Network for Health Technology Assessment (EUnetHTA) the EMA is currently looking into how the information on benefits and risks of medicines in European public assessment reports (EPARs) could better contribute to assessments by HTA bodies.<sup>82</sup> Quantitative instruments may further support this process.

### 2.2.4 Challenges for implementation

Introducing quantitative instruments as a tool to support scientific judgements might be challenging by requiring additional skills, supporting staff and time investment. Decision conferences are time intensive, although on the other hand a standardization of models used, an intensified preparation and using models to facilitate communication could save time.

It may also be possible to decide on a case-by-case basis how much quantitative modelling is needed. A first step here would be to study the time investments involved. It should also be taken into consideration that although quantitative instruments can incorporate statistical uncertainties about effects, these models can currently not account for other forms of 'uncertainty' such as different levels of validity: regulators need to assess the quality of studies before adding these into a model. Another challenge for implementation is finding

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

the best mode of visualization of model results. Finally, explicating value judgements through quantitative instruments and use this to communicate the rationale of benefit risk decisions to the public can pose challenges because the regulator's value judgements might be different from those of patients. The recent EMA initiatives to increase patient involvement in regulatory decision-making may address this challenge.

In the next section we will discuss a third key element in the regulatory process: the interaction between regulatory authorities and companies in the form of a scientific dialogue.

### Research priorities for benefit-risk assessment

All in all, further field tests and study of both descriptive and quantitative models is needed to guide further implementation. To further advance the methodology of benefit-risk assessment, research priorities should focus on:

- Conducting case studies of quantitative benefit-risk instruments to explore opportunities and limitations for further implementation in practice.
- Conducting simulations of assessments of previously (dis)approved marketing authorisations, to gain insight into how robust approval decisions are in relation to different perspectives about clinical relevance (e.g. by regulators, patients or prescribers).
- Improving methods for visualization of results of quantitative benefit-risk assessments to communicate the rationale of benefit risk decisions to companies and the public.
- Exploring how quantitative benefit-risk instruments could contribute to providing information on benefits and risks of medicines to assessments by Health Technology Assessment bodies.
- Developing methods for how prescribers and patients can better be involved in regulatory decision-making and how their preferences can be taken into account in models.

## 2.3 Scientific Dialogue

A constructive (scientific) dialogue between pharmaceutical companies and regulatory agencies can facilitate pharmaceutical innovation for several reasons, these include:

- The application of emerging science and technologies for drug discovery and development (e.g. proteomics, nanotechnology, synthetic biology, new statistical methods, quality by design etc.) have increased the needs of interaction and knowledge transfer<sup>83</sup>;
- New regulatory tools prompted by changes in legislation and updates in requirements (e.g. regulation for paediatric medicines, advanced therapies medicinal products, pharmacovigilance and risk management) have increased the need of interaction between companies and regulatory authorities to streamline the development process<sup>83</sup>;
- A scientific dialogue may enable a more flexible approach to regulatory requirements (e.g. in scientific guidelines) when it is discussed what requirements are actually relevant for a particular medicine in order to ensure a proper assessment of quality, safety and efficacy.

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

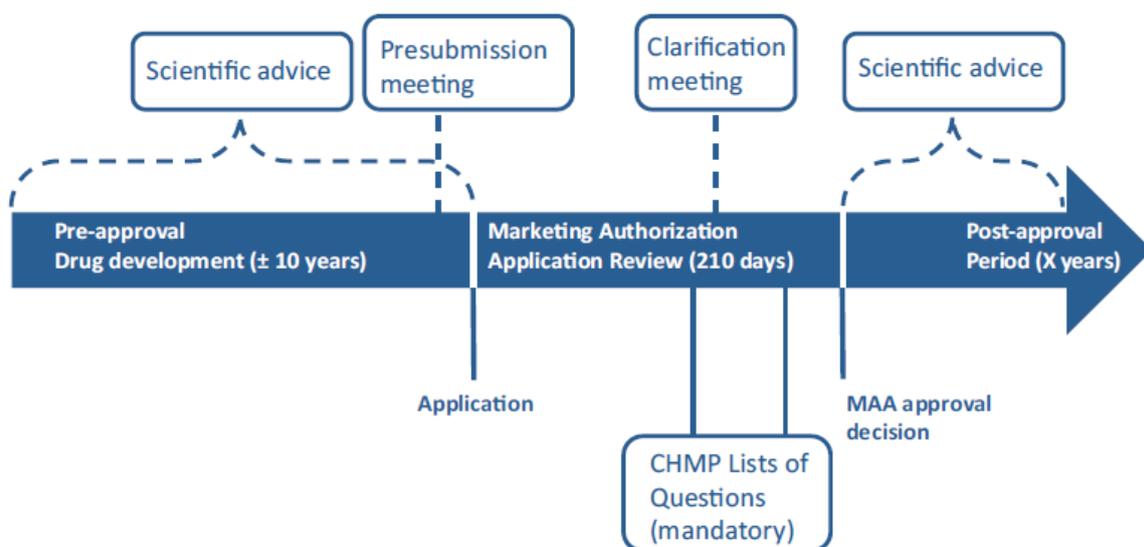
In this section we discuss opportunities to expand the scientific dialogue and explore how future research could help in this respect.

### 2.3.1 Types of interaction between pharmaceutical companies and regulatory authorities

An issue that was highlighted in the 2004 Report was the need for communication between stakeholders. An overview of recent discussions shows that this field has progressed considerably in recent years. For example, there is now widespread interest in how regulators and industry can further improve communication and most productively engage in an early dialogue in the drug development process and in how changes in regulations impact on product development.

Interaction between regulatory authorities and pharmaceutical companies about medicines can concern regulatory issues (interpretation of legislation), administrative issues (how to submit an application) and scientific issues. This latter kind of interaction concerns what data needs to be generated in order to demonstrate the quality, safety and efficacy of a medicine. Interaction on scientific issues can be of a more general nature such as takes place during workshops, information days, or guideline consultation procedures organized by regulatory agencies to discuss new methods, study designs and draft guidelines.<sup>84</sup> However, scientific interaction can also focus on a particular medicine. This kind of interaction takes place in all phases of a medicine's lifecycle: during initial drug development, during the marketing authorization procedure, and in the post-marketing phase (Figure 8.2.4 depicts the medicine-specific interaction between the European Medicines Agency and pharmaceutical companies).

**Figure 8.2.4: The figure shows that scientific advice can be requested during all phases of drug development, including the post-marketing phase**



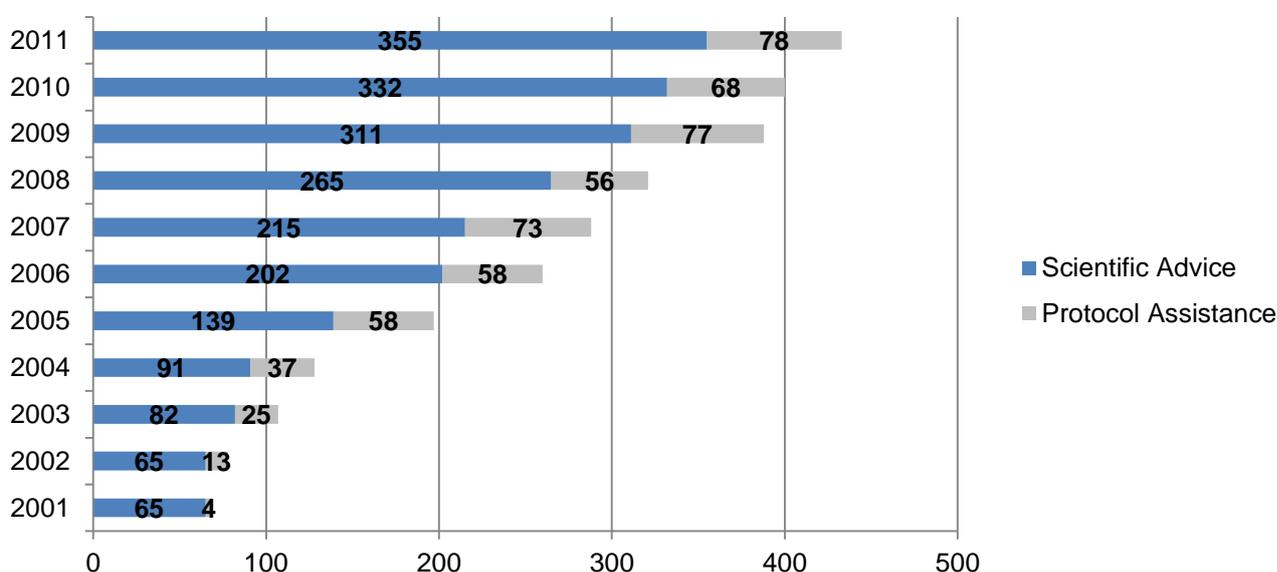
Most of the scientific interactions between applicants and the EMA on a medicine, such as *pre-submission meetings*, *CHMP list of questions* and *clarification meetings* (see Figure 8.2.4),

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

concern how additional information and justification can be provided in the dossier<sup>85</sup>. These types of interaction all concern interpretation of available evidence about a medicine, not evidence generation. However, in the *scientific advice* procedure the EMA can interact with companies about development plans *before* data are generated.<sup>86</sup> The scientific advice procedure thus provides companies the opportunity to tailor evidence generation to regulatory requirements, which is highly relevant for successful marketing authorization.<sup>87</sup>

In 2006, the scientific advice procedure of the EMA has been reformed to enable companies to discuss a broader set of issues concerning development plans with regulators.<sup>86</sup> Figure 8.2.5 shows how the number of scientific advice procedures has increased over the last decade: in 2011 76% of marketing authorization applications included scientific advice.<sup>88</sup>

**Figure 8.2.5: Number of scientific advice procedures (by CHMP) per year for the period 2001-2011**



Sources: Longgren T. Perspectives on the scientific dialogue. Presentation given in Escher workshop "Towards Adaptive Marketing Authorization" December 2012.<sup>89</sup>

The European Agency for the evaluation of medicinal products. Eight Annual Report 2002.<sup>90</sup>

Below, we discuss the following aspects of scientific advice in more detail (a) the objectives of scientific advice, (b) the timing, (c) its (legal) status, and (d) stakeholder involvement, and discuss opportunities for improvement.

### a. Objectives of scientific advice

In principle, issues related to all phases of medicine development can be discussed in the scientific advice procedure, e.g. quality (manufacturing, chemical, pharmaceutical and biological testing), preclinical (toxicological and pharmacological tests) or clinical issues (early and confirmatory clinical studies pre- and post-approval), as well as opportunities for conditional or exceptional approval<sup>91</sup>. The EMA emphasizes that scientific advice aims to discuss development plans prospectively and is not meant to pre-evaluate study results related to a marketing authorization application.<sup>91</sup> However, a recent study showed that companies request scientific advice primarily to get assurance that on-going development

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

plans are in compliance with regulatory requirements and guidelines and that scientific advice was used to a lesser extent to discuss development plans in cases where guidelines provided insufficient detail.<sup>92</sup> This current practice of scientific advice is not fully in line with the EMA's aim that scientific advice can help to set up a development plan. Also, this practice is not suitable for the implementation of adaptive approaches to marketing authorization which require a constructive dialogue about how much and what kind of evidence is required for a particular medicine.

### **b. Timing of scientific advice**

The EMA does not specify timelines for scientific advice but companies can seek scientific advice as many times as necessary and in all phases of the product lifecycle: either during the initial development of the medicine or during the post-marketing phase, e.g. related to risk management plans.<sup>91</sup> Since 2006 companies can also ask for follow-up advice when they have additional questions and post-marketing advice on risk management plans has been reinforced too. According to the EMA Roadmap to 2015, scientific advice should be further expanded towards *continuous* scientific support during the development of a medicine with an *earlier* appointment and involvement of (co-)rapporteurs, in order to augment the interaction between regulators and sponsors during the development of medicines.<sup>93</sup>

However, a recent study of scientific advice questions indicates that current scientific advice is neither provided at an early stage nor in a continuous fashion.<sup>94</sup> An analysis of the Dutch and European scientific advice procedures showed that most questions were asked about the later stages of the pre-authorization phase, e.g. discussion on the interpretation of phase III guidelines when phase III studies were already ongoing.<sup>94</sup>

### **c. (Legal) status of scientific advice**

Scientific advice in Europe is not legally binding, neither for companies nor for authorities with regard to a future marketing authorization application.<sup>95</sup> However, although companies are not obliged to follow scientific advice, compliance with scientific advice is associated with a higher rate of successful marketing authorization.<sup>96</sup> Furthermore, companies have to justify deviations from scientific advice to the CHMP when applying for marketing authorization, for example when the company has decided to use a different study design than recommended during scientific advice. Similarly, the CHMP has to explain during the review of a marketing authorization application why it deviates from previous advice.<sup>97</sup>

Although scientific advice is currently not binding in Europe, there could be good reasons to give advice a more formal status and come to some sort of agreement on development plans in an early stage. If regulators would want to evaluate the need for generating evidence on a product more on a case by case basis (for scientific reasons or reasons related to addressing medical need, for example in the context of an adaptive approach), and would thereby allow companies to deviate from guidelines, companies should feel confident that the evidence generated during the course of development will still be considered acceptable at time of marketing authorization application.

Otherwise, companies would be inclined to 'play safe' and comply with all available guidelines, also those guidelines that companies consider a waste of time because of limited added value or the availability of better alternatives. Naturally, there should be some process to adjust the agreements made, based on scientific developments, but in a recent interview

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

study Dutch small and medium enterprises indeed stressed the usefulness of making agreements with regulators about the clinical development plan<sup>Error! Bookmark not defined.</sup>.

In contrast to the EMA, the FDA does allow for formal agreement on plans for phase III studies in their 'Special Protocol Assessment' procedure.<sup>98</sup> In this procedure regulators and the applicant agree explicitly on the design, execution, and analyses in proposed study protocols [i.e., carcinogenicity protocols, stability protocols, and phase III protocols for clinical trials that will form the primary basis of an efficacy claim]. The FDA states that *"it will not later alter its perspective on the issues of design, execution, or analyses unless public health concerns unrecognized at the time of protocol assessment under this process are evident."*

Further research could identify opportunities and challenges for other regulatory agencies to offer such a procedure to applicants in specific circumstances.

### **d. Stakeholders involved in scientific advice**

The parties involved in current scientific advice procedures are companies and the EMA Scientific Advice Working Party (SAWP).<sup>99</sup> To strengthen the discussion, external stakeholders such as the FDA, but also health technology assessment bodies, patients and in particular cases the World Health Organization could be involved in the scientific dialogue.<sup>100</sup> Below we discuss several examples of on-going experiments in this respect.

The FDA and EMA have set up a 'parallel scientific advice' procedure which was revised in 2009. Parallel scientific advice provides a mechanism to exchange views on scientific issues during the development phase of new medicinal products (i.e., new human drugs and biologics) between the EMA and FDA regulators. The expected advantages from this interaction are intensified interactions between these two agencies and sponsors, especially in the beginning of the lifecycle of a new product, a better understanding of the basis of regulatory decisions, and the opportunity to optimize product development, e.g. by avoiding unnecessary replication of testing or use of diverse testing methodologies. Parallel scientific advice focuses primarily on important breakthrough drugs and on major safety issues that are considered important by both agencies.<sup>101</sup> In 2011 eight requests for parallel scientific advice were submitted.

A second example of expanding the number of stakeholders involved in scientific advice is the EMA's aim to increase the number of scientific advice procedures for medicines for unmet medical needs, neglected diseases and rare diseases.<sup>102</sup> According to a 2011 update, scientific advice with involvement of WHO experts has been reinforced.<sup>103</sup>

Finally, the EMA and EUnetHTA have begun to explore how scientific advice could be harmonized with advice given by HTA bodies, and aim to establish what evidence both parties need.<sup>103,104</sup> Since 2010, 17 procedures of joint scientific advice have been initiated for various therapeutic areas. In a recent joint meeting of the EMA and EUnetHTA, it was established that joint scientific advice in an early stage (e.g. the phase of non-clinical proof of concept studies) is most beneficial for companies in order to learn what would be needed in terms of general study designs. In a later stage, when exploratory clinical data are available, more precise responses could be given related to the choice of endpoints, duration, comparators, size of the trial and the statistical plan.<sup>105</sup>

### Research Priorities Scientific dialogue

To strengthen the scientific dialogue, research should focus on:

- Identifying opportunities and challenges for regulatory authorities to offer early and continuous scientific advice.
- Conducting qualitative studies on how to increase the number of scientific advice procedures for medicines for unmet medical needs, neglected diseases and rare diseases.
- Further exploring opportunities and preferences to make more binding agreements about clinical study programs in scientific advice.
- Monitoring the use of parallel scientific advice with FDA and identifying opportunities for improvement.
- Evaluating opportunities for shared (early) scientific advice between regulatory agencies and Health Technology Assessment bodies

### 3. Development in specific regulations

For certain specific disease categories, patient populations or type of products, regulatory incentives have been introduced at the European level to stimulate pharmaceutical innovation in areas that address public health needs (see Table 8.2.1). In this section, we describe various regulatory incentives for these topics and identify avenues for future research.

#### 3.1. Specific disease categories: rare diseases, neglected diseases and unmet medical needs

Specific disease categories discussed here are those diseases for which market conditions lead to a lack of incentives for developing medicines due to the low numbers of patients (e.g. rare diseases) and/or insufficient purchasing power (e.g. tropical neglected diseases). Additionally, the development of medicines for life threatening diseases with no alternative treatments available is also a specific group for which incentives have been introduced. Moreover, particular disease areas of high medical need are recognized, such as infectious diseases and the related need for the development of new antibiotics.<sup>106</sup>

##### 3.1.1 Regulatory incentives for rare diseases

Rare diseases are defined as life-threatening or chronically debilitating conditions that affect no more than five in 10 000 people in the EU. In general, for these conditions the cost of developing a medicinal product would not be recovered by the expected revenues because of the low number of patients. In the United States, the first Orphan Drug Act was introduced in 1983 and in 2000 the Orphan Regulation was introduced in the EU, which offers incentives for the development of medicinal products for rare diseases such as fee reductions, 10 years of market exclusivity and free protocol assistance for products with an orphan designation.<sup>107</sup> The total estimated number of rare diseases lies between 6 000 and 8 000.<sup>108</sup> From 2000-2010, more than 850 orphan designations were granted to medicines under development from the

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

1 235 requests submitted to the European Medicines Agency by the end of 2010.<sup>109</sup> In total, 63 orphan medicinal products have been approved for the market.<sup>109</sup>

Initiation of orphan drug development and successful marketing authorization seemed to focus on certain disease areas. Uncommon cancers represent the highest number of orphan designations and marketing authorizations in the EU and the United States.<sup>110,111</sup> Uncommon or rare cancers are often subtypes from more common cancers that have been stratified into molecular subsets. Research into these specific molecular subsets has led to valuable results for targeted agents, which can also be extrapolated to common cancers. Using the orphan definition in this way can create a 'perverse incentive' for developers to carve up the market of a medicine for a relatively common disease into components that fall within the orphan medicine category, this may be an 'adverse effects' of the orphan regulation.<sup>112</sup> For example, relatively high volumes of use of expensive orphan drugs, leads to a rise in healthcare costs.

In contrast to the rare cancers, for certain other types of rare diseases, such as neurodegenerative diseases, orphan designations are far less frequently requested.<sup>113</sup> Analyses of orphan designations demonstrated that prevalence and scientific output of the disease were determinants for an orphan designation request. For example, rare cancers could benefit from the amount of global research conducted and scientific output in the oncology field.<sup>114</sup> A recent study on exceptionally rare metabolic diseases confirmed the role of prevalence for orphan designation applications and identified that publicly available scientific output of preclinical proof of concept of a drug target was most relevant for an orphan designation application.<sup>115</sup>

Among the incentives for orphan drug development, financial incentives such as market exclusivity are generally perceived as most attractive to initiate drug development and request an orphan designation. Market exclusivity provides protection for an orphan medicinal product that has been authorized for a particular indication from similar products in the same indication. Market exclusivity can be challenged in case of lack of supply, proven clinical superiority of a different medicine or an agreement to share the market with the original sponsor. The likelihood of having such a follow-up marketing application of an orphan drug was also associated with disease prevalence, disease class and disease specific scientific output. In addition turnover of the first orphan medicinal product and age of onset of the disease were driving follow-up marketing applications.<sup>116</sup> Apparently disease scientific output is a relevant driver for initiation of development of medicinal products for rare diseases for which no therapy exists as well as for innovations with clinical superiority over existing therapies. Fundamental research on the pathophysiology of the disease and potential new drug targets is needed for those diseases for which no medicine development initiatives have been undertaken.<sup>117</sup>

The numbers of orphan designations are high compared to the number of marketing authorization applications and approvals. Critics state that orphan medicinal products that are approved, are based on submitted clinical studies with low quality of study designs including: insufficient sample sizes, inadequate outcome measures and follow-up.<sup>118</sup> A study of all orphan medicinal products evaluated by the CHMP since 2000 demonstrated the relevance of the clinical development plan e.g. study design and choice of endpoint for marketing approval.<sup>119</sup> Moreover, a study with FDA data also identified the clinical trial design to be associated with non- approval, which implies that regulators consider a robust study design relevant for marketing approval.<sup>120</sup> A recent analysis that compared marketing

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

approval review of orphan and non-orphan medicinal products demonstrated that regulatory standards for orphans were just as high as for non-orphan medicinal products.<sup>121</sup> Lower quality of study designs e.g. single arm studies were only allowed under the scope of conditional or exceptional approval, when alternative therapies were lacking. Apart from design characteristics of submitted studies, the level of experience of the company and dialogue with FDA regulators were also associated with marketing approval. In the EU protocol assistance (the special form of scientific advice available for companies developing designated OMPs for rare diseases) was received in 48% of OMPs that were submitted for marketing approval by 2010.

Overall, many consider the orphan regulations in the EU and the United States a success,<sup>122</sup> but improvements are still needed to stimulate (appropriate) clinical development of medicines for rare diseases. For example, for the numerous diseases for which orphan designations exist, but clinical development is a major challenge, how protocol assistance can be of optimal use should be further investigated.

### 3.1.2 Neglected tropical diseases and collaboration with the World Health Organization

( See also Chapter 6.9)

Another field of attention with regard to gaps in medicine development are neglected tropical diseases. The EMA works with the WHO on medicinal products intended for markets outside the EU on quality matters, and international non-proprietary names. Article 58 of Regulation (EC) No 726/2004 allows the EMA's CHMP to give opinions, in cooperation with the WHO, on medicinal products for human use that are intended exclusively for markets outside of EU to prevent or treat diseases of major public health interest. So far, six products have been evaluated by the EMA, mainly antiretroviral medicinal products for the treatment of human-immunodeficiency-virus (HIV-1)-infected patients, acute, uncomplicated malaria infection and diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccines.<sup>123</sup>

Article 58 will in itself not act as a regulatory incentive for the development of medicines for neglected tropical diseases. Non-regulatory initiatives such as Product Development Partnerships have been a critical driver of the considerable increase in drug development for neglected diseases in the EU.<sup>124</sup> In contrast to the EMA, in 2007 FDA did introduce incentives for drug development for neglected diseases by awarding 'Priority Review Vouchers' to any company obtaining marketing approval for a medicine that prevents or treats a neglected disease.<sup>125</sup> These vouchers can subsequently be used to accelerate approval of another medicine for a condition prevalent in wealthier countries that would not have normally qualified for priority review. This financial incentive for a company is considerable, as use of the voucher can take months off the standard FDA evaluation time, leading to earlier marketing authorization. These Priority Review Vouchers were criticized for being inefficient because the incentive is not directly linked with the innovation: the value of the voucher depends on the successful development of a potential 'blockbuster' for the United States market. Such a subsequent drug development initiative obviously is not certain.<sup>126</sup> For example, Novartis received a Priority Review Voucher for its anti-malarial drug Coartem® (an oral combination of artemether and lumefantrine). The company had used its voucher to obtain priority review for Ilaris® (canakinumab), a humanized antibody for gouty arthritis in

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

2009, but FDA recommended against marketing authorization.<sup>127</sup> Besides, apart from the uncertainty regarding future rewards, companies are also not encouraged to actually maximize patients' access to the neglected disease product after marketing authorization. In addition, small companies that are a relevant stakeholder in drug development for neglected diseases may not be able to use their vouchers, although they are allowed to sell the priority vouchers.<sup>128</sup>

Despite the criticism, the initiation of such a regulatory incentive is, in itself, commendable. However, it can be questioned whether a similar regulatory incentive could be introduced in the EU since introducing a similar incentive at EMA, besides FDA, may offer limited additional advantage to large pharmaceutical companies. Moreover, since SMEs play an important role in drug development for neglected diseases, alternative measures could be introduced aiming at small companies. Kesselheim argued that, in contrast to large companies, small companies' initiation of drug development for neglected diseases was driven by commercial reasons.<sup>126</sup> The introduction of fee reductions for protocol assistance, as is the case for orphan medicinal products, may therefore not mean a crucial improvement in the initiatives for neglected disease drug development by large companies, although it may be relevant for small companies.

### 3.1.3 Diseases with unmet medical needs

EMA, but also other regulatory agencies worldwide, have acknowledged the need to stimulate pharmaceutical innovation for medicines for areas of high medical need.<sup>129</sup> The 'conditional approval' pathway is the key incentive in this area. In the EU, medicinal products fall under the scope of 'unmet medical needs' if they are aimed at the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases, as well as medicinal products to be used in emergency situations, in response to public health threats and medicinal products designated as orphan medicinal products. In case of conditional approval, marketing authorization is granted based on a smaller package of clinical data, with follow-up obligations to submit additional clinical efficacy and safety evidence of the product.<sup>130</sup> For some products, such as certain orphan medicinal products for extremely rare diseases, it will usually never be possible to assemble a full dossier. These products may be approved under an 'exceptional approval' scheme, *without* further post-approval obligations.

Since the initiation in 2006, 18 medicinal products have been conditionally approved. Moreover, 26 products for human use were approved under exceptional circumstances, of which the majority were orphan medicinal products or influenza vaccines.<sup>131</sup> Out of all the orphan medicinal products that have been authorized until 2010, 38% of the marketing authorizations were granted 'under exceptional circumstances' and 6% were given 'conditional approval'.<sup>132</sup> Considering the low numbers, it can be questioned how much of an incentive conditional approval actually is. It may be questioned whether conditional approval was proposed by either the EMA or the applicant and for what reasons in order to increase the number of conditional approval requests.

A limited number of scientific studies exist that evaluate the EU conditional marketing authorization. A recent study investigated whether exceptional circumstances or conditional approval pathways for marketing authorization led to more safety issues, measured by the frequency and timing of Direct Healthcare Professional Communications (DHPCs). The

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

study included 289 new medicinal products approved in Europe between 1999 and 2009 and found that conditionally and exceptionally approved drugs were not associated with an increase in the risk of serious safety issues emerging after marketing approval.<sup>133</sup> In addition, conditional rather than exceptional approval was found to be associated with shorter clinical development timelines than other innovative drugs, whereas review time lines were about the same, leading to earlier patient access to new drugs.<sup>134</sup>

These results show that the use of conditional approval pathways can be supported with properly designed studies. One major area in which research is still needed is on post-approval marketing authorization studies after conditional approval.<sup>135</sup> Experience of the FDA accelerated approval procedure demonstrated post-approval commitments take long or are not fulfilled.<sup>136</sup> These studies can result in specific challenges. For example, patients may be less willing to participate in randomized clinical trials when the drug is available in standard care or companies are reluctant to fulfil post-marketing obligations.<sup>137</sup> The recently introduced EU pharmacovigilance legislation aims to strengthen the conduct of post-marketing studies. The effects of this legislation should be closely monitored and evaluated, not only from the perspective of whether it delivers the data that is promised, but also whether the resources that are required for data collection and interpretation warrant the additional knowledge that is gained and whether efficiently used (see Chapter 8.4 on observational studies).

### 3.1.4 Antimicrobials

(See Chapter 6.1)

One particular group of medicines that has been recognized as a high priority area, already in the previous Priority Medicines Report, are the antibiotics for the treatment of infectious diseases.<sup>138</sup> In a 2009 report, the EMA concludes that a particular lack exists of medicinal products under development with new targets or mechanisms of action against multidrug resistant Gram-negative bacteria.<sup>139</sup> Unfavourable market conditions for new antibiotic agents play an important role in the availability of new products.<sup>140</sup> Governments, and regulatory agencies have responded to this high medical need with the launch of various joint initiatives to address the lack of development of antibiotics and the misuse of antimicrobials in human and veterinary medicine, leading to resistance issues.<sup>141</sup> Examples are the governmental work performed within the context of the Trans-Atlantic Task Force on Antimicrobial Resistance (TATFAR), to which the EMA contributes, as well as to activities jointly undertaken by the EMA and other EU agencies such as the European Centre for Disease Prevention and Control (ECDC).<sup>142,143</sup>

On the regulatory side, strategies to improve the pipeline of new antibacterial medicines in the EU have been limited to the provision of guidance documents. In 2012, the EMA released a guideline on how to optimize research and development of pathogen-specific antibacterial drugs, in particular for small numbers of patients.<sup>144</sup> In addition to adhering to the guideline, companies are recommended to consult the addenda to guidelines with further explanations as well as to request scientific advice.<sup>145</sup> No specific regulatory incentives exist to stimulate the development of antibiotics. In contrast, the FDA incorporated incentives to address the long-recognized shortfall in new antibiotics to combat resistant bacteria. The Generating Antibiotic Incentives Now (GAIN) Act Regulation in Prescription Drug User Fee Act (PDUFA) V, which came into effect at the start of October 2012, provides an additional five

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

years of market exclusivity to 'qualified infectious disease products', as well as automatic priority review. In addition, specific guidance will be introduced for pathogen-specific antibacterial drug development as provided by EMA.

European research activities for antibacterial medicines are a newly launched public private partnership (PPP) that is part of the Innovative Medicines Initiative (IMI): the 'Drugs4BadBugs' consortium, which brings together several pharmaceutical and biotechnology companies and academia to focus on targeting resistant bacteria that cause serious infections and boost the pipeline<sup>146</sup>, and ReAct, an independent global network, which plays a role in advocating and supporting concerted action on antibiotic resistance.<sup>147</sup> For more information about this topic consult the background paper to Chapter 6.1.

Thus, from the many projects that have been initiated, it becomes clear that awareness of the need for antimicrobial development is high and that collaboration between academics, companies, *and* regulators is deemed necessary to collect the knowledge, investments and experience to bring new antimicrobials to the market. In the coming years monitoring of whether these activities yield the results required and identifying which incentives are most effective (also including access and reimbursement issues) to help fill the gap in new antimicrobials is warranted.

### 3.1.5 Specific patient groups: paediatrics, elderly and women

In Chapter 7 of the Priority Medicines Report (cross-cutting themes) various groups of particular interest and importance from a pharmacotherapeutic gap perspective are highlighted: children, elderly and women (see Background Papers 7.1, 7.3 and 7.2, respectively). The development of medicinal products for these *specific patient groups* are discussed below from a regulatory perspective.

### 3.1.6 Paediatrics

(See Background Paper 7.1)

Since 2007, the Paediatric Regulation is in force in the EU to improve the health of children by: (i) facilitating the development and availability of medicines for children from birth to less than 18 years, (ii) ensuring that medicines for use in children are of high quality, ethically researched, and authorized appropriately, and (iii) improving the availability of information on the use of medicines for children. In addition, the Paediatric Regulation should prevent children from participating in unnecessary trials, or prevent delaying the authorization of medicinal products for use in adults.<sup>148</sup>

To help realize this, the European Network of Paediatric Research at the EMA (ENPREMA) has been established in 2010, coordinated by the WHO. This network aims to provide expertise and access to infrastructure for companies to conduct studies in children, define consistent and transparent quality standards, harmonize clinical trial procedures, and define strategies for resolving major challenges.<sup>149</sup>

The Paediatric Committee (PDCO) at the EMA is primarily responsible for the assessment and agreement of Paediatric Investigational Plans (PIPs) and waivers. The PIP describes the studies and measures proposed to generate the data for paediatric use of medicine. In

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

principle, a PIP is mandatory for new applications. However, in some cases, studies can be deferred until after studies in adults have been conducted, this to ensure that studies in children are only done when it is safe and ethical. Nevertheless, in case of deferrals, the PIP will still include details of the paediatric studies and their timelines. For those diseases that do not affect children, a PIP is not required and it will be waived.<sup>150</sup>

At the time of a marketing authorization application, compliance with the PIP will be checked and is needed for a company to receive specific rewards. Once authorization is obtained in all Member States and study results are included in the product information, the medicine is eligible for six months of supplementary protection certificate (SPC) extension. Medicines developed specifically for paediatric use not covered by an SPC or eligible for an SPC, can benefit from a 'paediatric use marketing authorization', with a 10-year period of data/market protection.<sup>151</sup> For orphan-designated medicinal products, the 10-year period of market exclusivity will be extended to 12 years.<sup>152</sup>

From 2007-2010, the PDCO has agreed on more than 400 PIPs, granted 176 product-specific waivers, and adopted several class waivers. Deferrals have been granted for 91% of new products, and for 64% of the already authorised products, which means that the paediatric development may be completed after the adult development.<sup>153</sup> By the end of 2011, 29 PIPs were completed in compliance with the PDCO decisions. The plans resulted in 24 new paediatric indications and seven new pharmaceutical forms appropriate for children. Data from five completed PIPs provided important information which did not support the use in children and which has been included in the product information of these medicines. Between 2008 and 2012, 10 out of 113 new active substances were centrally authorised and received a paediatric indication. The EMA granted the first paediatric use marketing authorization to Buccolam® (midazolam, oromucosal solution) which was specifically licensed for infants, toddlers, children and adolescents to treat severe convulsions and epileptic seizures.<sup>154</sup>

According to the EMA, the paediatric regulation has stimulated high-quality research and has produced valuable clinical trial data for the industry, has resulted in an increase in the number of applications to develop paediatric treatments, new paediatric formulations and important labelling changes, including paediatric dosing recommendations.<sup>155,156</sup> However, the fact that only one paediatric use marketing authorization has been requested and granted means that the paediatric regulation may not be an effective incentive. Although it takes time to conduct studies with off-patent medicines in children, the period of five years that has passed since the introduction should be sufficient and one would have expected a higher number of PUMA requests. Limitations to license off-patent medicines for paediatric indications, may be because of financial prospects: it was suggested that the target population for a PUMA is too small, that national reimbursement rules may not offer rewards to cover research costs for off patent medicines and that investment sources for paediatric research among generic companies may be lacking.<sup>157</sup>

Regarding the paediatric regulation in general, critics emphasize the system fails to stimulate research in areas of unmet medical need, and instead has resulted in companies adding paediatric information to medicines developed for adults in lower priority areas.<sup>158</sup> Additionally, a survey of companies of the European Federation of Pharmaceutical Industries and Associations (EFPIA) indicated that the paediatric regulations are overly bureaucratic and have led to delays in marketing authorization. The survey indicated that

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

paediatric development and trials are more expensive per subject than adult development. In addition, according to some, the system failed to focus global research on areas of high medical need, but rather focuses resources on adding paediatric information to medicines licensed for adults in low priority areas.<sup>159</sup>

Apparently, a discrepancy exists between the evaluation of the Paediatric regulation by regulators, companies and other stakeholders (e.g. medical researchers). Considering the lack of interest for the paediatric use marketing authorization incentive, other forms of incentives to generate paediatric data in off-patent medicines may need to be considered. It may prove more sustainable to create incentives to also collect and analyse the existing knowledge on off-label use of medicines using real life data (see Chapter 8.4) in children, and disseminate the information among health practitioners.<sup>157</sup> For future research different types of incentives are of particular interest.

### 3.1.7 Elderly

(See Chapter 5 and Background Paper 7.3)

Medicinal products for the elderly are an important topic on the agenda of policymakers. In Europe, the median age is high compared to other regions, and the elderly population will grow rapidly in the next decades.<sup>160</sup> Off-label use of medicines occurs frequently in elderly patients, for example the use of antipsychotics in nursing homes.<sup>161</sup> Additionally, co-morbidity and polypharmacy are a major topic in this population. To take the needs of elderly patients into account, the EMA introduced the 'EMA geriatric medicines strategy' in 2011 to ensure that the needs of the elderly are considered in the development and evaluation of new medicines and in the post-authorization follow-up of already approved medicines. Additionally, it is suggested to improve the availability of information on the responsible use of medicines for the elderly to support better informed prescribing.<sup>162</sup>

To achieve both objectives the EMA wants to ensure that medicinal products are developed in accordance with current guidelines, particularly guideline E7 of the International Conference on Harmonisation. The EMA has identified gaps in regulatory and scientific knowledge and wants to address these by drafting guidelines and the provision of scientific advice. In addition, an experts' pool has been established to make full use of the experts available within the EMA.<sup>162</sup> Currently, the conduct of clinical trials in the elderly is not an obligation and no specific incentives exist for this. Whether the EMA strategy focus on specific scientific and regulatory guidance will be sufficient for development of geriatric medicines in elderly should be evaluated.

### 3.1.8 Women

(See Chapter and Background Paper 7.2)

There may be a need to explicitly include women in clinical studies as, for example, metabolism rates may differ and some drugs have adverse effects that women are known to be more susceptible to than men, including cardiac effects like QT interval prolongation.<sup>163</sup>

The inclusion of women in studies is addressed in guidelines for clinical trials in variable ways. On the one hand, the International Conference on Harmonisation of (ICH) guidelines

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

only briefly mentions women in more general clinical trial guidelines. On the other hand, both the USA and Canada have for many years had well-respected policies and guidelines on inclusion of women in clinical trials.<sup>164,165,166</sup>

To explore the need for introducing specific guidelines for the inclusion of women in clinical trials, the EMA has undertaken a review of pivotal marketing application trials for evidence of gender bias. The review involved marketing applications filed between 2000 and 2003, involving 84 products and 240 pivotal clinical trials, to assess whether the percentage of females in trial populations is comparable to the target population. In addition, ten randomly selected products were examined to assess whether the sponsor performed subgroup analyses by sex. The review demonstrated that in general women were adequately represented in pivotal trial populations, well reflecting the gender prevalence of the disease or condition in the target population. In assessing deviations, the difficulty in determining accurate estimates of disease prevalence in target populations and the variation in relative disease prevalence in the sexes with age should be considered; for example, the delayed onset of heart disease in women as compared to men. While women appear to be participating in all phases of study development, participation is lower in early (phase 1 to 1/2) studies.<sup>167</sup>

According to the review, ICH guidelines do address gender, in particular guidelines M4E and E3, which require adequate demographic (including gender) characterization, analysis and assessment of the patient population. Guidelines express the need to explore possible demographic (including gender) differences in dose-response (E4, M4E) and define certain safety precautions (E8, M3). The results of reviews and experience argue against the need for a separate ICH guidelines on women as a specific population in clinical trials.<sup>167</sup>

### 3.2 Specific products: advanced therapy medicinal products

#### 3.2.1 The ATMP regulation: scope and objectives

The regulatory system stimulates pharmaceutical product innovation by means of advanced therapy medicinal products. The EU regulation on advanced therapy medicinal products (ATMPs) ("Regulation (EC) No 1394/2007") was adopted in 2007 and came into force on 30 December 2008. The regulation defines an ATMP as a product intended for gene therapy; a product intended for (somatic) cell therapy or tissue engineered products (TEPs).<sup>168</sup> Before the regulation came into force, gene therapy and cell therapy products were considered as medicinal products. However, TEPs, were not covered by EU legislation. TEPs were excluded from the scope of the medical devices legislation and did not fall within the scope of medicinal products legislation leaving them unregulated. To fill this legal gap, new legislation was designed. Originally a specific regulation on TEPs was proposed, but the proposal was withdrawn and TEPs were included in the ATMP Regulation.

The ATMP Regulation was designed to ensure the free movement of advanced therapy medicines within the EU, to facilitate their access to the EU market, and to foster the competitiveness of European pharmaceutical companies in the field, while guaranteeing the highest level of health protection for patients. The regulation aims to (i) authorise existing ATMPs and to (ii) boost the development and of new ATMPs. Therefore, ATMP legislation describes how these medicinal products are authorized, supervised and monitored to ensure that they are safe and effective and provides incentives to encourage research and

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

development in the area of advanced therapies. The incentives consist of a (partial) waiver of authorization fees and fees for scientific advice and protocol assistance, support by the SME office, introduction of certification of parts of the authorization dossier, etcetera (see Table 8.2.1). A relatively new procedure is the certification of ATMPs developed by SMEs that provides an evaluation of the submitted quality and (when available) non-clinical studies performed by the applicant SME during their ATMPs development.<sup>169</sup>

At the EMA, a new scientific committee, the Committee for Advanced Therapies (CAT) was established, which recommends on the classification of advanced therapy medicines and contributes towards giving scientific advice. Moreover, the CAT conducts the scientific assessment of advanced-therapy medicines and prepares a draft opinion on the quality, safety and efficacy of an advanced-therapy medicine for the CHMP.

Until December 2010, 39 ATMP classifications have been awarded and the final conclusions have been published on the EMA website. In 2011, twelve requests for scientific recommendations on advanced-therapy classification were submitted and an equal number of scientific recommendations were adopted. However, this number of new requests for classification may be lower than expected at the start of the implementation of the ATMP Regulation, as most ATMPs are put under the national 'hospital exemption' scheme. One certification has been finalised on the quality package of an ATMP.<sup>169</sup>

Additionally, the expectations of the Regulation to authorise existing ATMPs and to boost the development of new ATMPs are not reflected in the results so far. Since 30 December 2008, only eight applications for a marketing authorization for an ATMP have been submitted to the EMA. In these applications no ATMP that was already on the market was present. At this moment only two ATMPs have been authorised: one cell therapy product (ChondroCelect®)<sup>170</sup> and one product for gene therapy (Glybera®).<sup>171</sup>

The question is why the expectations were not met. The development of TEPs, cell therapy and gene therapy often takes place in an academic environment, usually as spinoffs of fundamental research done in university hospitals. For these types of organizations, the clinical development process as required for medicinal products regulated by the EMA may be too ambitious. Even with the support offered to the possible applicants for an ATMP marketing authorization, the level of regulatory experience and the necessary means to complete such a process are unavailable.

In terms of future studies, these could find out why existing products do not follow the ATMP- marketing authorization procedure. New ATMPs that received a certification could be followed to identify bottlenecks in bringing those innovative products to the market.

It is fair to conclude that the Regulation has not been able to promote innovation in light of the number of available authorised ATMPs. However, the regulation has provided clarity on which regulatory pathway has to be followed and 'gaps' in EU legislation have been patched.

### **Research Priorities for Regulations for specific disease areas, patients or products**

To optimize the regulatory system in stimulating pharmaceutical innovation, research should focus on:

- Re-evaluating the components of regulation to support development of orphan medicinal products, in particular incentives for fundamental research on the pathophysiology and drug candidates for those rare diseases for which no development initiatives have been undertaken.
- Exploring new opportunities for regulatory incentives for drug development for neglected diseases, e.g. fee reductions for scientific advice for SMEs.
- Further evaluating the conditional approval procedure: To what extent is conditional approval an incentive for pharmaceutical industry? And closely monitoring the follow-up of conditionally approved products and evaluating whether post-approval commitments are fulfilled and how frequent the benefit-risk balance remains positive.
- Identifying whether/which regulatory tools are most effective to fill the gap in new antimicrobials development.
- Studying forms of incentive to generate paediatric data in off-patent medicines in the right indications.
- Exploring the need for regulatory requirements or incentives for the conduct of clinical studies in elderly
- Studying why the ATMP-marketing authorisation procedure is not followed for existing products and identifying bottlenecks in bringing new and certified ATMPs to the market.

## **4. Developments in the context of the regulatory system**

Not only the regulatory system has changed since the last Priority Medicines Report, the world around this system probably has changed even more. In this section we describe four topics in more detail that we believe are of special interest for a future research agenda aimed at pharmaceutical innovation and for developments in the regulatory system. First, HTA bodies have been through important changes, and streamlining the interaction between marketing authorization and HTA is on many agendas. Second, regulation of medicines has also seen important developments in the area of the 'globalization' of regulation. Third, increasing interest in products that can be viewed as a combination of a medicines and a medical device has fuelled the discussion about the extent to which the regulation of medical devices may be aligned with medicines. Fourth, the past decade has also seen a changing perspective on the role of the patient. Also through experiences with medicines such as natalizumab (Tysabri®) and bevacuzimab (Avastin®), the patient is seen more and more as a relevant actor in the decision-making process about the marketing authorization of medicines.

### **4.1 Collaboration with Health Technology Assessment bodies**

For companies a marketing authorization is but the first step in bringing a new medicine to patients. Especially in the European setting, marketing authorization is followed by a set of

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

reimbursement decisions at the national level. In these reimbursement decisions, several aspects are considered: whether the medicine should be considered as eligible for reimbursement and how much of the price the public payer should cover. These reimbursement decisions are of prime importance to companies, as they are critical for the commercial fate of a new product. For more information about relevant developments in the pricing and reimbursement arena, we refer to the Background Paper Chapter 8.2.

Health Technology Assessment (HTA) is commonly used to inform reimbursement decisions. HTA is a multidisciplinary process in which medical, social, economic, and ethical issues related to the use of a health technology are assessed in a systematic, transparent, unbiased, and robust manner.<sup>172,173</sup> HTA focuses on the incremental value of new medical technologies such as medicines, and tries to assess this in the context of a real world setting.

At the moment of marketing authorization, a medicine is accompanied by an extensive data package that provides information about the safety and efficacy of the medicine in a clinical trial setting. This data package is shaped by the requirements of regulatory bodies such as the EMA and FDA.

Within the evidentiary needs of HTA bodies the Relative Effectiveness (RE) of a new medicine is of special importance and constitutes an important input for potential cost-effectiveness assessments. Relative Effectiveness has been defined by the High Level Pharmaceutical Forum as *“the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice”*.<sup>174</sup>

The ‘real world’ setting of medicines use cannot be compared to the clinical trial setting. This means that making an assessment of how effective a new medicine truly is compared to other health care interventions, or doing nothing, can be hard to tell if only based on the data that is used for regulatory approval. This is described as the ‘efficacy’ – ‘effectiveness’ gap and remains one of the key challenges in medicine development, regulation and use<sup>175</sup>. This means that the evidence generated based on these regulatory requirements is often not ideally suited to meet the needs of Health Technology Assessment (HTA) bodies who start from the evidence available at registration but have to make an assessment about the medical, social, ethical, and economic implications of a new therapy.

At the moment, several initiatives are on-going between the EMA and the HTA bodies collaborating in EUnetHTA Joint Action. The topics for collaboration between the EMA and EUnetHTA include:

- Scientific advice: the EMA and EUnetHTA have begun to explore how scientific advice could be harmonized with advice given by HTA bodies, and to establish the evidence that both groups need (see Section 5).<sup>176, 177</sup>
- European Public Assessment Report (EPAR): a joint activity to discuss how the EPAR can provide the best contribution to the assessment of relative effectiveness by HTA bodies in Member States.<sup>178</sup>

Alignment of requests for evidence by marketing authorization agencies and health technology assessment bodies is a major topic in strategy documents from various regulatory authorities. Without some form of alignment, HTA bodies may decide that proper information is lacking for granting reimbursement of new medicines. For example, it could lead to the situation that medicines would be granted early access to the market for a specific

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

patient population but without the necessary reimbursement and user access.<sup>179</sup> Moreover, alignment of the requests to conduct post-marketing studies could contribute significantly to a well-functioning regulatory system.<sup>180</sup>

For research agendas, investing in tools to better assess RE during drug development, at the marketing authorization stage and afterwards is of key importance. In general, two routes can be identified for generating evidence on RE in a 'real world' setting: observational studies and (pragmatic) controlled trials. When the aim is to generate evidence on the RE of new therapies, observational research can pose limitations for valid interpretation (e.g. due to unquantifiable or unrecorded confounders). Pragmatic trials aim to evaluate long-term effects in real world populations of interventions that are directly relevant to clinical care. The design of better pre-launch (pragmatic) trials can therefore provide decision makers with more confidence about the RE of a new medicine based on existing data. Issues of pragmatic trials are non-adherence among patients, loss to follow-up and the need for large sample sizes. Generalizability and validity of pragmatic study results need to be balanced carefully. Furthermore, the implementation and integration of different state-of-the-art mathematical, epidemiological, statistical analytic and decision-making techniques to employ comparative effectiveness can also positively impact current regulatory, therapeutic and reimbursement strategies.

### 4.2 Globalization of regulatory requirements and decision-making

The majority of new medicines are approved in at least two of the three leading regulatory authorities the FDA, the Japanese Pharmaceutical and Medical Devices Agency (PMDA) and EMA.<sup>181</sup> Thus, they increasingly have to meet requirements of multiple regulatory authorities. To restrict the costs of R&D and to minimize the delay in making safe and efficacious innovative treatments available to patients, harmonization of regulatory requirements is valuable. Regulatory agencies and pharmaceutical companies worldwide have responded to the need for harmonization of regulatory guidelines about twenty years ago, by establishing the International Conference of Harmonization (ICH). The ICH has yielded harmonized guidelines on quality, safety, efficacy and multi-disciplinary issues<sup>182</sup>. For the future, it is of utmost importance for the European pharmaceutical industry to have the ICH reach beyond the original triad and into the emerging markets<sup>183</sup>. An example of regulatory harmonization of emerging markets with those of advanced countries is the East Asia Harmonization which includes China, Korea and Japan.<sup>184</sup>

EMA now has bilateral confidentiality arrangements with the U.S. FDA, Health Canada, the Japanese Pharmaceutical and Medical Devices Agency (PMDA)/Ministry of Health Labour, the Welfare and the Australian Therapeutic Goods Administration and Swissmedic. Interactions with these regulatory authorities continue to intensify, with increasing exchanges of information on product-related activities, but also the development of new cluster activities, in particular with the FDA.<sup>185</sup> An example of such an activity with FDA is the opportunity for parallel scientific advice to applicants on request. However, although scientific information is exchanged between the two agencies, the advice towards the pharmaceutical company is not harmonized, an independent advice is given to the applicant by both agencies.<sup>186</sup> Furthermore, despite harmonized guidelines and parallel scientific advice differences in marketing approval decisions occur based on the same application dossier, as was demonstrated in an analysis of FDA and EMA approval decisions on anticancer drugs.<sup>187</sup> For the many applicants that aim to market their medicine worldwide,

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

this may seem unneeded delay of the licensing of their product. It would be worth further studying to what extent differences in marketing authorizations occur and what would be the practical implications of these differences.

### 4.3 Patient involvement in regulatory decision-making

Regulatory agencies, including EMA, have recognized the need to involve patients in the scientific dialogue around marketing approval of medicines, and have introduced varying instruments to respond to this need.<sup>188,189</sup> The EMA established the Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP), which consists of a large network of patient organisations that represent and provide recommendations on patients' interests.<sup>190</sup> The PCWP also coordinates patient participation in scientific advisory group meetings, committees and conferences and workshops of EMA. Patient representatives are involved in scientific discussions by taking part in scientific committees such as the Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO) and the Committee for Advanced Therapies (CAT).<sup>191</sup> The U.S. FDA also organizes public hearings to involve patients' perspectives on marketing approval of medicines.<sup>192</sup> The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA has recently started with public hearings on urgent safety concerns. Experiences with these public hearings should be evaluated and may lead to more broadly applied public hearings by the EMA in the future.<sup>193</sup> Patient involvement will in particular be relevant in adaptive approaches to help define acceptable levels of risk and uncertainty. The exact role of patients and their contributions to the scientific discussion around marketing approval is still something that needs to be assessed in more detail (for a broader discussion of the topic of patient involvement we wish to refer readers to Background Paper Chapter 8.5).

### 4.4 Integration with devices and diagnostics

Some pharmaceutical innovations combine a medicine and a device, drug-eluting coronary stents are a well-known example of this. In order to effectively allow such products to the market regulatory harmonized requirements for medicinal products and devices are needed and introduced. In the EU, device approval is overseen by a governmental body called a Competent Authority. These Competent Authorities are designated by the Member States. In some EU countries these Competent Authorities could also be the drug regulatory agency, such as the Medicines and Healthcare Products Regulatory Agency in the United Kingdom.<sup>194</sup> In addition, Notified Bodies are appointed that are responsible for pre-market evaluation of medical devices and monitor all aspects of the evaluation from manufacturing process to post-market surveillance.

According to the European regulation, medical devices are categorized into four classes (I, IIa, IIb and III) on the basis of increasing risks associated with their intended use (e.g. class I devices are wheelchairs and adhesive bandages, class III are implantable prosthetic joints, drug-eluting stents and artificial heart valves).<sup>195</sup> The Medical Devices Directive and its corresponding Guidelines state that in the case of (active) implantable devices and devices of class III, evidence of the clinical performance and safety of a medical device is provided by means of clinical data. Clinical data submitted can come from clinical trials, from scientific publications or through a documented clinical evaluation of an equivalent medical device. Once a device is reviewed and deemed acceptable, it receives the CE marking.<sup>195</sup>

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

In case that a medical device contains a drug substance, both the device regulation and the drug regulation apply. According to the medical device legislation, the Notified Body has to consult one of the competent bodies of the Member States or the EMA with regards to the quality, safety and usefulness of the medicinal substance incorporated as integral part of the device.

An example of a combination of medical substance and a medical device is, as already mentioned, the drug-eluting (medicinal substance-eluting) coronary stent (DES). The EMA has made a specific guideline to assist applicants and Notified Bodies in the consultation procedure to the competent bodies of the Member States or the EMA regarding the assessment of usefulness and safety applied to a medicinal substance. The level of clinical evidence required depends on whether the active substance of the combination is known to the Competent Authority as a medicinal product or in the setting of a DES.<sup>196</sup>

It has been said that specific requirements for premarketing clinical studies of devices are sometimes unclear, and details of trials are typically not made available to the public. Although clinical data are required for high-risk devices, guidelines for the nature of these studies are not binding on manufacturers or Notified Bodies.<sup>197</sup> Opportunities are explored to consolidate and streamline consultation and interactions with notified bodies for medical devices for the evaluation of combined ATMPs. Procedural advice on the evaluation of combined products and the consultation of Notified Bodies was adopted and published in February 2011. The procedure provides details of possible scenarios and timelines for interaction between the CAT and Notified Bodies in order to establish timely and effective interactions for companies developing an ATMP combined with a medical device. Such interaction should enable the CAT to perform an adequate benefit-risk assessment and to adopt a draft opinion for the combined ATMP.<sup>198</sup> Evaluation of this procedure should indicate whether such a procedure is sufficient to harmonize both regulations.

### **Research priorities in the context of the regulatory system**

To improve efficiency of bringing innovative medicines to patients by further collaboration with external parties, research should focus on:

- Making better predictions about relative effectiveness during drug development, at marketing authorization and afterwards.
- Further studying to what extent differences in marketing approval decisions occur between leading regulatory authorities and what would be the practical implications of these differences.
- Exploring the role of patients and their contributions to the discussion of efficacy and safety evidence needed for marketing authorisation
- Evaluating regulatory procedures for combined devices and medicinal products should indicate whether these are sufficiently harmonized to facilitate such product innovations.

### 5. Conclusions and research priorities

The 2013 'Priority Medicines for Europe and the World' Update has been initiated to determine the priority needs for pharmaceutical innovation and to formulate a research agenda towards 2020. In this chapter we have discussed developments in the marketing authorization system in relation to pharmaceutical innovation and addressing priority health care needs at four levels: (1) the overall system of marketing authorization; (2) key components of the system; (3) specific regulations within the system; and (4) broader developments surrounding the system. At each of these levels we have identified research priorities, which are highlighted at the end of each corresponding section. However, in addition to these individual research priorities, we believe that there are four key messages for the methodology of future research agendas:

#### **1. Continue to develop and pilot new methods for evidence generation and benefit-risk assessment**

In the last few years the regulatory system has been subject to various proposals for renewal. To actually decide about supplementing elements of the regulatory system in practice, such as introducing changes regarding evidence requirements or allowing innovative methods such as new biomarkers and study designs, proposals should be substantiated by multiple, thorough and robust studies.

Additional research is needed on promising instruments (such as the use of surrogate outcome measures and adaptive study designs) to optimize regulatory requirements for initial marketing approval. In addition, the increased use of post-marketing observational studies for effectiveness and safety should be explored. In line with the adaptive licensing proposals, effectiveness studies would also be needed to make better assessments for the (future) real-world effectiveness of medicines under development based on trial efficacy. Improving this kind of learning could help to achieve an adequate level of (safety and efficacy) knowledge while requiring less data to be collected before the medicines are approved.

For example, the various collaborative initiatives proposed in order to develop structured benefit-risk assessments, based on qualitative and quantitative instruments, could help to increase the consistency and transparency of benefit-risk assessments and thereby the predictability of the marketing authorization procedure. However, introducing quantitative instruments for benefit-risk assessment requires substantial changes in a regulator's way of decision-making and in the way companies' prepare submission documents. At present, little evidence exists on how quantitative instruments affect the quality of regulatory decision-making or public health. Additional field studies should identify practical limitations and test optimal ways of data visualization. In addition, field studies of quantitative benefit-risk instruments could gain insight into uncertainties in benefit-risk assessments and demonstrate how robust decisions are in relation to different perspectives about clinical relevance (e.g. by patients or prescribers) and how (new) real-world data would affect the balance. Recently, pilot studies have been initiated and collaborations have been established to further implement current concepts.

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

### **2. Clearly identify expectations and key performance indicators for new regulations and set up prospective studies**

Measuring the success of regulatory policies is often difficult. In order to evaluate and improve existing regulations and to base new incentives on best practices, expectations should be made explicit and performance indicators should be defined and reported on.

European Union regulatory incentives for pharmaceutical innovation for specific disease areas, specific populations and specific products have demonstrated that introducing regulation does not always take into account all factors involved in successfully bringing a medicine to the market. In case of orphan regulation, the market exclusivity incentive has, without doubt yielded an enormous increase in the number of potential drug candidates for rare diseases. However, some instruments, such as free protocol assistance, may not be a key driver for generating more innovative medicines. Other incentives, such as the significant investments by governments in research into rare diseases, may play a far more important role. The paediatric regulation could be looked at in a similar manner. Future research could establish which incentives provide added value from a societal perspective and help to achieve public health goals. The research climate for rare diseases apparently needs additional or different incentives to increase the number of successful marketing authorization applications.

The regulation of conditional approval offers an opportunity to bring medicines to the market for life threatening diseases for which no alternatives exist. However, the numbers of applications for conditional marketing authorization procedures are limited. In addition, the follow-up of post-marketing commitments seems problematic in some cases. The 2012 EU pharmacovigilance legislation will enforce post-marketing obligations and complement the conditional approval regulation. For the newly established pharmacovigilance guideline EMA regulators explicitly defined measures of impact such as change of behaviour in prescribing, dispensing and consumption and outcomes such as mortality, morbidity and quality of life<sup>199</sup>. For this purpose, the effective use of Electronic Health Record (EHR) databases and real-life data is of critical importance (see also Chapter 8.4). Formulating expectations by qualitative and quantitative performance indicators, and monitoring them through carefully designed studies, could enforce timely adjustments in regulations and provide evidence for new policies.

### **3. Set up constructive collaborations and dialogues with key actors**

Many actors are involved in the marketing authorization of medicines. Collaboration and dialogue between all these parties is essential for an effective regulatory process and should be supported at multiple levels. Creating such dialogues and collaborations is not easy. Often, it is not part of the tradition of the parties involved. As a result, different actors speak different languages.

First, both regulators and pharmaceutical companies could be stimulated to have a dialogue in a very early stage of drug development (e.g. in the preclinical phase or during Phase I), especially for those products using innovative approaches for development. Ways to optimally structure these interactions should be studied. For example, scientific advice could improve the success rate of the marketing authorization procedure, provided that it is given early and frequently to discuss the relevance of evidence before studies are initiated. New

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

formats for scientific advice, and the interaction between applicants and regulators in practice should be studied in order to focus scientific advice on what evidence is actually needed and feasible.

Second, involving Health Technology Assessment and Pricing and Reimbursement bodies in such a scientific dialogue is important in order to harmonize requirements and post-marketing obligations. Close collaboration with HTA bodies could create faster patient access to innovative medicines. The EMA and EUnetHTA have begun to explore how scientific advice could be harmonized with advice given by HTA bodies, and to establish what evidence both groups need.<sup>200,201</sup> These activities should be continued and could be fuelled by input from regulatory science (e.g. new tools for benefit-risk assessment).

Third, involving patients and prescribers could help to better adjust benefit-risk assessments to their preferences and risk perceptions. Although networks of patients have been established e.g. in the EMA Patients and Consumers Working Party, there is need to determine how patients can most effectively contribute to decision making. At present, little is known about how to best involve patients in decision making nor at what stage they can contribute effectively (see Chapter 8.5).

### 4. Invest in sharing and analysis of regulatory documents

In order to support evidence/based improvements of the regulatory system and to test and explore new methods for drug development and regulatory decision making, close collaboration is needed between regulatory agencies and academia, as well as input from companies. For the purpose of regulatory science, regulatory databases should also be examined to learn from previous marketing authorization procedures and to evaluate tools and regulations as discussed in this paper. Regulatory review documents could be examined to learn from previous marketing authorization procedures and to evaluate tools and regulations as discussed in this paper. The EMA publishes the European Assessment Reports of both approved *and* withdrawn or non-approved products on its website. Although this offers the opportunity to evaluate previous marketing authorization procedures to some extent, certain informative documents that could add to the learning process, such as the objections made during the marketing authorization procedure also offer insight in regulator's priorities and perspectives. These should become available for the purpose of regulatory science. More detailed data on outcome measures and confidence intervals are also needed in order to validate quantitative benefit-risk instruments. A positive development in this respect is the 'Ask EMA' project which was introduced in 2010 and answers requests for publication of regulatory documents, resulting in a release of over 1 000 000 pages in 2011.<sup>202</sup> The project will consider more proactive publication of documents in the next phase.

Furthermore, the EMA has committed to publish clinical-trial data and enable access to full data sets by interested parties to enable the independent re-analysis of the evidence generated for marketing authorization. As a first step, in 2011 the EMA launched the clinical trial register, which has been welcomed by patient and consumer organisations as an important step in increasing transparency about medical research.<sup>203</sup> However, a number of practical and policy issues need to be addressed before complex data sets can be made public. The EMA does not consider clinical trial data to be commercially confidential, but is concerned that the publication of raw datasets may lead to breaches of patient

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

confidentiality. Besides, re-analysis by third parties may not be free of conflicts of interest nor lead to high quality analyses, e.g. information may be distorted by competitors through the use of biased selection criteria for data or inappropriate statistical analysis methods. To address these issues, several policies need to be developed such as standards for the protection of patient confidentiality, standards for good analysis practice and rules of engagement for sharing raw data from clinical trials to ensure scientific valid analyses of data across clinical trials.<sup>203</sup>

Another important area of research is the comparison between different medicines for a therapeutic indication (relative effectiveness). Therefore, recent IMI initiatives in this area should be supported and expanded, as they bring together academia, regulators, and industry to develop new models for defining drug development strategies and regulatory frameworks. Projects such as these can help to reconcile data requirements needs from authorities with efficient drug development programs.

In conclusion, the many changes introduced since 2004 demonstrate that regulators in Europe and elsewhere understand their responsibilities with regard to supporting pharmaceutical innovation and addressing priority health care needs. This progress has created challenges and controversies, but regulators have shown a clear role in stimulating innovation. Regulators have a range of tools at their disposal that can help increase the efficiency of drug development and stimulate the development of needed medicines. However, which of these tools are most effective and at what cost to society is not always evident. The research priorities described in this paper hopefully contribute to setting an agenda for the study of regulatory tools and practices that can help find better ways to address public health needs and to assure that patients have access to safe and effective medicines. Regulations play a critical role in balancing people's expectations for new medicines to address unmet medical needs against the need to ensure that medicines are efficacious and have a positive benefit-risk ratio. For regulators and companies to adapt to a changing world, research on the regulatory process is needed.

Regulatory science has not been a research priority, but many forms of drug innovation need to be supported by research in regulatory science in order to be able to move forward in the most effective way.

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

### Reference

- <sup>1</sup> Eichler HG, Oye K, Baird LG, Abadie E, Brown J, Drum CL, et al. Adaptive licensing: taking the next step in the evolution of drug approval. *Clin Pharmacol Ther* 2012;91:426-37.
- <sup>2</sup> Centre for Innovation in Regulatory Science (CIRS). New drug approvals in ICH countries: 2002-2011. Available from: <http://cirsci.org/white-papers> (Accessed 25 February 2013).
- <sup>3</sup> European Federation of Pharmaceutical Industries and Associations (EFPIA). The Pharmaceutical Industry in Figures. Key data 2012. Available from: <http://www.efpia.eu/sites/www.efpia.eu/files/EFPIA%20Figures%202012%20Final.pdf> (Accessed 25 February 2013).
- <sup>4</sup> Light D, Lexchin J. Pharmaceutical research and development: what do we get for all that money? *BMJ* 2012;344:e4348.
- <sup>5</sup> Kaitin KI, DiMasi JA. Pharmaceutical Innovation in the 21st Century: New Drug Approvals in the First Decade, 2000–2009. *Clin Pharmacol Ther* 2011;89(2):183-188.
- <sup>6</sup> Eichler HG, Oye K, Baird LG, Abadie E, Brown J, Drum CL, et al. Adaptive licensing: taking the next step in the evolution of drug approval. *Clin Pharmacol Ther* 2012;91:426-437.
- <sup>7</sup> Executive Office of the President, President's Council of Advisors on Science and Technology. Report to the President on propelling innovation in drug discovery, development and evaluation. Available from: <http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf> (Accessed 25 February 2012).
- <sup>8</sup> Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council. *Official Journal of the European Union*.
- <sup>9</sup> European Medicines Agency (2005). Guideline on Procedures for the granting of a marketing authorisation under exceptional circumstances, pursuant to Article 14 (8) of Regulation (EC) NO 726/2004. *EMEA/357981/2005*.
- <sup>10</sup> Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines. *Official Journal of the European Union*.
- <sup>11</sup> US Food and Drug Administration Website. Fast Track, Accelerated Approval and Priority Review. Available from: <http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm> (Accessed 25 February 2013).
- <sup>12</sup> US Food and Drug Administration. Special Medical Use. Available from: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/UCM343671.pdf> (Accessed 2 April 2013).
- <sup>13</sup> Eichler HG, Oye K, Baird LG, Abadie E, Brown J, Drum CL, et al. Adaptive licensing: taking the next step in the evolution of drug approval. *Clin Pharmacol Ther* 2012;91:426-437.
- <sup>14</sup> Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. *Nat Rev Drug Discov* 2008;7:818-26.
- <sup>15</sup> Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

- 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines.
- <sup>16</sup> New Drug Development Paradigms (NEWDIGS) Available at: <http://cbi.mit.edu/research-overview/newdigs/> (Last accessed 21 March 2013).
- <sup>17</sup> New Drug Development Paradigms (NEWDIGS) Available at: <http://cbi.mit.edu/research-overview/newdigs/> (Last accessed 21 March 2013).
- <sup>18</sup> Centre for the Advancement of Sustainable Medical Innovation Available at: <http://casmi.org.uk/> (Last accessed 21 March 2013).
- <sup>19</sup> Escher Project. Available at: <http://www.escher-project.org> (Last accessed 21 March 2013).
- <sup>20</sup> European Medicines Agency (2010). Road map to 2015 – the European Medicines Agency’s contribution to science, medicines and health. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/01/WC500101373.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101373.pdf) (Accessed 25 February 2013).
- <sup>21</sup> US Food and Drug Administration. Initiatives by CDER. Available from: <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/WhatWeDo/Initiatives/default.htm> (Accessed 25 February 2013).
- <sup>22</sup> Dutch Medicines Evaluation Board, CBG-MEB (2008). Strategic Business Plan 2009-2013. Broadening the scope of regulation: beyond gatekeeping. Available from: [http://www.cbg-meb.nl/NR/rdonlyres/6772072F-890D-4E07-BE43-D57809696D0F/0/CBG\\_Business\\_Plan\\_0913.pdf](http://www.cbg-meb.nl/NR/rdonlyres/6772072F-890D-4E07-BE43-D57809696D0F/0/CBG_Business_Plan_0913.pdf) (Accessed 25 February 2013).
- <sup>23</sup> Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. *Nat Rev Drug Discov* 2008;7:818-26.
- <sup>24</sup> Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat Rev Drug Discov* 2012;11:191-200.
- <sup>25</sup> Miller W, Robinson LA, Lawrence RS. Valuing health for regulatory cost-effectiveness analysis. National Academies Press, Washington DC, USA 2006.
- <sup>26</sup> Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, et al. How to improve R&D productivity: the pharmaceutical industry’s grand challenge. *Nat Rev Drug Discov* 2010;9:203-214.
- <sup>27</sup> Morgan P, Van Der Graaf PH, Arrowsmith J, Feltner DE, Drummond KS, Wegner CD, Street SD. Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival. *Drug Discov Today* 2012;17:419-24.
- <sup>28</sup> Hutchinson L, Kirk R. High drug attrition rates-where are we going wrong? *Nat Rev Clin Oncol* 2011;30:8:189-90.
- <sup>29</sup> Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? *Nat Rev Drug Discov* 2004;3:711-715.
- <sup>30</sup> Putzeist M, Mantel-Teeuwisse AK, Aronsson B, Rowland M, Gispen-de Wied CC, Vamvakas S, et al. Factors influencing non-approval of new drugs in the EU marketing authorisation procedure. *Nat Rev Drug Discov* 2012;11:903-904.
- <sup>31</sup> Van Meer PJ, Kooijman M, Gispen-de Wied CC, Moors EH, Schellekens H. The ability of animal studies to detect serious post marketing adverse events is limited. *Regul Toxicol Pharmacol* 2012;64:345-349.

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

- <sup>32</sup> Van der Baan FH, Knol MJ, Klungel OH, Egberts AC, Grobbee DE, Roes KC. Potential of adaptive clinical trial designs in pharmacogenetic research. *Pharmacogenomics* 2012;13:571-578.
- <sup>33</sup> Boessen R, Knol MJ, Groenwold RH, Grobbee DE, Roes KC. Increasing trial efficiency by early reallocation of placebo nonresponders in sequential parallel comparison designs: Application to antidepressant trials. *Clin Trials* 2012;9:578-587.
- <sup>34</sup> Boessen R, Groenwold RH, Knol MJ, Grobbee DE, Roes KC. Classifying responders and nonresponders; does it help when there is evidence of differentially responding patient groups? *J Psychiatr Res* 2012;46:1169-1173.
- <sup>35</sup> Orloff J, Douglas F, Pinheiro J, Levinson S, Branson M, Chaturvedi P, et al. The future of drug development: advancing trial design. *Nat Rev Drug Discov* 2009;8:949-57.
- <sup>36</sup> European Medicines Agency (2007). Committee for Medicinal Products for Human Use. Reflection Paper on Methodological Issues in Confirmatory Clinical Trials planned with an Adaptive Design. CHMP/EWP/2459/02. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003616.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003616.pdf) (Accessed 25 February 2013).
- <sup>37</sup> Putzeist M, Heemstra HE, Garcia JL, Mantel-Teeuwisse AK, Gispén-De Wied CC, Hoes AW, et al. Determinants for successful marketing authorisation of orphan medicinal products in the EU. *Drug Discov Today* 2012;17:352-358.
- <sup>38</sup> Miao Y, Smink PA, de Zeeuw D, Lambers Heerspink HJ. Drug-induced changes in risk/biomarkers and their relationship with renal and cardiovascular long-term outcome in patients with diabetes. *Clin Chem* 2011;57:186-195.
- <sup>39</sup> Smink PA, Miao Y., Eijkemans MJC, Bakker SJL, Raz I, Parving HH et al. The importance of short term off-target effects in estimating the long- term renal and cardiovascular protection of Angiotensin Receptor Blockers. Submitted for publication.
- <sup>40</sup> Altar C. The Biomarkers Consortium: On the Critical Path of Drug Discovery. *Clin Pharmacol Ther* 2008;83:361-4.
- <sup>41</sup> Innovative Medicines Initiative. Ongoing Projects. Available from: <http://www.imi.europa.eu/content/ongoing-projects> (Accessed 25 February 2013).
- <sup>42</sup> European Medicines Agency (2012). Concept paper on extrapolation of efficacy and safety in medicine development (draft). EMA/129698/2012. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2012/06/WC500129285.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129285.pdf) (Accessed 25 February 2013).
- <sup>43</sup> Stefansdottir G, Knol MJ, Arnardottir AH, van der Elst ME, Grobbee DE, Leufkens HG, et al. Safety learning from drugs of the same class: room for improvement. *Clin Pharmacol Ther* 2012;91:872-880.
- <sup>44</sup> Arnardottir AH, Haaijer-Ruskamp FM, Straus SM, de Graeff PA, Mol PG. Effect of safety issues with HIV drugs on the approval process of other drugs in the same class: an analysis of European Public Assessment Reports. *Drug Saf* 2011;34:1101-14.
- <sup>45</sup> Ratanawijitrasin, S. Effective drug regulation: A multicountry study, World Health Organization. 2002. Available from: <http://whqlibdoc.who.int/hq/2002/9241562064.pdf> (Accessed 25 February 2013).
- <sup>46</sup> Hamburg MS. Advancing regulatory science. *Science*. 2011;25:987.
- <sup>47</sup> Leufkens HGM, Eichler HG. Innovative methods in drug regulatory sciences. *Drug Discovery Today: Technologies*. 2011;8:e1-e42.

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

- <sup>48</sup> Arnardottir AH, Haaijer-Ruskamp FM, Straus SM, Eichler HG, de Graeff PA, Mol PG. Additional safety risk to exceptionally approved drugs in Europe? *Br J Clin Pharmacol* 2011;72:490-499.
- <sup>49</sup> Ebbers HC, Crow SA, Vulto AG, Schellekens H. Who's afraid of biosimilars? Accepted for publication in *Nature Biotechnology*.
- <sup>50</sup> European Medicines Agency (2009). Procedure for European Union Guidelines and related documents within the pharmaceutical legislative framework. EMEA/P/24143/2004 Rev. 1 corr. 2009. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/10/WC500004011.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004011.pdf) (Accessed 25 February 2013).
- <sup>51</sup> European Medicines Agency (2010). Road map to 2015, The European Medicines Agency's contribution to science, medicines and health. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/01/WC500101373.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101373.pdf) (Accessed 25 February 2013).
- <sup>52</sup> Hartley K, Lavers RJ, Maynard AK. Regulation and development times in the U.K. pharmaceutical industry. *Scott J Polit Econ* 1986;33:355-369.
- <sup>53</sup> Miller W, Robinson LA, Lawrence RS. Valuing health for regulatory cost-effectiveness analysis. National Academies Press, Washington DC, USA. 2006.
- <sup>54</sup> Bouvy JC, Koopmanschap MA, Shah RR, Schellekens H. The cost-effectiveness of drug regulation: the example of thorough QT/QTc studies. *Clin Pharmacol Ther* 2012;91:281-288.
- <sup>55</sup> Bouvy JC, Ebbers HC, Schellekens H, Koopmanschap MA. The cost-effectiveness of Periodic Safety Update Reports (PSURs) for biologicals in Europe. *Clin Pharmacol Ther* Article preview. Available from: <http://www.nature.com/clpt/journal/vaop/naam/abs/clpt201313a.html> (Accessed 25 February 2013).
- <sup>56</sup> Priority medicines for Europe and the world. Geneva, WHO, 2004
- <sup>57</sup> Eichler HG, Oye K, Baird LG, Abadie E, Brown J, Drum CL, et al. Adaptive licensing: taking the next step in the evolution of drug approval. *Clin Pharmacol Ther* 2012;91: 426-437.
- <sup>58</sup> Franken M, Le Polain M, Cleemput I, Koopmanschap M. Similarities and differences between five European drug reimbursement systems. *Int J Technol Assess Health Care* 2012;28: 349-357.
- <sup>59</sup> European Medicines Agency (2009). Benefit-Risk Methodology Project. EMEA/108979/2009. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/07/WC500109477.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/07/WC500109477.pdf) (Accessed 25 February 2013).
- <sup>60</sup> Bernabe RD, van Thiel GJ, Raaijmakers JA, van Delden JJ. The risk-benefit task of research ethics committees: An evaluation of current approaches and the need to incorporate decision studies methods. *BMC Med Ethics* 2012;13:6.
- <sup>61</sup> Bernabe RD, van Thiel GJ, Raaijmakers JA, van Delden JJ. Decision theory and the evaluation of risks and benefits of clinical trials. *Drug Discov Today* 2012;17:1263-1269.
- <sup>62</sup> European Medicines Agency (2007). Report of the CHMP working group on benefit-risk assessment models and methods. EMEA/CHMP/15404/2007. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2010/01/WC500069668.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500069668.pdf) (Accessed 25 February 2013).
- <sup>63</sup> European Medicines Agency (2011). Benefit-risk methodology project. Work package 3 report: Field tests. EMA/718294/2011. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/09/WC500112088.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500112088.pdf) (Accessed 25 February 2013).

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

- <sup>64</sup> Philips L, Fasolo B, Zafiroopoulos N, Beyer A. Is quantitative benefit–risk modelling of drugs desirable or possible? *Drug Discovery Today: Technologies* 2011;8:e3-e10.
- <sup>65</sup> European Medicines Agency. Benefit-risk methodology project (2010). Work package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment. EMA/549682/2010. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2010/10/WC500097750.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/10/WC500097750.pdf) (Accessed 25 February 2013).
- <sup>66</sup> Centre for Innovation in Regulatory Science. Available at: <http://cirsci.org/UMBRA> (Accessed 11 March 2013).
- <sup>67</sup> Innovative Medicines Initiative. Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium <http://www.imi-protect.eu/wp5.shtml> (Accessed 11 March 2013).
- <sup>68</sup> European Medicines Agency. Benefit-Risk Methodology Project (2009). EMEA/108979/2009. Available from: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/special\\_topics/document\\_listing/document\\_listing\\_000314.jsp&mid=WC0b01ac0580223ed6](http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000314.jsp&mid=WC0b01ac0580223ed6) (Accessed 11 March 2013).
- <sup>69</sup> European Medicines Agency (2012). Benefit-risk methodology project. Work package 4 report: Benefit-risk tools and processes. EMA/297405/2012 – Revision 1. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2012/03/WC500123819.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/03/WC500123819.pdf).
- <sup>70</sup> European Medicines Agency (2010). Road map to 2015 – the European Medicines Agency’s contribution to science, medicines and health. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/01/WC500101373.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101373.pdf) (Accessed 25 February 2013).
- <sup>71</sup> Bernabe RD, van Thiel GJ, Raaijmakers JA, van Delden JJ. Decision theory and the evaluation of risks and benefits of clinical trials. *Drug Discov Today* 2012;17:1263-9.
- <sup>72</sup> European Medicines Agency (2011). Benefit-risk methodology project. Work package 3 report: Field tests. EMA/718294/2011. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/09/WC500112088.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500112088.pdf) (Accessed 11 March 2013).
- <sup>73</sup> Philips L, Fasolo B, Zafiroopoulos N, Beyer A. Is quantitative benefit–risk modelling of drugs desirable or possible? *Drug Discovery Today: Technologies* 2011;8: e3-e10.
- <sup>74</sup> van Valkenhoef G, Tervonen T, Zwinkels T, de Brock B, Hillege H. ADDIS: a decision support system for evidence-based medicine. *Decision Support Systems* 2012, in press.
- <sup>75</sup> Liberti L, Breckenridge A, Eichler HG, Peterson R, McAuslane N, Walker S. Expediting patients’ access to medicines by improving the predictability of drug development and the regulatory approval process. *Clin Pharmacol Ther* 2010;87:27-31.
- <sup>76</sup> Walker S, Liberti L, McAuslane N, Levitan BS. Refining the benefit-risk framework for the assessment of medicines: valuing and weighting benefit and risk parameters. *Clin Pharmacol Ther* 2011;89:179-82.
- <sup>77</sup> European Medicines Agency (2010). Benefit-risk methodology project. Work package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment. EMA/549682/2010; Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2010/10/WC500097750.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/10/WC500097750.pdf) (Accessed 11 March 2013).
- <sup>78</sup> European Medicines Agency. Benefit-risk methodology project (2011). Work package 3 report: Field tests. EMA/718294/2011. Available from:

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

- [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/09/WC500112088.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500112088.pdf)  
(Accessed 11 March 2013).
- <sup>79</sup> <http://www.drugis.org/addis> (Accessed 11 March 2013).
- <sup>80</sup> European Medicines Agency (2012). Benefit-risk methodology project. Work package 4 report: Benefit-risk tools and processes. EMA/297405/2012 – Revision 1. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2012/03/WC500123819.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/03/WC500123819.pdf)  
(Accessed 11 March 2013).
- <sup>81</sup> Innovative Medicines Initiative Protect. Available from: <http://www.imi-protect.eu/documents/AshbyIreland2012.pdf> (Accessed 11 March 2013).
- <sup>82</sup> European Medicines Agency. Partner. Available from:  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners\\_and\\_networks/general/general\\_content\\_000476.jsp&mid=WC0b01ac0580236a57](http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000476.jsp&mid=WC0b01ac0580236a57) (Accessed 11 March 2013).
- <sup>83</sup> European Medicines Agency (2011). Report on the implementation of the EMA/CHMP think-tank recommendations. EMA/585687/2010. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/09/WC500113212.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500113212.pdf)  
(Accessed 11 March 2013).
- <sup>84</sup> European Medicines Agency. News and Events. Workshops. Available from:  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fnews\\_and\\_events%2Flanding%2Fnews\\_search\\_landing\\_page.jsp&mid=WC0b01ac058004d5c1&searchkwByEnter=true&isNewQuery=true&keyword=workshop&committeeSelect=All&month=All&year=All&keywordSearch=Submit](http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fnews_and_events%2Flanding%2Fnews_search_landing_page.jsp&mid=WC0b01ac058004d5c1&searchkwByEnter=true&isNewQuery=true&keyword=workshop&committeeSelect=All&month=All&year=All&keywordSearch=Submit) (Accessed 11 March 2013).
- <sup>85</sup> European Medicines Agency (2007). EMEA Guidance on Pre-Submission Meetings for initial Marketing Authorisation Applications for Human Medicinal Products in the Centralised Procedure. EMEA/382712/2006.
- <sup>86</sup> European Medicines Agency (2006). New framework for Scientific advice & Protocol assistance. EMEA/267187/2005/ Rev. 1. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/10/WC500004245.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004245.pdf) (Accessed 11 March 2013).
- <sup>87</sup> Putzeist M, Mantel-Teeuwisse AK, Aronsson B, Rowland M, Gispén-de Wied CC, Vamvakas S, et al. Factors influencing non-approval of new drugs in the EU marketing authorisation procedure. *Nat Rev Drug Discov* 2012;11:903-904.
- <sup>88</sup> European Medicines Agency (2012). Performance of the Agency's scientific procedures: 2011 report for medicinal products for human use. EMA/MB/157253/2012. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2012/04/WC500124937.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/04/WC500124937.pdf).  
(Accessed 11 March 2013).
- <sup>89</sup> Longgren T. Perspectives on the scientific dialogue. Presentation given in Escher workshop "Towards Adaptive Marketing Authorisation" December 2012.
- <sup>90</sup> The European Agency for the evaluation of medicinal products. Eight Annual Report 2002. Available from:  
[http://www.emea.europa.eu/docs/en\\_GB/document\\_library/Annual\\_report/2009/12/WC500016741.pdf](http://www.emea.europa.eu/docs/en_GB/document_library/Annual_report/2009/12/WC500016741.pdf)  
(Last accessed 2 April 2013).
- <sup>91</sup> European Medicines Agency (2006). New framework for Scientific advice & Protocol assistance. EMEA/267187/2005/ Rev. 1. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/10/WC500004245.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004245.pdf) (Accessed 11 March 2013).

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

- <sup>92</sup> Putzeist M, Mantel-Teeuwisse AK, Wied CCG, Hoes AW, Leufkens HG. Regulatory scientific advice in drug development: Does company size make a difference? *Eur J Clin Pharmacol* 2010;67:157-64.
- <sup>93</sup> European Medicines Agency (2010). Road map to 2015. The European Medicines Agency's contribution to science, medicines and health. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2010/01/WC500067952.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500067952.pdf)  
(Accessed 11 March 2013).
- <sup>94</sup> Putzeist M, Mantel-Teeuwisse AK, Gispén-de Wied CC, Hoes AW, Leufkens HG. Regulatory scientific advice in drug development: Does company size make a difference? *Eur J Clin Pharmacol* 2010;67:157-64.
- <sup>95</sup> European Medicines Agency (2006). New framework for Scientific advice & Protocol assistance. EMEA/267187/2005/ Rev. 1. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/10/WC500004245.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004245.pdf) (Last accessed 11 March 2013).
- <sup>96</sup> Regnstrom J, Koenig F, Aronsson B, Reimer T, Svendsen K, Tsigkos S, et al. Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. *Eur J Clin Pharmacol* 2010;66:39-48.
- <sup>97</sup> European Medicines Agency (2010). Guidance for Companies requesting Scientific Advice and Protocol Assistance. EMEA-H-4260-01-Rev. 6. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/10/WC500004089.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004089.pdf). (Accessed 11 March 2013).
- <sup>98</sup> Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2002). Guidance for Industry: Special Protocol Assessment. Available from: <http://www.fda.gov/downloads/Drugs/Guidances/ucm080571.pdf>. (Accessed 11 March 2013).
- <sup>99</sup> European Medicines Agency (2012). Mandate, objectives and rules of procedure of the Scientific advice working party (SAWP). EMEA/CHMP/SAWP/69686/04 Rev 9. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2010/02/WC500073585.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/02/WC500073585.pdf)  
(Accessed 11 March 2013).
- <sup>100</sup> European Medicines Agency (2011). Report on the implementation of the EMA/CHMP think-tank recommendations. EMA/585687/2010. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/09/WC500113212.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500113212.pdf).  
(Accessed 11 March 2013).
- <sup>101</sup> European Medicines Agency and U.S Food and Drug Administration (2009). General Principles EMEA- FDA Parallel Scientific Advice. EMEA/24517/2009. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2009/11/WC500014868.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/11/WC500014868.pdf)  
(Accessed 11 March 2013).
- <sup>102</sup> European Medicines Agency (2010). Road map to 2015. The European Medicines Agency's contribution to science, medicines and health. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2010/01/WC500067952.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500067952.pdf)  
(Accessed 11 March 2013).
- <sup>103</sup> European Medicines Agency (2011). Report on the implementation of the EMA/CHMP think-tank recommendations. EMA/585687/2010. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/09/WC500113212.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500113212.pdf)  
(Accessed 11 March 2013).
- <sup>104</sup> European Medicines Agency and EUnetHTA Joint Action start collaboration on European Public Assessment Report (EPAR) contribution to relative effectiveness assessments. Available from:

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

- [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2010/02/WC500073909.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/02/WC500073909.pdf) (Accessed at 19 March 2013).
- <sup>105</sup> EMA-EUnetHTA meeting Copenhagen November 2013. Presentations. Available from: <http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Presentations%2013%20from%20the%20EMA-EUnetHTA%20meeting,%20%20November%202012.pdf> (Accessed at 11 March 2013).
- <sup>106</sup> So AD, Ruiz-Esparza Q, Gupta N, Cars O. 3Rs for innovating novel antibiotics: sharing resources, risks, and rewards. *BMJ* 2012;3,344:e1782.
- <sup>107</sup> Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on Orphan Medicinal Products. Official Journal of The European Union.
- <sup>108</sup> Report on rare disease research, its determinants in Europe and the way forward. May 2011. Available from: [http://asso.orpha.net/RDPlatform/upload/file/RDPlatform\\_final\\_report.pdf](http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf) (Accessed at 19 March 2013).
- <sup>109</sup> The Committee for Orphan Medicinal Products and the European Medicines Agency Scientific Secretariat. European regulation on orphan medicinal products: 10 years of experience and future perspectives. *Nat Rev Drug Discov* 2011;10:341-349.
- <sup>110</sup> Braun M.M, Farag-El-Massah S, Xu K, Coté TR. Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years. *Nat Rev Drug Discov* 2010;9:519-522.
- <sup>111</sup> The Committee for Orphan Medicinal Products and the European Medicines Agency Scientific Secretariat. European regulation on orphan medicinal products: 10 years of experience and future perspectives. *Nat Rev Drug Discov* 2011;10:341-349.
- <sup>112</sup> Leung Y. Harvard College Global Health Review. October 2012. Available from: <http://www.hcs.harvard.edu/hghr/print/student/orphan-drug-act/> (Accessed 27 January 2013).
- <sup>113</sup> Burke KA, Freeman SN, Imoisili MA, Coté TR. The Impact of the Orphan Drug Act on the Development and Advancement of Neurological Products for Rare Diseases: A Descriptive Review. *Clinical pharmacol & Ther.* 2010;88:449-453.
- <sup>114</sup> Heemstra HE, van Weely S, Büller HA, Leufkens HG, de Vrueth RL. Translation of rare disease research into orphan drug development: disease matters. *Drug Discov Today* 2009;14:1166-73.
- <sup>115</sup> Putzeist M, Mantel-Teeuwisse AK, Gispén-de Wied CC, Hoes AW, Leufkens HGM, de Vrueth RLA. Level of scientific knowledge drives drug development for ultra-rare metabolic diseases. Submitted for publication.
- <sup>116</sup> Brabers AE Moors EH, van Weely S, de Vrueth RL. Does market exclusivity hinder the development of Follow-on orphan medicinal products in Europe? *Orphanet J Rare Dis* 2011;6,59.
- <sup>117</sup> Committee for Orphan Medicinal Products. European regulation on orphan medicinal products: 10 years of experience and future perspectives. *Nat Rev Drug Discov* 2011;10:341-349.
- <sup>118</sup> Joppi R, Bertele V, Garattini S. Orphan drugs, orphan diseases. The first decade of orphan drug legislation in the EU. *Eur J Clin Pharmacol* 2012; (Epub ahead of print).
- <sup>119</sup> Putzeist M, Heemstra HE, Garcia JL, Mantel-Teeuwisse AK, Gispén-De Wied CC, Hoes AW, et al. Determinants for successful marketing authorisation of orphan medicinal products in the EU. *Drug Discov Today* 2012;17:352-8.
- <sup>120</sup> Heemstra HE, Leufkens HG, Rodgers RP, Xu K, Voordouw BC, Braun MM. Characteristics of orphan drug applications that fail to achieve marketing approval in the USA. *Drug Discov Today* 2011;16:73-80.

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

- <sup>121</sup> Putzeist M, Mantel-Teeuwisse AK, Llinares-Garcia J, Gispen-De Wied CC, Hoes AW, Leufkens HGM. EU marketing authorisation review of orphan and non-orphan drugs does not differ. Submitted for publication.
- <sup>122</sup> Committee for Orphan Medicinal Products. European regulation on orphan medicinal products: 10 years of experience and future perspectives. *Nat Rev Drug Discov* 2011;10:341–349.
- <sup>123</sup> Article 58 of Commission Regulation (EC) No 726/2004. A CHMP scientific opinion in the context of co-operation with the World Health Organization (WHO) for the evaluation of medicinal products intended exclusively for markets outside the Community. *Official Journal of the European Union*.
- <sup>124</sup> Moran M. A breakthrough in R&D for neglected diseases: New ways to get the drugs we need. *PLoS Med* 2005;2:e302.
- <sup>125</sup> Kermani F. Maintaining the Focus for Neglected Diseases: Product development partnerships seek to bridge the healthcare gap.  
Available from: [http://www.contractpharma.com/issues/2011-10/view\\_features/maintaining-the-focus-for-neglected-diseases/](http://www.contractpharma.com/issues/2011-10/view_features/maintaining-the-focus-for-neglected-diseases/) (Accessed at 11 March 2013).
- <sup>126</sup> Kesselheim AS. Drug Development for Neglected Diseases —The Trouble with FDA Review Vouchers; 2008 *N Engl J Med* 359:1981-3.
- <sup>127</sup> Kermani F. Maintaining the Focus for Neglected Diseases: Product development partnerships seek to bridge the healthcare gap.  
Available from: [http://www.contractpharma.com/issues/2011-10/view\\_features/maintaining-the-focus-for-neglected-diseases/](http://www.contractpharma.com/issues/2011-10/view_features/maintaining-the-focus-for-neglected-diseases/) (Accessed at 11 March 2013).
- <sup>128</sup> Moran M. A breakthrough in R&D for neglected diseases: New ways to get the drugs we need. *PLoS Med* 2005;2:e302.
- <sup>129</sup> Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit-risk data: a mounting dilemma. *Nat Rev Drug Discov* 2008;7:818-26.
- <sup>130</sup> Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council. *Official Journal of the European Union*.
- <sup>131</sup> European Medicines Agency. European Public Assessment report. Search by Type. [http://www.emea.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar\\_search.jsp&mid=W00b01ac058001d124](http://www.emea.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=W00b01ac058001d124) (Accessed at 11 March 2013).
- <sup>132</sup> Committee for Orphan Medicinal Products. European regulation on orphan medicinal products: 10 years of experience and future perspectives. *Nat Rev Drug Discov* 2011;10:341–349.
- <sup>133</sup> Arnardottir AH, Haaijer-Ruskamp FM, Straus SM, Eichler HG, de Graeff PA, Mol PG. Additional safety risk to exceptionally approved drugs in Europe? *Br J Clin Pharmacol* 2011;72:490-9.
- <sup>134</sup> Boon WP, Moors EH, Meijer A, Schellekens H, et al. Conditional Approval and Approval Under Exceptional Circumstances as Regulatory Instruments for Stimulating Responsible Drug Innovation in Europe. *Clinical Pharmacology & Therapeutics* 2010;88:848–53.
- <sup>135</sup> Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit-risk data: a mounting dilemma. *Nat Rev Drug Discov* 2008;7:818-26.
- <sup>136</sup> Finkelstein JB. Accelerated Approval Regulations May Need Overhaul, Panel Suggests. *JNCI J Natl Cancer Inst* 2005;97:1802-04.

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

- <sup>137</sup> Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit-risk data: a mounting dilemma. *Nat Rev Drug Discov* 2008;7:818-26.
- <sup>138</sup> Kaplan W, Laing R. Priority Medicines for Europe and the World. World Health Organization. Department of Essential Drugs and Medicines Policy 2004; WHO/EDM/PAR/2004.7.
- <sup>139</sup> European Centre for Disease Prevention and Control /European Medicines Agency (2009). European Centre for Disease Prevention and Control The bacterial challenge: time to react. EMEA/576176/2009. Available from: [http://www.ecdc.europa.eu/en/publications/Publications/0909\\_TER\\_The\\_Bacterial\\_Challenge\\_Time\\_to\\_React.pdf](http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf) (Accessed 19 March 2013).
- <sup>141</sup> Tsuey Tse M, Kirkpatrick P. 2012 in reflection. *Nat Rev Drug Discov* 2013;12:8-10.
- <sup>142</sup> European Medicines Agency (2010). Road map to 2015. The European Medicines Agency's contribution to science, medicines and health. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2010/01/WC500067952.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500067952.pdf) (Accessed 11 March 2013).
- <sup>143</sup> ECDC/EMA Joint Technical Report. The bacterial challenge: time to react; A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents. Available from: [http://www.ecdc.europa.eu/en/publications/Publications/0909\\_TER\\_The\\_Bacterial\\_Challenge\\_Time\\_to\\_React.pdf](http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf) (Accessed 19 March 2013).
- <sup>144</sup> Tsuey Tse M, Kirkpatrick P. 2012 in reflection. *Nat Rev Drug Discov* 2013;12:8-10.
- <sup>145</sup> European Medicines Agency (2010). Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. CPMP/EWP/558/95 rev 2. Available from: [http://www.emea.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2010/03/WC500079928.pdf](http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500079928.pdf) (Accessed 19 March 2013).
- <sup>146</sup> Innovative Medicines Initiative. Uniting European Researchers in the fight against antibiotic resistance. Press release. Available from: <http://www.imi.europa.eu/sites/default/files/uploads/documents/Press%20Releases/IMIpressRelease6thCallFINAL.pdf> (Accessed 19 March 2013).
- <sup>147</sup> ReAct, Action on Antibiotic Resistance. Available from: <http://www.reactgroup.org/who-we-are.html> (Accessed 19 March 2013).
- <sup>148</sup> Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use, amended by Regulation (EC) No 1902/2006.
- <sup>149</sup> European Medicines Agency (2011). Report on the implementation of the EMA/CHMP think-tank recommendations. EMA/585687/2010. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/09/WC500113212.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500113212.pdf) (Accessed 11 March 2013).
- <sup>150</sup> European Medicines Agency. Paediatric investigation plans, waivers and modifications. Available from: [http://www.emea.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000293.jsp&mid=WC0b01ac0580025b91](http://www.emea.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000293.jsp&mid=WC0b01ac0580025b91) (Accessed 19 March 2013).
- <sup>151</sup> European Medicines Agency. Paediatric-use marketing authorisations. Available from: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000413.js&mid=WC0b01ac0580025ea2](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000413.js&mid=WC0b01ac0580025ea2) (Accessed 19 March 2013).

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

- <sup>152</sup> Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use, amended by Regulation (EC) No 1902/2006.
- <sup>153</sup> European Medicines Agency (2011). Report on the implementation of the EMA/CHMP think-tank recommendations. EMA/585687/2010. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/09/WC500113212.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500113212.pdf) (Accessed 11 March 2013).
- <sup>154</sup> European Medicines Agency. Buccolam. Available from: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002267/smops/Positive/human\\_smop\\_000234.jsp&mid=WC0b01ac058001d127&murl=menus/medicines/medicines.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002267/smops/Positive/human_smop_000234.jsp&mid=WC0b01ac058001d127&murl=menus/medicines/medicines.jsp) (Accessed at 19 March 2013).
- <sup>155</sup> European Medicines Agency (2010). Report on the survey of all paediatric uses of medicinal products in Europe. EMA/794083/2009. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/01/WC500101006.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101006.pdf) (Accessed 20 March 2013).
- <sup>156</sup> <http://www.pharmafile.com/news/166770/ema-puma-viropharma-buccolam> (Accessed 19 March 2013)
- <sup>157</sup> Ivanovska V, Mantel-Teeuwisse AK, van Dijk L. Priority Medicines for Children. Draft Background paper 7.2 for Priority Medicines II 2013.
- <sup>158</sup> Jack A. Concerns over paediatric trials. Financial Times 2011. Available from: <http://www.ft.com/cms/s/0/f006d940-aaee-11e0-b4d8-00144feabdc0.html#axzz2LQn1q16G> (Accessed 19 March 2013).
- <sup>159</sup> Koreith K. Critics raise concerns over research, incentives of European pediatric exclusivity regulations. Centerwatch News Online 2011. Available from: <http://www.centerwatch.com/news-online/article/2005/critics-raise-concerns-over-research-incentives-of-european-pediatric-exclusivity-regulations> (Accessed 19 March 2013).
- <sup>160</sup> Cerreta F, Eichler HG, Rasi G. Drug Policy for an Aging Population — The European Medicines Agency's Geriatric Medicines Strategy. *n engl j med* 2012;367:1972-1974.
- <sup>161</sup> Maher AR, Maglione M, Bagley S, Suttrop M, Hu JH, Ewing B, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. *JAMA* 2011;306:1359-1369.
- <sup>162</sup> European Medicines Agency (2011). EMA geriatric medicines strategy. EMA/CHMP/137793/2011. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2011/02/WC500102291.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/02/WC500102291.pdf) (Accessed 19 March 2013).
- <sup>163</sup> Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. *JAMA* 1993;270:2590-7.
- <sup>164</sup> Food and Drug Association (1993). Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs. Available from: <http://www.fda.gov/cder/guidance/old036fn.pdf> (Accessed 19 March 2013).
- <sup>165</sup> National Institute of Health (2001). Guidelines for the Inclusion of Women and Minorities in Clinical Research. Available from: [http://grants1.nih.gov/grants/funding/women\\_min/guidelines\\_amended\\_10\\_2001.htm](http://grants1.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm) (Accessed 19 March 2013).

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

- <sup>166</sup> Authority of the Minister of Health Health Canada (1997). Therapeutic Products Programme. Guidelines Inclusion of women in clinical trials. Available from: [http://www.hc-sc.gc.ca/dhp-mps/alt\\_formats/hpfb-dgpsa/pdf/prodpharma/womct\\_femec-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/womct_femec-eng.pdf) (Accessed 19 March 2013).
- <sup>167</sup> European Medicines Agency (2005). ICH Gender Considerations in the Conduct of Clinical Trials. EMEA/CHMP/3916/2005. Available from: [http://www.emea.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2010/01/WC500059887.pdf](http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500059887.pdf) (Accessed at 19 March 2013).
- <sup>168</sup> Regulation (EC) No 1394/2007 of the European Parliament and of the council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. Official Journal of the European Union.
- <sup>169</sup> European Medicines Agency (2011). Report on the implementation of the EMA/CHMP think-tank recommendations. EMA/585687/2010. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/09/WC500113212.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500113212.pdf) (Accessed 11 March 2013).
- <sup>170</sup> Authorised on 5 October 2009, EU/1/09/563
- <sup>171</sup> Authorised on 29 October 2012, EU/1/12/791, after a reevaluation by the EMA at the request of the Commission
- <sup>172</sup> European network for Health Technology Assessment (EunetHTA) (2013). What is Health Technology Assessment? Available from: <http://www.eunetha.eu/about-us/faq#t287n73> (Accessed 19 March 2013).
- <sup>173</sup> European Commission, DG Health & Consumers (2013). Health Technology Assessment. Available from: [http://ec.europa.eu/health/technology\\_assessment/policy/index\\_en.htm](http://ec.europa.eu/health/technology_assessment/policy/index_en.htm) (Accessed 19 March 2013).
- <sup>174</sup> European Commission. High Level Pharmaceutical Forum. Core principles on relative effectiveness. Available from: [http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea\\_principles\\_en.pdf](http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea_principles_en.pdf) (Accessed 8 February 2013).
- <sup>175</sup> Eichler HG, Abadie E, Breckenridge A, Flamion B, Gustafsson LL, Leufkens HGM. Bridging the efficacy–effectiveness gap: a regulator's perspective on addressing variability of drug response. *Nat Rev Drug Discov* 2011;10:495-506.
- <sup>176</sup> European Medicines Agency and EUnetHTA Joint Action start collaboration on European Public Assessment Report (EPAR) contribution to relative effectiveness assessments. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2010/02/WC500073909.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/02/WC500073909.pdf) (Accessed 19 March 2013).
- <sup>177</sup> European Medicines Agency (2011). Report on the implementation of the EMA/CHMP think-tank recommendations. EMA/585687/2010. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/09/WC500113212.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500113212.pdf) (Accessed 11 March 2013).
- <sup>178</sup> European Medicines Agency and EUnetHTA Joint Action start collaboration on European Public Assessment Report (EPAR) contribution to relative effectiveness assessments. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2010/02/WC500073909.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/02/WC500073909.pdf) (Accessed 19 March 2013).
- <sup>179</sup> Eichler HG, Oye K, Baird LG, Abadie E, Brown J, Drum CL, et al. Adaptive licensing: taking the next step in the evolution of drug approval. *Clin Pharmacol Ther* 2012;91: 426-37.

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

- <sup>180</sup> Breckenridge A, Woods K, Walley T. Medicines regulation and health technology assessment. *Clin Pharmacol Ther* 2010;87:152-4.
- <sup>181</sup> Tsuji K, Tsutani K. Approval of new drugs 1999-2007: Comparison of the US, the EU and Japan situations. *Journal of Clinical Pharmacy and Therapeutics* 2010;35:289-301.
- <sup>182</sup> International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).  
<http://www.ich.org> (Accessed 2 April 2012).
- <sup>183</sup> Mintz C. The Slow Progression Of Pharma Regulatory Harmonization. Available from:  
<http://www.lifescienceleader.com/magazine/current-issue-3/item/4245-the-slow-progression-of-pharma-regulatory-harmonization>. (Accessed 2 April 2013).
- <sup>184</sup> Morrison A. Rethinking emerging markets for regulatory affairs with the creation of a Regulatory Authority Development Index. *Regulatory Rapporteur* 2012;4:5-7. Available from:  
[http://www.topra.org/sites/default/files/regrapart/1/4216/rethinking\\_emerging\\_markets\\_for\\_regulatory\\_affairs\\_morrison\\_singh.pdf](http://www.topra.org/sites/default/files/regrapart/1/4216/rethinking_emerging_markets_for_regulatory_affairs_morrison_singh.pdf) (Accessed 2 April 2013).
- <sup>185</sup> European Medicines Agency annual report 2011 (2012). Overview of the Agency's contribution to science, medicines and health in the European Union. Available from:  
<http://www.europarl.europa.eu/document/activities/cont/201209/20120904ATT50488/20120904ATT50488EN.pdf> (Accessed 19 March 2013).
- <sup>186</sup> European Medicines Agency and U.S Food and Drug Administration (2009). General Principles EMEA- FDA Parallel Scientific Advice. EMEA/24517/2009. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2009/11/WC500014868.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/11/WC500014868.pdf) (Accessed 11 March 2013).
- <sup>187</sup> Trotta F, Leufkens HG, Schellens JH, Laing R, Tafuri G. Evaluation of Oncology Drugs at the European Medicines Agency and US Food and Drug Administration: When Differences Have an Impact on Clinical Practice. *J Clin Oncol* 2011;29:2266-72.
- <sup>188</sup> European Medicines Agency (2009). Reflection Paper on the Further Involvement of Patients and Consumers in the Agency's Activities. EMA/MB/753771/2009. Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2010/01/WC500038080.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/01/WC500038080.pdf) (Accessed 11 March 2013).
- <sup>189</sup> US Food and Drug Administration (2010). Guidance for the public, FDA Advisory Committee Members, and FDA Staff: The Open Public Hearing at FDA Advisory Committee Meetings. FINAL GUIDANCE. Available from:  
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM236144.pdf> (Accessed 2 April 2013).
- <sup>190</sup> European Medicines Agency (2010). Mandate, objectives and rules of procedure for the European Medicines Agency Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP) Available from:  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2010/02/WC500073497.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/02/WC500073497.pdf) (Accessed 11 March 2013).
- <sup>191</sup> Eichler HG, Oye K, Baird LG, Abadie E, Brown J, Drum CL, et al. Adaptive licensing: taking the next step in the evolution of drug approval. *Clin Pharmacol Ther* 2012;91:426-37.
- <sup>192</sup> US Food and Drug Administration (2010). Guidance for the public, FDA Advisory Committee Members, and FDA Staff: The Open Public Hearing at FDA Advisory Committee Meetings. FINAL GUIDANCE. Available from:

## Update on 2004 Background Paper, BP 8.2 Regulatory Practices

- <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM236144.pdf> (Accessed 2 April 2013).
- <sup>193</sup> Sukkar E. Sunshine at the European regulator. *BMJ* 2012;344.
- <sup>194</sup> Kramer DB, Xu S, Kesselheim AS. Regulation of Medical Devices in the United States and European Union. *n engl j med* 2012;366:848-855.
- <sup>195</sup> Tice JA, Helfand M, Feldman MD. Clinical evidence for medical devices: regulatory processes focusing on Europe and the United States of America. Background Paper 3 to the World Health Organization Priority Medical Devices Project 2010. Available from: [http://whqlibdoc.who.int/hq/2010/WHO\\_HSS\\_EHT\\_DIM\\_10.3\\_eng.pdf](http://whqlibdoc.who.int/hq/2010/WHO_HSS_EHT_DIM_10.3_eng.pdf) (Accessed 19 March 2013).
- <sup>196</sup> European Medicines Agency (2007). Guideline on the development of active substances contained in drug eluting coronary stents. EMEA/CHMP/EWP/110540/2007. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003278.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003278.pdf) (Accessed 19 March 2013).
- <sup>197</sup> Kramer DB, Xu S, Kesselheim AS. Regulation of Medical Devices in the United States and European Union. *n engl j med* 2012; 366:848-855.
- <sup>198</sup> European Medicines Agency (2010). Procedural advice on the evaluation of combined advanced therapy medicinal products and the consultation of Notified Bodies in accordance with Article 9 of Regulation (EC) No. 1394/2007. EMA/354785/2010. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2010/07/WC500095323.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/07/WC500095323.pdf) (Accessed 19 March 2013).
- <sup>199</sup> Arlett P. Head Pharmacovigilance and Risk Management, Patient Health Protection, European Medicines Agency. Stakeholder meeting November 2012. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Presentation/2012/12/WC500136112.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2012/12/WC500136112.pdf) (Accessed 11 March 2013).
- <sup>200</sup> <http://www.ema.europa.eu>
- <sup>201</sup> European Medicines Agency (2011). Report on the implementation of the EMA/CHMP think-tank recommendations. EMA/585687/2010. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/09/WC500113212.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500113212.pdf) (Accessed 11 March 2013).
- <sup>202</sup> European Medicines Agency (2012). Annual report 2011. Overview of the Agency's contribution to science, medicines and health in the European Union. Available from: <http://www.europarl.europa.eu/document/activities/cont/201209/20120904ATT50488/20120904ATT50488EN.pdf> (Accessed 19 March 2013).
- <sup>203</sup> European Medicines Agency. Release of data from clinical trials. Available from: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/special\\_topics/general/general\\_content\\_000555.jsp&murl=menus/special\\_topics/special\\_topics.jsp&mid=WC0b01ac0580607bfa](http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp&murl=menus/special_topics/special_topics.jsp&mid=WC0b01ac0580607bfa) (Accessed 19 March 2013).