TESTING THE PATIENCE OF PATIENTS?

Early access to medicines initiatives discussed by regulators, patient organisations and industry

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Cover illustration: Blood cells representing the testing of patients with life-threatening or seriously debilitating conditions to allow access to medicines for which licences have not yet been approved.

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It is clear that developing a new medicine is a lengthy process. In November 2014, the Tufts Center for the Study of Drug Development estimated the average time taken from synthesis of a new compound to regulatory approval of an application for marketing authorisation to be 128 months – almost 13 years. (See ‘Cost of Developing a New Drug’, 18 November 2014.) When this is coupled with the increased access that patients have to information on new drug development, for example through patient organisations, social media, pharmaceutical company websites and regulatory documentation, it is not surprising that there is pressure on industry and regulators to allow patients access to medicines in a timely, and sometimes early, manner. This pressure is welcomed by industry, which is keen to allow patients access to new medicines, and it has been taken on board by regulators who have devised a variety of mechanisms to allow this access to take place. Our focus this month is on this very important area of early/timely access to new medicines.

To give us some insight from a patient perspective we have an article from three members of the European Medicines Agency’s Committee for Orphan Medicinal Products (COMP), each of whom represents different rare disease patient organisations (the European Genetic Alliance Network, European Organisation for Rare Diseases and Cystic Fibrosis Europe, respectively). Their article discusses the importance of early access to medicines for patients suffering from rare diseases, and highlights the various aspects which are of particular importance for rare diseases as opposed to more common diseases.

Regulators around the world have taken on board this need for timely/early access to new medicines, most recently in the EU with the Safe and Timely Access to Medicines for Patient (STAMP) expert group established by the European Commission, and the EMA’s proposed Priority Medicines (PRIME) scheme. In this issue, we have two further focus articles looking at schemes which are available in Europe (focusing on the UK) and North America (US and Canada). An article from a regulator’s perspective is provided by the Medicines and Healthcare products Regulatory Agency (MHRA). This discusses the UK’s Early Access to Medicines Scheme (EAMS), which gives patients with life-threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need.

Our North American article looks at the market access and expedited regulatory review programmes available in this region. Market access programmes include expanded access (US) and the special access program (Canada). Expedited regulatory review programmes discussed include the accelerated approval pathway, the fast track and breakthrough therapy designations (US) and priority review (US and Canada).

In addition to our focus articles, we also have articles which will be interesting for developers of different types of product at different stages of development. First, we have an article from the EMA’s SME Office which provides some fascinating EMA insights on marketing authorisations, regulatory assistance and briefing meetings for SMEs in the biologics and advanced therapies fields. This is followed by an interview with Anja Holm of the Danish Medicines Agency, who is also Chair of the Committee for Veterinary Medicinal Products (CVMP) and has been involved in many areas of the regulation of medicinal products. Finally, we have a meeting report which provides an update following two recent webinars hosted by the EMA on the new functionality of the PSUR repository.
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The importance of early access to medicines for patients suffering from rare diseases

Abstract
Rare disease patients face unique challenges in order to achieve standards of healthcare comparable to those of common diseases: from getting an accurate diagnosis to receiving treatments that substantially improve their quality of life and extend their life expectancy. Innovative regulatory approaches are being tested to address the lack of available treatments and ensure faster access for patients with unmet medical needs. The success of these strategies relies on the early incorporation of patients’ views and preferences into clinical trial design and during benefit-risk evaluation and health technology assessment (HTA). The development of reliable patient-relevant outcome measures (PROMs) as well as its consistent gathering during pre- and post-marketing phases would help in reducing overall drug development time and accelerating access to market. Early collection of data on the natural course of disease can also help in determining the added benefit of medicinal products developed later on.

Impact of rare diseases: diagnosis and lack of treatments
Although the prevalence of a rare disease in the EU is less than five in 10,000 people, they collectively affect more than 30 million people in Europe, which is equivalent to 6–8% of the population. Children are particularly affected; around 80% of rare diseases are inherited, and the onset of symptoms occurs at a very early age in approximately 50% of rare diseases. The severity varies from one disease to another, but life expectancy is generally reduced and a patient’s physical and emotional health can be profoundly affected. The fact that there are between 6,000 and 8,000 different identified rare diseases highlights the complexity and lack of scientific knowledge that surrounds them and that ultimately hampers diagnosis and development of effective treatments.

The effects of rare diseases on the wellbeing of patients and their families are profound and continue throughout the entire patient’s life. The first challenge faced by rare disease patients and their relatives is obtaining an accurate diagnosis. Being correctly diagnosed is usually a lengthy obstacle race characterised by a lack of general understanding and public awareness of the disease, limited scientific knowledge or clinical experience and even rejection of the patient or carers concerns by some healthcare professionals. Patients and families commonly share feelings of isolation and helplessness, as getting information about the condition and support from qualified specialists is hard to achieve. More often than not, reaching the right diagnosis takes years to decades, because symptoms are inappropriately assessed or may be too vague or similar to those of more common diseases. Initial misdiagnosis is known to occur in around 40% of cases, leading to inadequate medical interventions with detrimental consequences for the patient’s health. In addition, if the condition remains undiagnosed long enough for the first-born child, such a delay could impact on unborn siblings and parents. The former will not be able to access measures to be treated as early as possible, while the latter will not be able to make a fully informed decision as to whether they wish to extend their family or not.

Alarming, misdiagnosis delays the access to quality care to the point where it is no longer useful because the disease has already progressed and the treatment window of opportunity has been missed. This disheartening scenario exerts a tremendous influence on patient’s physical and mental wellbeing. However, it should be noted that the impact of rare disease diagnosis might be different depending the age of the patient. Thus, affected children may not perceive this situation as significantly detrimental to their future health as their parents or caregivers. Furthermore, while parents may feel guilty to have passed along to their children a genetic condition with long-lasting, devastating consequences for their lives, children have lived with their condition for as long as they can remember, and feel loved and protected by their families. Nevertheless, the impact on children’s mental wellbeing is greater as the disease progresses and life functions start to decline. Once the diagnosis is obtained, the embedded stress that comes with it may be overwhelming and adds to the physical burden of the disease. Young adult patients may see their dreams and expectations shut down after diagnosis and may not have the courage to ask for psychological support. They may also feel socially isolated at a time when peer pressure is having a maximum influence on their development. Similarly, parents of very young patients have to readjust and develop a resilience to find the best way to help their child as they race against time.

The second biggest shock is to discover that there is no specific treatment for the disease. At this point, many sufferers and family members frequently turn to patient advocacy groups for information on therapies and psychological support, only to realise that their disease may be so rare that access to quality information is non-existent. In this context, patients – and especially parents – have been instrumental in creating the environment for medicines to be developed, by starting up their own advocacy associations to raise awareness of the disease.

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Keywords
Rare disease; Orphan medicine; Early access; Patient-relevant outcome measure (PROM); Adaptive pathway; Scientific advice; Health technology assessment (HTA).
and provide funding for scientific research.

Financial burdens associated with rare diseases are many and can also damage the emotional health of patients and their carers. Travelling long distances to find specialised physicians or even relocating to facilitate access to care, multiple medical consultations, the need for non-medical and social support and the inability to work are common situations in the life of rare disease patients. Household income may be significantly decreased when parents or close relatives are forced to resign work – partially or completely – to meet these new demands in patient care. The economic repercussions of this scenario may even be long-lasting, as pension contributions will be reduced. While common chronic conditions share similar challenges, the distinctive features of rare diseases in terms of late diagnosis and lack of available treatments only aggravate an already complex scenario. For rare disease patients, this situation is only made worse by lack of understanding or awareness by those who should be there to support them.

**Drug development process and early market access**

Although most rare diseases have no cure, the long road to diagnosis prevents the early access to medicines that could delay or alleviate a patient’s symptoms. Restoring health, as early and as much as possible, is often the goal of the patient who has endured an ordeal to identify her/his condition. In the absence of a cure, best maintenance treatment is often regarded to be as good as a cure. It helps to regain some of the lost independence, but in most cases only temporarily reduces symptoms of the underlying condition and does not fight the cause of disease. In addition, the lack of marketed drugs may prompt patients to seek other treatment options which, in desperate situations, may involve alternative medicines or use of medicines off-label. Fortunately, most patients and carers can now access current information about compassionate-use programmes or clinical trials and elect to join them where possible.

In the EU, compassionate-use programmes allow controlled access to unauthorised drugs for life-threatening, chronically or seriously debilitating conditions that are in late-stage clinical trials or that have obtained approval in a country different from the patient’s home country.¹ National government authorities regulate these programmes and rules for access may vary among EU member states, being more tightly regulated in some countries than others. The French Temporary Authorisation for Use (ATU), for example, may incorporate more flexibility to the process and significantly shorten the time to drug access before it gets full market approval.⁴ However, there is a large difference in access to compassionate use and off-label medicines throughout Europe, and in many countries access involves difficult and long-lasting procedures, and may not even be possible. These delays and inequalities in the process—sometimes inherent to these treatment schemes—are often perceived as another barrier to drug access, due to the patient’s pressing need to stop or slow disease progression.

Bringing a drug from the laboratory bench through clinical trials until it is finally approved for patient use takes between ten and 15 years, a journey regarded as inconceivably long by patients with unmet medical needs, but also by the general public. Although more information and education would probably help understand the complexity of the drug development process, regulatory agencies worldwide are responding to public demands with initiatives aimed at reducing development times.

In Europe, the urgency to improve the development of therapies for unmet medical needs was initially recognised in 2000 with the European Regulation on Orphan Medicinal Products.¹ Conditional marketing authorisation can be granted to orphan medicines provided they have a positive benefit–risk balance at the time of authorisation and further clinical efficacy and safety data are provided by the manufacturer.⁷ More recently, the European Medicines Agency (EMA) started its adaptive pathways pilot project (also known as Medicine Adaptive Pathways to Patients, MAPPs), an initiative to improve timely access to treatments for patients suffering from serious conditions where there is an unmet medical need.⁸–⁹ One of the scenarios within this model contemplates the initial approval of a treatment studied in a well-defined patient population with an unmet medical need, which will be then extended to a larger group or a wider indication, provided subsequent safety and efficacy data are collected. Another model includes conditional drug approval based on surrogate endpoints followed by the gathering of real-world post-marketing data, particularly to complete the knowledge about the drug’s efficacy and safety profile. This flexible approach would be particularly beneficial in the context of rare diseases, where recruitment of a sufficient number of patients to demonstrate a given clinical outcome is often challenging. For this strategy to be successful, patient advocacy groups should engage early in the process to contribute the patient’s view and preferences in the design of clinically meaningful trials and the evaluation of patient-relevant outcomes. Where regulatory bodies are trying to facilitate easier market access through innovative authorisation schemes, HTA bodies seem to become more and more rigorous, and even exclude authorised therapies from reimbursement because they doubt their added therapeutic value. To overcome this discrepancy between the views of regulators and HTA bodies, the involvement of the latter early in the discussion is highly recommended and should markedly benefit the subsequent pricing and reimbursement negotiation that stalls drug market access on too many occasions.

**Patients’ willingness to take greater risk for early access**

Within the classical paradigm of drug approval, the clinical benefits of a product should outweigh its harmful effects before being used by patients. Although systematic and structured methodologies are currently being tested, evaluation of the benefit–risk balance has traditionally relied on expert judgement of often limited data.¹⁰ The degree of uncertainty willing to be accepted by regulators differs from that of patients and families. Since there is no effective cure, patients and their families may be more open to consider a greater risk than regulators. In addition, among rare disease patients, risk assessment may be different if done by a young or an adult patient, let alone by a parent of a very young child. Disease stage and level of pain suffered may be different if done by a young or an adult patient, let alone by a parent of a very young child. Disease stage and level of pain suffered also strongly influence this kind of appraisal. Clinical studies are powered to demonstrate efficacy, so there will always be limited safety data. Although rare disease patients are not prepared to accept higher toxicity (this impacts on their quality of life, since most treatments would be lifelong), they are prepared to accept higher uncertainty at the time of market approval in exchange for an effective treatment for their disease.

**Increasing patients’ influence on the regulatory process**

The influence of patients on regulatory processes at the EMA has progressively increased during the past decade with their representation in the EMA’s management board, the Committee for Orphan Medicinal Products (COMP), the Committee for Advanced Therapies (CAT), the Paediatric Committee (PDCO) and the Pharmacovigilance and Risk Assessment Committee (PRAC). Within these committees, patients are formal, full and permanent members with equal voting rights. Patient expertise is actually valued at each phase of the medicines lifecycle within activities that can range from the review of medicines information documents for the public, to consultation with regard to scientific advice and benefit–risk assessment procedures.¹¹ In fact, since 2014 the Committee for Medicinal Products for Human Use (CHMP) has regularly involved patients in specific discussions on
the benefit–risk aspects of medicines. Their continuous presence in these fora has allowed the transformation of drug regulation into a patient-centred process, in which patients are experts on the disease and its management and bring the real-life experience perspective into the scientific discussion, thus contributing to a more comprehensive decision-making process. For instance, during benefit–risk assessment, patients highlight the impact of the drug on quality-of-life aspects that may be underestimated by medical experts, especially in orphan diseases where treatments are often lifelong.

While the involvement of patients in the regulatory process has influenced how medicines are evaluated, the patient perspective still needs to be consistently incorporated earlier into the clinical development pathway. Generating the evidence that will support the access of a new medicine to the market may take several years, a timeframe that most rare disease patients cannot afford. Therefore, it is of utmost importance to design robust clinical studies to avoid misleading results that may ultimately translate into ineffective treatments. Carefully selecting the population of interest and the relevant endpoints to be tested will save some valuable time and eventually help patients to access faster and better treatments based on more solid data.

There is a current debate on how to reflect patient views and preferences in the design of clinical trials and emerging public and private projects aim to address this issue by developing reliable validated patient-relevant outcome measures (PROMs). Besides potentially accelerating clinical development, the consistent use of PROMS in the research for rare disease therapies would also provide the evidence needed to support payers’ decisions when evaluating the value of a healthcare intervention.

The currently available general quality-of-life assessment tools are too general, do not address the real items and are too insensitive to detect differences. Furthermore, standard clinical endpoints do not assess the items which really matter to patients. Therefore, there is a high need for disease PROMS. As with any other research tool, PROMS should be scientifically validated and be as specific as possible for the disease of interest. The Patient-Centered Outcomes Research Institute (PCORI) was the pioneer in setting methodology standards to carry out research that would produce evidence-based, patient-centred health interventions. Engaging the population of interest, namely patients and caregivers, is crucial in the development of patient-reported outcomes, especially for those conditions in which other outcome measures are not available. Having a solid methodology framework that ensures collection of high-quality data will contribute to overcoming the scepticism of medical experts and health technology assessors and favour the change to a new paradigm of how clinical research should be conducted.

The COMET (Core Outcome Measures in Effectiveness Trials) initiative (www.comet-initiative.org) focuses on developing an agreed minimum set of outcomes that should be measured and reported in clinical trials for a specific condition, thus reducing the heterogeneity between studies. This would help patients, physicians and regulators alike to decide what the best treatments are. The International Rare Diseases Research Consortium (IRDRC) set up a task force on patient-centred outcome measures with representatives from public and private organisations in the field of rare diseases. The objective of this task force is to accelerate the development and validation of PROMS specifically for rare diseases. Patient groups are a source of knowledge and expertise for the development of these tools. A good example of this is the Duchenne Parent Project, which, together with clinicians and researchers worldwide, designed a new instrument – the Performance of the Upper Limb (PUL) module, to assess upper limb functionality in patients with Duchenne muscular dystrophy (DMD). In contrast to the traditional six-minute walking test (6MWT) used only in DMD ambulant patients, the PUL can also be assessed in non-ambulant boys as upper limb weakness occurs later in the natural history of the disease (see Box below). Thus, this tool is able to show if the tested drug is effective in a sample population who would have been excluded from the clinical trials if the typical 6MWT had been used. In this particular case, DMD-affected boys actively participated in the development of the tool by testing it, but also contributed to the discussion on its clinical significance.

**HTA involvement in access to new therapies**

Europe showcases a complex scenario in which marketing authorisation is granted at European level, but national authorities are the real gatekeepers of access to new therapies. Health technology assessment (HTA) is then decisive and critical for the introduction of healthcare interventions to the public. At times of increasing budget constraints and ever higher prices for all medicines, HTAs tend to focus too much on the social benefits of the medicine. An in-depth understanding of the natural history of the disease is absolutely necessary when developing these instruments.

**Case 1: Performance of the Upper Limb (PUL) module for Duchenne muscular dystrophy (DMD)**

Patients with DMD lose their ability to walk between nine and 14 years of age. Therefore, testing the effect of a medicine only on the ambulatory ability will exclude many patients that are at a later stage of the disease and will leave out other performance aspects relevant for everyday life. The items assessed in the PUL reflect the different levels of upper body functioning such as the ability to flex the arm to touch the top of his head or if they can reach their mouth with their hands or put their hands up on the table. These measurements reflect the impact of the medicine on daily activities which are particularly important from a social viewpoint, such as being able to eat and drink independently, or use a computer keyboard.

**Patient-reported outcomes (PROs) provide the information on the patient’s health status directly from the patient, without the interpretation of the response by a physician or any other intermediary.**

**Case 2: Exposure Times [multiplied by] Freedom from Pain (ETP) in erythropoietic protoporphyria (EPP)**

Skin phototoxicity is the main symptom in EPP, a rare inherited disease in which heme biosynthesis is impaired, leading to the accumulation of the photosensitising substance protoporphyrin IX. Light exposure triggers acute reactions of stinging pain in patients’ skin, followed by erythema, oedema, more severe skin lesions or incapacitating pain if sun exposure is prolonged.

**Table 1:** Case study of the upper limb (PUL) module in Duchenne muscular dystrophy (DMD)

<table>
<thead>
<tr>
<th>Module</th>
<th>Description</th>
<th>Benefits</th>
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<tr>
<td>PUL</td>
<td>Assesses upper limb functionality</td>
<td>Helps to show if the tested drug is effective in a sample population who would have been excluded from the clinical trials if the typical 6MWT had been used.</td>
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costs and too little on benefits. Of course, industry should play its part by lowering prices, but a better rewarding of the benefits of the medicines is also helping to reduce the cost per quality-adjusted life year (QALY). Therefore, patient involvement in this process is essential to ensure those aspects of the treatments that will fulfil patients’ expectations about improving quality of life (their own and that of their carers) are properly taken into consideration – to prolong survival; to improve or protect their ability to carry out their activities for daily living or slow the progression of the disease.

The participation of patients/patient groups in HTA discussions is highly valued and essential, as they have a unique perspective on the impact of the disease on their lives and how a medicine will influence their daily activities. They are also experts on the use of current available treatments and have clear expectations about the added value new therapies should have. The input from rare disease patients is particularly important, as usually the new treatment cannot be compared with any existing standard of care. HTA relies on real-world data to analyse the impact of the medical intervention on patient’s quality of life, productivity or the sustainability of the health system. Therefore, when quality of life has not been investigated in clinical trials, further evidence (ie, patient or drug registries) should be provided, but this leads to substantial lags between the drug’s approval and its actual launch onto the market and use by the patient who so desperately needs it.

As already mentioned, medicine developers should carefully plan for early data collection of meaningful patient-centred outcomes to help close this gap. To address these issues the following should be considered: (1) the need for early dialogue and harmonisation between regulators, companies, HTA bodies and payers to equally evaluate medicines and medical interventions; and (2) the establishment of a specific framework for interaction between patient groups and HTA bodies in order to incorporate patient preferences and expectations of treatments into the value assessment. The EMA’s pilot project on parallel HTA/scientific advice is one of the strategies aiming to facilitate this early dialogue between multiple stakeholders, namely patients, regulators, HTA bodies, and drug manufacturers.16

Conclusion

There is still a long way to go for rare disease patients to experience healthcare standards comparable with those of common conditions. Regulations have advanced to make drug research and development a flexible process that will eventually accelerate drug approval, thus partially addressing the inequalities in terms of healthcare and speed of access to appropriate treatments faced by rare disease patients. However, decisions are made in a context of greater uncertainty, a fact that concerns medical experts, regulators, HTA bodies and payers. This suggests apparent reservations with regard to the reliability of conclusions based on early data. Shifting the current paradigm of drug approval and market access will undoubtedly require the alignment and mutual understanding of all relevant parties, the continuous generation of reliable data at all stages and the early inclusion of patient views for benefit–risk and HTA assessments.

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Focus – Early access to medicines

A regulator’s guide to the UK Early Access to Medicines Scheme

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Keywords
Early Access to Medicines Scheme (EAMS); Medicines and Healthcare products Regulatory Agency (MHRA); Benefit–risk; Promising innovative medicine (PIM); PIM designation; Scientific opinion; Pre-submission meeting (PSM).

Abstract
The UK Early Access to Medicines Scheme (EAMS) gives patients with life-threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. Unmet medical need means a condition for which there exists no satisfactory method of diagnosis, prevention or treatment or, if such a method exists, the medicinal product will be of major therapeutic advantage to those affected. The Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for the scientific aspects of the scheme and a benefit–risk scientific opinion is issued after a two-step evaluation process: Step I, the promising innovative medicine (PIM) designation and Step II, the EAMS scientific opinion. The PIM designation gives an early indication that a medicinal product is a potential candidate for the EAMS. The EAMS scientific opinion describes the benefits and risks of the medicine in a public assessment report and supports the prescriber and patient in making a decision on using the medicine before its licence is approved, through the provision of the EAMS treatment protocol. As at October 2015, nine PIM designations have been issued and four EAMS scientific opinions. This article describes the background to the scheme, an overview of how the scheme operates, MHRA experience to date and ongoing developments.

Background
The ministerial industry strategy group (MISG) brings together government and the research-based pharmaceutical industry to promote a strong and profitable UK-based pharmaceutical industry. In 2008, a proposal for an “early access to medicines scheme” was developed as part of a series of events established by the MISG. The Regulatory Working Group forum considered that earlier access to medicines could bring significant benefits to patients.

In December 2011, the Prime Minister announced a new Strategy for UK Life Sciences. The publication detailed actions aimed at maintaining the UK’s world-class reputation in life sciences, improving patient health and acting as a catalyst for economic growth. One of these commitments was that the MHRA would bring forward for consultation proposals for a new “early access scheme”. The MHRA and Department of Health launched the joint public consultation in July 2012. The consultation introduced the Early Access to Medicines Scheme (EAMS) based on the work of the MISG, the MHRA and the Department of Health.

Another commitment from the Strategy was to establish an Expert Group on innovation in the regulation of healthcare: “A group of experts drawn from government, regulators, the NHS [National Health Service], industry and the academic and third sector communities will meet quarterly to discuss healthcare regulation issues, including the development of new initiatives and innovations...” (established June 2012). The Expert Group was tasked with maximising the impact of, and learning from, the EAMS consultation and published a report in September 2013. The Expert Group welcomed the proposal for a UK EAMS, endorsed the draft Government response to the consultation and advised that the scheme should be launched as soon as cross-Government agreement was obtained. In addition, it recommended that the Government consider the possibility of adopting a medicinal product designation that would send positive signals to investors (as does the US breakthrough therapy designation), perhaps in the context of the proposed UK Early Access Scheme. On the basis of this recommendation, the MHRA introduced the new “promising innovative medicine” (PIM) designation, Step I of the scheme.

The Government’s response to the consultation was published in March 2014. There were 52 responses from a variety of stakeholders and, overall, there was overwhelming support for a scheme. In the response, the Government considered that the EAMS addresses a public health need to improve access to important innovative medicines for patients with life-threatening or seriously debilitating conditions without adequate treatment options and demonstrates a commitment from the UK to pharmaceutical innovation, through the PIM designation and earlier patient uptake of new innovative medicines in the health service. The scheme was launched by the MHRA in April 2014, with a dedicated EAMS webpage, covering the application process for the PIM designation and the EAMS scientific opinion. The scheme was introduced within the current medicines legal framework, is voluntary and does not replace the normal licensing procedures for medicines. The EAMS is primarily aimed at medicines that have completed Phase III trials, but may apply in the Phase II setting in exceptional circumstances (for example, patients with rare diseases).

Step I – PIM designation
A PIM designation is an early indication that a medicinal product is a potential candidate for the EAMS, intended for the treatment, diagnosis or prevention of a life-threatening or seriously debilitating condition,
Focus – Early access to medicines

with the potential to address an unmet medical need. The designation is issued to a new chemical or biological entity or for a new indication for an established medicine in a defined disease area after a MHRA designation scientific meeting. (The routes for PIM designation are shown in Figure 1.) Companies may apply when data from early stages in a clinical development programme indicate that the medicinal product fulfils the designation criteria, or later, and request a joint PIM/pre-submission meeting (PSM).

All of the following three criteria must be fulfilled in order to gain a PIM designation:

- The condition should be life-threatening or seriously debilitating and with high unmet clinical need
- The medicinal product is likely to offer major advantage over methods currently used in the UK
- The potential adverse effects of the medicinal product are likely to be outweighed by the benefits, allowing for the reasonable expectation of a positive benefit/risk balance.

Applicants apply by submitting a completed PIM designation template, covering the designation criteria. The designation application is reviewed by a team of assessors and the applicant attends a designation meeting. The focus of the designation meeting is the potential of the medicinal product to fulfill the PIM criteria. Following the designation meeting, the assessment team will make a recommendation to the internal scientific consistency review group, which will advise the Director of Licensing on whether a designation should be granted. Following a positive outcome, PIM designation holders are expected to complete a clinical development programme within a reasonable period of time, in order to continue with an application under the EAMS (Step II). Designation holders are also strongly encouraged to utilise the MHRA’s support services including its Innovation Office and scientific advice service, and liaise with the NHS and National Institute for Health and Care Excellence (NICE) on patient access issues.

Step II – Scientific opinion

The scientific opinion describes the risks and benefits of the medicine based on data gathered from patients who will benefit from the medicine. The opinion supports the prescriber and patient to make a decision on whether to use the medicine before its licence is approved. The four EAMS criteria are:

- (a) Life-threatening or seriously debilitating condition, and (b) high unmet need, ie, either there are no methods available or existing methods have serious limitations
- The medicinal product is likely to offer significant advantage over methods currently used in the UK
- The potential adverse effects of the medicinal product are considered to be outweighed by the benefits, allowing for the reasonable expectation of a positive benefit/risk balance
- The Applicant is able to supply the product and to manufacture it to a consistent quality standard (GMP).

To enter Step II, the applicant must hold a PIM designation and request and attend a PSM in person or via telecommunications. The aim of the PSM is to discuss the suitability criteria for the scheme and the final content and structure of the EAMS dossier. The assessment timetable is illustrated in the Figure 2. The initial benefit–risk opinion is given by Day 45 of the procedure. If a preliminary positive opinion is given, the procedure then follows the Day 75 timetable or if the preliminary benefit–risk opinion is negative, the procedure follows the Day 90 timetable.

A positive scientific opinion is only issued if the criteria for the EAMS are fulfilled. The positive scientific opinion is published on the MHRA webpage alongside a public assessment report and the EAMS

Figure 1: Routes for PIM designation (Step I) to scientific opinion (Step II).
Figure 2: Timetable for the EAMS scientific opinion assessment (Step II).

<table>
<thead>
<tr>
<th>Day 75 timetable</th>
<th>Day 90 timetable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Days 0–45</strong></td>
<td><strong>Days 0–45</strong></td>
</tr>
<tr>
<td>MHRA assessment and consultation with CHM/EAG, list of outstanding issues communicated to applicant, with provisional benefit–risk (B–R) opinion</td>
<td>MHRA considers Day 90 procedure required</td>
</tr>
<tr>
<td>Preliminary positive opinion (minor issues outstanding)</td>
<td>Applicant requests revert to Day 90 procedure</td>
</tr>
<tr>
<td>15-day clock stop</td>
<td>Preliminary negative opinion (major issues outstanding)</td>
</tr>
<tr>
<td>Days 46–75: Final B–R decision positive on or before Day 75</td>
<td>Days 46–90: Final B–R decision made on or before Day 90 – positive or negative opinion</td>
</tr>
<tr>
<td>Days 46–75: Preliminary B–R decision now negative</td>
<td></td>
</tr>
</tbody>
</table>

*In exceptional circumstances, the applicant can request additional 30 days (30+30).

Treatment Protocol (provides more detailed information to the patient and the physician). The opinion is valid for one year and lapses at this time or at the time of the grant of a marketing authorisation (MA). During the opinion year, it is expected that the scientific opinion holder will provide regular updates as per the agreed risk management plan (RMP) and pharmacovigilance activities. Any new information that the opinion holder considers may impact the benefit–risk balance must be reported as soon as is reasonably practical. As with any unlicensed medicine, the General Medical Council guidance states that patients using such medicines should be made aware of the status of these products and give informed consent to take them. Patient access issues are the responsibility of the NHS in England, Wales, Scotland and Northern Ireland, and should be discussed by the applicant early in the scheme.

**MHRA experience to date**

In the first year of operation, there were ten PIM designation applications and four EAMS scientific opinion applications. As at October 2015, there have been nine PIM designations issued and three scientific opinions in the cancer area (two indications for melanoma and one indication for lung cancer) and one indication for heart failure. Detailed information on these scientific opinions can be found on the MHRA’s EAMS webpage.

**Future development of the scheme**

The MHRA is updating its guidance documentation for the PIM designation and EAMS scientific opinion in light of MHRA experience to date, and following on from discussions and agreement at a government-industry task group.

The EAMS Government–Industry Stakeholder Task Group was established to bring together key stakeholders from the biopharmaceutical industry, government and “arms’ length” bodies to inform the development of EAMS procedures, to establish consistent lines of communication between stakeholders and to clarify, address and accelerate the resolution of emerging issues since launch. The group’s membership includes the MHRA, NICE, NHS England, Office for Life Sciences, Department of Health, Devolved Administrations, Scottish Medicines Consortium, All Wales Therapeutics and Toxicology Centre, ABPI, BIA, EMIG, invited representative companies, and other stakeholders including the Centre for the Advancement of Sustainable Medical Innovation (CASMI). The stakeholder group has produced and agreed supporting material to help further explain the scheme. This includes an agreed EAMS “principles” document (agreed across the NHS in the UK), and an operational guidance and schematic showing the relationships between MHRA, NICE, NHS England and the company (to be published in the near future and accessible from the MHRA’s EAMS webpage).

The operational guidance will include devolved administration annexes and the guidance will be updated in the light of experience and future developments, eg, the outcome of the Accelerated Access Review. Such changes that have been implemented to date include the MHRA sharing the PIM designation and notification of a preliminary positive benefit–risk balance at Day 45 of Step II assessment to contacts in the NHS/NICE/devolved administrations in confidence. These notifications are intended to facilitate communication between the Company and the other stakeholders involved in the EAMS.
Focus – Early access to medicines

The UK Government’s accelerated access review (AAR) aims to speed up access to innovative drugs, devices and diagnostics for NHS patients. The review was launched in March 2015, with evidence gathering between July and October, and publication of a final report will take place in April 2016. The review will make recommendations to government on reforms to accelerate access. These recommendations could include the role of statutory bodies including NICE and the MHRA, and the review’s ambition is to develop a joined-up, globally competitive landscape across the whole of the UK. The EAMS is included as part of the review to “...consider how we might strengthen the Early Access to Medicines Scheme, taking into account how this fits with the Adaptive Pathways Pilot, NICE Technology Appraisal, the NICE Implementation Collaborative and other schemes such as Evaluation through Commissioning.”

Summary
A key challenge confronting regulators and other stakeholders is earlier patient access to innovative medicines, particularly in areas of unmet medical need. The UK EAMS addresses a public health need to improve access to important innovative medicines. Patients are able to access the next generation of breakthrough medicines before they are licensed and the scientific opinion supports prescribers in deciding to use an unlicensed medicine for conditions where there are no adequate treatment options available to them.

The MHRA is responsible for the scientific aspects of the scheme and the EAMS scientific opinion is provided after a two-step evaluation process: Step I, the Promising Innovative Medicine (PIM) designation and Step II, the Early Access to Medicines Scientific Opinion. To date, nine PIM designations have been awarded and four scientific opinions issued, benefitting numerous patients with serious and life-threatening conditions.

Two currently ongoing initiatives, the Government/Industry Stakeholder Task Group and the Government’s accelerated access review are considering the EAMS. The Task Group has developed additional guidance documents setting out the principles between different stakeholders involved in the scheme and the AAR is due to report in Spring 2016, with proposals to strengthen the existing scheme.

References
5. Accelerated Access Review. Available at: https://engage.dh.gov.uk/acceleratedaccess/
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ENABLING AND PROMOTING EXCELLENCE IN THE HEALTHCARE REGULATORY PROFESSION
Therapeutic product access and expedited review pathways in North America

The FDA therefore created its “expanded access program” (EAP) so that patients with serious or immediately life-threatening diseases with no comparable or satisfactory therapeutic alternatives can access investigational therapeutic products outside of a clinical trial. Different expanded access categories exist as outlined in Figures 1 and 2, each with its own set of eligibility criteria. All eligibility criteria must be met for consideration under an expanded access pathway. In general, the criteria ensure that: (1) only patients with critical need and no alternative can access investigational products; (2) investigational products are sufficiently safe and effective for the intended use under expanded access; and (3) existing clinical trials and market application plans for investigational therapeutic products can proceed without disruption from the EAP. The FDA centers (Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER)) have allowed most of the expanded access INDs and protocols received between 2010 and 2014 to proceed, with 99% of applications to CDER and 95% of those to CBER allowed to proceed (see Figure 3).

Expedited review programmes for serious conditions – drugs & biologics

Drugs, including biologics, intended to treat serious or life-threatening conditions can receive an expedited FDA review. Factors that determine if a condition is serious can vary and include survival, day-to-day functioning, or the likelihood that the condition, if left untreated, will progress from a less severe condition to a more serious one. Four expedited review programmes exist: fast track designation (FTD), breakthrough therapy designation (BTD), accelerated approval pathway (AAP) and priority review designation. The FDA has approved many drugs via fast track and priority review designations as well as via the AAP.

Fast track designation

The FTD can be applied to drugs intended to treat serious conditions and address an unmet medical need. Drugs that are considered for FTD include drugs that: (1) show superior effectiveness, an effect or improved effects on serious outcomes; (2) improve diagnosis of a serious condition where early diagnosis produces an improved outcome; (3) do not produce side-effects of available therapies; (4) decrease a clinically significant toxicity of an available therapy that is common and causes treatment discontinuation; and (5) address an anticipated or emerging public health need.

Drug manufacturers must request FTD during drug development. This can be done with an IND but no later than a pre-new drug application (pre-NDA) or pre-biologic license application (pre-BLA) meeting. FDA review time is 60 days. Drugs that receive FTD can benefit from some or all of the FTD features, which include frequent meetings and written correspondence with the FDA, a rolling review whereby the FDA reviews sections of a new NDA or a BLA as they become ready. If relevant criteria are met, drugs that receive FTD may even become eligible for accelerated approval or priority review.

Introduction

Access to investigational drugs, biologics and medical devices can be sought outside of clinical trials to treat serious or life-threatening diseases. When applying for market approval, these therapeutic products can receive an expedited review by regulatory agencies. The US FDA and Health Canada have different regulatory mechanisms that are highly sought after by manufacturers in a competitive industry.

Expanded access

In the US, to conduct a clinical trial, an investigational new drug (IND) submission or an investigational device exemption (IDE) must be submitted to the FDA. Patients with serious or immediately life-threatening diseases who have no comparable or satisfactory therapeutic alternatives on the market look to participate in clinical trials to receive promising investigational therapies. However, this is not always possible as current clinical trials may have study protocols with subject criteria that exclude such patients from participating. At times, there may not be ongoing clinical trials available for participation.
Drugs that no longer meet the qualifying criteria for FTD listed above can have their designation rescinded.

**Breakthrough therapy designation**

Drugs intended to treat serious conditions and which have preliminary clinical evidence demonstrating substantial improvement, such as improved duration or magnitude of treatment effect, in one or more clinically significant endpoints over an available therapy are considered breakthrough therapies. Clinically significant endpoints can include:

- A significantly improved safety profile compared with available therapy (eg, less dose-limiting toxicity for an oncology agent), with evidence of similar efficacy
- An effect on a pharmacodynamic biomarker that fails criteria for an acceptable surrogate endpoint, but strongly suggests the potential for a clinically meaningful effect on the underlying disease
- An effect on an established surrogate endpoint such as a laboratory measurement, radiographic image, physical sign or other measure thought to predict clinical benefit, but is not itself a measure of clinical benefit
- An effect on an intermediate clinical endpoint, such as an effect on irreversible morbidity and mortality (IMM), considered reasonably likely to predict a clinical benefit (ie, the accelerated

**Figure 1: Expanded access – drugs, including biologics.**

<table>
<thead>
<tr>
<th>Individual patient access</th>
<th>Intermediate-size patient population access</th>
<th>Widespread use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual patient expanded access IND/Single patient IND (new IND)</td>
<td>Intermediate-size patient population expanded access IND (new IND)</td>
<td>Treatment IND (new IND)</td>
</tr>
<tr>
<td>Individual patient expanded access protocol/Single patient protocol (protocol amendment to existing IND)</td>
<td>Intermediate-size patient population expanded access protocol (protocol amendment to existing IND)</td>
<td>Treatment protocol (protocol amendment to existing IND)</td>
</tr>
<tr>
<td>Emergency IND/Individual patient access IND for emergency use (new IND)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency protocol/Individual patient expanded access protocol for emergency use (protocol amendment to existing IND)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2: Expanded access – medical devices.**

- **Emergency use**
  - For emergency access before or after initiation of a clinical trial
  - Investigational device exemption (IDE) report within five days of use to FDA
- **Emergency research**
  - For emergency access when no informed consent possible
  - Separate original IDE to FDA, IRB & physician approve
- **Compassionate use**
  - For access during a clinical trial for a single patient/small group
  - IDE supplement for FDA approval, IDE report follow-up to FDA & IRB
- **Treatment use**
  - For access during a clinical trial
  - Treatment IDE submission to FDA, IDE reports follow
- **Continued access**
  - For access after completion of a clinical trial
  - IDE supplement to FDA
Ideally, drug manufacturers can request BTD with the IND or as an IND amendment before the end of Phase II meeting or before the clinical trial for demonstration of efficacy. Like the FTD, the BTD has an FDA review time of 60 days. Another feature shared with the FTD is the rescinding of the BTD if a drug does not meet the above qualifying criteria. Drugs receiving BTD can be eligible for FTD features and will gain organisational commitment from the FDA including senior managers to provide intensive guidance on an efficient drug development programme that begins as early as Phase I. CDER and CBER have granted less than a third of all the BTD requests received, but at a high review performance rate of 99% and 73% respectively (see Figure 4).

**Accelerated approval pathway**
A drug may be approved via the AAP if it meets all of the following criteria:

- Indicated for a serious medical condition
- Generally provides a meaningful advantage over available therapies
- Demonstrates (a) an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit; or (b) an effect on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM; or (c) other clinical benefit (ie, an intermediate clinical endpoint).

Post-market controlled confirmatory trials are required for drug approval to verify that the drug’s effect on the surrogate endpoint or the intermediate clinical endpoint predicts a clinical benefit. The FDA and the sponsor must agree on study design and conduct.

**Priority review designation**
Drug manufacturers can request a priority review designation with their NDA, BLA or efficacy supplement. Priority review designation is assigned at the time of original filing but the FDA has a 60-day response timeframe. If designated, the marketing application review time is shortened to six months.

Different qualifying criteria exist for the priority review designation, including the need to demonstrate significant improvements when compared with standard applications. Examples of significant improvements include evidence of increased effectiveness in treatment, prevention, or diagnosis of condition; evidence of safety and effectiveness in a new subpopulation; elimination or substantial reduction of a treatment-limiting drug reaction; or documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes.

**Special access program**
In Canada, “special access programs” (SAPs) exist for drugs and medical devices. Practitioners can request access to drugs intended for serious or life-threatening conditions if evidence supports the intended use and marketed alternatives do not exist, have failed or are unsuitable. Similarly, practicing healthcare professionals can request access to custom-made and unlicensed medical devices for emergency use or when conventional devices have failed, are

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**Figure 3: Expanded access INDs and protocols.**

<table>
<thead>
<tr>
<th>Fiscal year</th>
<th>CDER/CBER</th>
<th>Received</th>
<th>Allowed to proceed</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Allowed to proceed (2010–2014)</td>
<td>CDER</td>
<td></td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CBER</td>
<td></td>
<td>95%</td>
<td></td>
</tr>
</tbody>
</table>
unsuitable or unavailable. Under the SAP, healthcare professionals and manufacturers bear responsibilities such as drug record-keeping and reporting with respect to adverse drug reactions and device problems. Manufacturers additionally control various conditions of sale such as price and conditions of use.

While not a mechanism for expedited regulatory review or a substitute for a clinical trial, the SAP can be used in cases of drug shortage, drug discontinuation, or to gather new or confirmatory safety and efficacy evidence when a clinical trial is inappropriate. SAP can also be used under certain conditions for access to a drug that has received a negative regulatory response.

**Priority review**

Health Canada may consider a new drug submission (NDS) or supplemental new drug submission (SNDS) for priority review status if the drug meets eligibility criteria. Drugs considered must be intended for serious, life-threatening or severely debilitating diseases or conditions. Drugs with no marketed alternatives must demonstrate effective treatment, prevention or diagnosis. Alternatively, drugs for priority review must reveal a significant increase in efficacy and/or significant decrease in risk such that the overall benefit–risk profile is improved over existing therapies, preventative or diagnostic agents. For instance, in its benefit–risk evaluation, Health Canada will consider a reduction in toxicity over the marketed drug, an improved serious outcome or a favourable effect on a serious symptom of the condition. At least two well-controlled clinical studies are generally required as substantial evidence for clinical effectiveness.

Health Canada expects that drugs granted priority review status will have submissions filed within 60 calendar days. The priority review status means drugs will have a shorter review timeframe of 180 calendar days. With initial processing and screening, this brings the total processing time to 215 calendar days.

**Notice of compliance with conditions**

Drug therapies for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating diseases/conditions that either have no available alternative Canadian therapy or represent a significant improvement in the benefit–risk profile over existing products are eligible for “notice of compliance with conditions” (NOC/c) consideration by Health Canada. The NOC/c provides for earlier market approval but with conditions such as an agreement by the sponsor to: (a) undertake confirmatory trials to prove clinical benefit; (b) perform enhanced post-market surveillance and reporting for drug safety; and possibly (c) conform to restrictions with respect to advertising and drug distribution. New drugs (NDS, SNDS) and generic drugs (abbreviated new drug submission (ANDS), supplemental abbreviated new drug submission (SANDS)) can utilise the NOC/c policy. Generic drugs (ANDS) would probably not require confirmatory trials; though there can be exceptions, eg, a circumstance where the Canadian reference product (CRP) sponsor withdraws their drug from the market prior to completing and/or submitting the confirmatory trial(s).

NOC/c can be granted directly by Health Canada on review completion of any submission if there is substantial evidence of effectiveness. The sponsor can also request advanced consideration under the NOC/c at the pre-submission meeting. The sponsor must then submit the drug submission within 60 calendar days following notification of eligibility. NDS and SNDS under the NOC/c advance consideration policy can have a review period of 200 calendar days (+35 days receipt and screening) while an ANDS or SANDS that

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**Figure 4: Breakthrough therapy designation requests since programme inception (9 July 2012 – FDA Safety and Innovation Act).**

<table>
<thead>
<tr>
<th>Fiscal year</th>
<th>CDER/ CBER</th>
<th>Total requests received</th>
<th>Granted</th>
<th>Denied</th>
<th>FDA review performance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CBER</td>
<td>14</td>
<td>4</td>
<td>9</td>
<td>73%</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>CDER</td>
<td>31%</td>
<td>51%</td>
<td>99%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CBER</td>
<td>27%</td>
<td>67%</td>
<td>73%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Figure 4: Breakthrough therapy designation requests since programme inception (9 July 2012 – FDA Safety and Innovation Act).**

<table>
<thead>
<tr>
<th>Fiscal year</th>
<th>CDER/ CBER</th>
<th>Total requests received</th>
<th>Granted</th>
<th>Denied</th>
<th>FDA review performance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CBER</td>
<td>14</td>
<td>4</td>
<td>9</td>
<td>73%</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>CDER</td>
<td>31%</td>
<td>51%</td>
<td>99%</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>CBER</td>
<td>27%</td>
<td>67%</td>
<td>73%</td>
<td></td>
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</tr>
</tbody>
</table>
references a CRP with NOC/c status will be subject to a review target of 180 days. Various drugs have been issued the NOC/c by Health Canada.4

Conclusion
The fact that very many drugs have already received approvals (expanded access, BTD, FTD,1 priority review designation,6 AAP; NOC/c) are a testament that regulatory mechanisms for early or expedited market access are highly coveted in a competitive industry. For instance, recently, Merck KGaA and Pfizer received both BTD and FTD foravelumab, a drug in its investigational stage for a rare form of skin cancer, metastatic Merkel cell carcinoma (MCC).3 Bristol-Myers Squibb, Roche and AstraZeneca all have immunotherapies further in development than avelumab but, according to journalist Nick Paul Taylor in FierceBiotech, Merck KGaA and Pfizer hope to “leapfrog rivals” in this corner of the market.2 In another example, Daiichi Sankyo, with its patent losses for blood pressure drug Benicar and diabetes treatment Welchol, has coveted BTD for its Phase III cancer drug, pexidartinib.6

Thus, the various regulatory mechanisms for access and expedited review can prove strategic when incorporated into the marketing plans of drug and medical device manufacturers. Regulatory professionals play a key navigational role with their design and execution of custom, objective-based regulatory strategies.

References
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‘I will apply almost everything as we are planning to have parallel advice’

‘I now know the importance of HTA consideration in early development’

‘I found the presentations and information on the differences between the HTA agencies beneficial’

‘I now understand the need for economic models and the differences in HTA data requirements versus regulatory requirements and how to manage divergent advice’

‘I continue to network with people we met, as regulatory affairs is very much about learning from each others’ experiences, and this knowledge forms an important part of our career development’

‘The content of the course will definitely be very useful regarding the services that my consultancy company can provide to its customers’

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A regulator’s insights for SMEs in the biologics and advanced therapies sectors

Introduction and background

Over the past ten years two major pieces of legislation were introduced at European level to spearhead policies to support innovation-driven small and medium-sized enterprises (SMEs) in the fields of advanced therapies and biological therapeutics.

Regulation (EC) No 1394/2007 defined advanced therapy medicinal products (ATMPs) as gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products, and tissue-engineered products (TEPs). The Regulation came into force in 2008 with the aim of providing a consolidated framework for developers of gene, cell and tissue engineering medicinal products, which often originate in academic spin-offs or small and medium-sized enterprises (SMEs).

Commission Regulation (EC) No 2049/2005 was the second major policy which aimed at supporting innovation and the development of new medicinal products, specifically focusing on SMEs. The initiative, launched in December 2005, introduced financial fee incentives and administrative assistance targeted at smaller business structures in the pharmaceutical sector.

The size of applicant companies at the time of marketing authorisation application (MAA) may be one of the factors associated with an unfavourable outcome of an MAA at the European Medicines Agency (EMA), with smaller companies facing a higher probability of failure in the review of their dossiers. In this respect, the SME and advanced therapies regulations introduced “pull mechanisms” to draw SMEs into the existing regulatory development support structures, with fee incentives for scientific advice and regulatory assistance, and for ATMPs, additionally, a regulatory classification procedure and a certification process. These mechanisms aim at incentivising sponsors during development, and at ultimately increasing regulatory certainty at the stage of application for marketing authorisation.

In this paper we look into the profile of registered SMEs in the biopharmaceuticals and advanced therapies fields, to gain some insight into the issues encountered during the marketing authorisation review, as well as into the regulatory assistance that has been provided to these companies through the SME initiative.

Biological and biopharmaceutical products (“biologics”) include a wide variety of products, which vary in terms of types of molecule, size, complexity, and manufacturing: those considered in the paper refer to monoclonal antibodies, recombinant proteins and extracted proteins.

Profile of SMEs active in biologics and advanced therapies

A total of 1,338 SMEs were registered with the EMA at mid-year 2015. Sixteen percent were biopharmaceutical companies developing or marketing biologicals and advanced therapies.

Of those companies in contact with the EMA, the large majority in the biologics and advanced therapies fields are development-stage companies in the human medicines field (87%), 10% are developing products for both human and veterinary use, and 3% are active in the veterinary medicines field. The highest proportion of these companies are based in the UK (20%), France (15%), Germany (10%), the Netherlands (9%) for biologics, and for advanced therapies the UK (20%), France (15%), Belgium (13%) and Germany (12%).

The sector also seems to show buoyancy, as 19% of these companies are academic spin-offs and a third of them were incorporated in the last three years. Around 43% of companies are micro-sized companies (less than ten staff; turnover and balance sheet less than £2 million) and most products in the pipelines originate from in-house development (42%), with products being in-licensed limited to 21%. The percentage of academic spin-offs for companies in the ATMPs field is double the figure in biologics, highlighting the importance of academic structures for incubating start-up companies.

The medicines and medical devices sectors seem to intersect, with around 21% of companies performing their activities in the medical device and technology fields; the figure reaches 27% for advanced therapies due to the combined nature of some of the products being developed.

The majority of registered SMEs are privately owned either by individuals or by private corporations through equity stakes. Funding by venture capital – 9% – and other private investments (eg, investment firms, institutional investors, angel finance) accounts for 19% of companies’ capital share.

When looking at the products under development by companies in the fields of advanced therapies and biologicals, the following can be highlighted: there are a limited number of products in the pipelines (an average of two products), with 60% of products in these pipelines being at the research and development (R&D) and nonclinical development stage and 28% in exploratory and confirmatory clinical phases. Therapeutic medicines are predominant with vaccines, diagnostics and imaging agents representing a minority. The biologics category includes monoclonal antibodies (31%), recombinants proteins (44%), extracted proteins (25%) and ATMPs include cell therapy medicinal...
Table 1: Analysis of scope of questions received through regulatory assistance for SMEs in the advanced therapies and biologics sectors.

<table>
<thead>
<tr>
<th>Type of assistance</th>
<th>Timing/scope of questions</th>
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<tbody>
<tr>
<td>SME briefing meeting for biologics and advanced therapies: 7 23% of all SME briefing meetings</td>
<td>Early during development or late discussion ahead of dossier submission. Topics discussed: CMC [chemistry, manufacturing and controls], nonclinical, clinical, paediatric investigational plans; orphan designations; GxP; scientific advice, fees, clinical trial applications, legal basis for submissions; filing strategy for multiple paediatric and adult indications.</td>
</tr>
</tbody>
</table>
| Regulatory and administrative assistance for biologics and advanced therapies: 246 26% of all requests for regulatory assistance | Top 10 most frequent areas in the scope of regulatory assistance:  
**Administrative and procedural assistance:**  
1. Eligibility to centralised procedure*, preparation and submission of dossier: 11%  
2. SME definition, incentives and translations: 11%  
3. EMA and national fee queries: 9%  
4. GCP/GMP inspection: 3%  
5. Packaging and labelling requirements: 2%  
**Scientific advice:**  
6. Guidance on scientific advice procedure and dossier contents: 9%  
7. Assistance on identification and interpretation of CHMP/CVMP/ICH scientific guidelines relating to CMC, nonclinical, clinical, statistical aspects and environmental risk assessment: 8%  
**Orphan drugs:**  
8. Assistance and guidance on dossier contents of orphan drug designation applications: 8%  
**Regulatory:**  
9. Assistance on legal basis for dossier submission, including conditional marketing authorisation, approval under exceptional circumstances, dossier reviews under accelerated conditions, paediatric use marketing authorisations and adaptive pathways: 5%  
**Paediatric:**  
10. Procedural assistance on PIPs and requirements/waivers: 5%.  
*SMEs, which have mixed pipelines including biologics and chemical entities.*

products (39%), tissue engineering products (32%), gene therapy products (29%). Companies developing biologics and ATMPs also seem to have an increased focus on orphan diseases, oncology and immunological conditions, and nanotechnology.

Where can SMEs make improvements at the MAA stage?  
To get some insight into the issues encountered by SMEs during the review process, we analysed deficiencies elicited on the quality/nonclinical/clinical modules for SME applications submitted in the centralised procedure between 2011 and 2013. We reviewed the well-known “Day 120 list of questions” raised on the CTD Modules 3, 4 and 5 of 39 MAAs submitted by SMEs to the EMA between 2011 and 2013. Overall, approximately 46% of major objections were on the quality documentation, 47% on the clinical safety and efficacy documentation and 7% on nonclinical. For biologics and advanced therapies, approximately 51% of major objections were on the quality documentation, 39% on the clinical efficacy and safety documentation and 10% on the nonclinical development.

Although biologics and advanced therapies dossiers represented less than 26% of the total number of SME applications, they experienced more major objections during their review and fared less favourably in terms of outcomes – 65% overall success rate versus 50% for biologics. Major objections averaged 15 per dossier, a figure three times higher compared with medicines with chemical entities (average of five per dossier).

The most frequent problem areas in the quality documentation (Module 3) related, in descending order, to the following:
- Incomplete manufacturing process validation  
- Lack of control and/or characterisation data of the active substance/finished product  
- Lack of justification for the setting of specifications  
- Issues on the manufacturing process development and control strategy  
- Issues on the pharmaceutical development  
- Lack of evidence on batch-to-batch consistency  
- Issues on good manufacturing practice (GMP) compliance and GMP certification.

Deficits in the preclinical data (Module 4) were identified, in descending order, on the following:
- Design of toxicity study  
- Pharmacodynamics  
- Carcinogenicity  
- Pharmacokinetics  
- Reproductive performance and developmental toxicity  
- Toxic effects particularly at doses with inadequate safety margin when compared with clinical dose range.
Major deficiencies in the clinical documentation (Module 5) related to the following:
- Issues related to study design
- Issues on the analysis and robustness of pivotal data
- Serious adverse events
- Insufficient long-term follow-up data
- Inconsistent data on clinical efficacy
- Pharmacodynamics and pharmacokinetics
- Lack of quality and long term safety data.

Compared with a previous analysis, we found that deficit areas in the quality and clinical modules of the dossiers continued to be identified for these applications.

Deficiencies outlined above are data-driven and can only be assessed at the time of marketing authorisation. However, what is clear is that some of the issues commonly identified could have been addressed at the time of development through regulatory and scientific advice, whose compliance has been shown to be associated with higher success rates of MAAs.

Profile of assistance to SMEs active in biologics and advanced therapies
Regulatory aspects of developments may have an enormous impact on regulatory compliance because they interweave with aspects ranging from manufacturing through nonclinical and clinical requirements. Addressing them is essential, in particular in view of the limited number of products in the pipeline of SMEs.

It is known that smaller structures with limited resources are disadvantaged compared with larger organisations with regard to the capacity to navigate the required regulatory procedures and performing a regulatory intelligence data-gathering exercise. It is often put aside when conflicting priorities emerge during the preparation of regulatory submissions for development programs or submissions. In comparison with large, multinational companies, SMEs generally have limited or no regulatory affairs staff and find it particularly difficult to define their regulatory strategy with this lack of experienced staff in regulatory affairs.

The SME Regulation introduced the concept of an office – the SME Office – as a support mechanism dedicated to providing regulatory assistance to SMEs in light of the regulatory constraints that small structures might be facing. One of the core activities of the SME Office is to respond to queries from SMEs on a broad range of administrative or regulatory topics within the framework of the pharmaceutical legislation (see Table 1).

To date, SMEs developing biologics or ATMPs have benefited from at least 246 direct assistance through the programme. The assistance has varied from queries on finding relevant regulatory and scientific guidance, to how to interpret and comply with it and thus contribute to more effectively designing successful regulatory strategies and development plans. Scientific issues and topics can also be addressed depending on their complexity, with validation of development plans routed through scientific advice.

SME briefing meetings, which are offered free of charge, are a specific type of regulatory assistance to enterprises which are unfamiliar with the EU regulatory approval process. They allow a company to have an early dialogue with the EMA on its planned regulatory strategy or discuss how to prioritise regulatory procedures to support the development programme, dossier preparation and submission. The topics raised can be multiple, and the meetings are attended by a multidisciplinary EMA team depending in the issues raised, with ad-hoc support from representatives of the agency’s scientific committees. This platform for early dialogue may be instrumental for some companies, that in they can receive clarification on the impact of legislation to better structure their regulatory strategies and development plans. It eventually contributes to the overall due diligence of their regulatory strategies, development plans and dossier submissions.

Conclusion
The important role SMEs play in terms of R&D as engines to spur pharmaceutical innovation in the EU is acknowledged. A favourable European framework for SMEs in the pharmaceutical sector has been in place at the European level over the past ten years. The programme has been particularly important in providing targeted information and supporting SMEs in overcoming potential regulatory hurdles leading up to marketing authorisation.

Scientific platforms such as briefing meetings with the EMA Innovation Task Force, or scientific advice, have been a mainstay for initiating a scientific dialogue with regulators early in a product’s development. They have contributed to the scientific due diligence process, with the ultimate goal of de-risking developments programmes, and minimising delays in product authorisations.

SMEs, particularly in the biologics and advanced therapies fields, are highly innovative, often academic spin-off structures with constrained resources. Their size directly impacts on their capacity to navigate the required procedures, address regulatory aspects of development programmes and implement effective regulatory intelligence strategies.

Platforms for dialogue such as those introduced by the SME Regulation have created new opportunities for SMEs to engage with regulators. They have not only provided a means to address the gap in regulatory knowledge experienced by smaller business structures, but more importantly helped them to strengthen their regulatory due diligence process. Ultimately, they have contributed to the increasing role of regulatory authorities as facilitators and enablers, contributing to better informed drug development programmes, which in turn are less likely to be summarily rejected on grounds of methodological issues or poor design.

Disclaimer
The views expressed in this article are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

References
Anja Holm, CVMP Chair, discusses striking the right balance between scientific detail and pragmatism when authorising veterinary medicines. Interview conducted by Dr med vet Birgit Roser

Q: Could you tell our readers a bit about your background, what attracted you to the regulatory arena and how you came to join the Danish Health and Medicines Authority (DHMA)?

A: I graduated in veterinary medicine (DVM) from Copenhagen University in 1994 and worked in veterinary practice for four years. However, a student job at Lundbeck and an interest in pharmacology and immunology had sparked my curiosity about this field. In 1998, I took on a role at the Danish Medicines Agency as a clinical assessor of pharmaceuticals and vaccines. The job covered the development of the veterinary side of our pharmacovigilance scheme, which introduced me to the European regulatory network and the interesting work coordinated by the European Medicines Agency (EMA).

After a number of years as a clinical assessor and pharmacovigilance expert, and a year in DNA vaccine research, I became the Danish member of the EMA's Committee for Medicinal Products for Veterinary Use (CVMP) in 2004. As a member of the Committee, I have been Rapporteur for several products in the centralised procedure, leading a team of assessors and the discussion to final conclusions. Over the years, I have added education in regulatory science, communication, negotiation and management to my academic qualifications to meet the expectations in a constantly developing job.

Q: What does your current role involve, and what are your favourite aspects of this role?

A: As Chief Advisor in the Department of Medicines Authorisation and Availability, I have a broad range of responsibilities. The main role is as Chair of CVMP, of course, and that occupies most of my workdays with interesting and challenging scientific and strategic issues. As CVMP Chair, I also represent EU regulators in the Steering Committee for the Veterinary International Conference on Harmonisation (VICH). I participate in the EMA's Scientific Coordination Board, in the CVMP’s Strategic Planning Group and other coordinating and visionary roles, which I enjoy a lot. For the Danish agency, I have been a member of the Danish Antibiotics Board since its inception, and of the European Surveillance Strategy (ESS) – a pharmacovigilance subgroup of the Heads of Medicines Agencies (HMA). In addition, I am the so-called national training champion for assessor training, which gives me the opportunity to use my broad experience and have many rewarding contacts both inside and outside the agency.

Q: You have been the CVMP Chair since 2010 – could you explain what your main role is on this Committee?

A: Together with the EMA secretariat, I prepare and run the committee meetings where we discuss the assessment reports for new product applications, variations, referrals, etc, and adopt guidelines, reflection papers and regulatory decisions. A specific veterinary field is the evaluation of food safety for consumers of animal products like meat and milk, after the animal has been treated with medicines. This is a separate toxicological and exposure assessment resulting in a maximum residue level (MRL) for each substance, so the farmer can be sure he does not deliver unsafe milk or meat. The environmental risk assessment for veterinary medicines is also a lot more complex than for human medicines, because animals may be raised and treated directly in the environment.

The committee consists of more than 30 highly skilled and experienced members from the EU member states, who meet for three days every month. My job is to lead the discussions, uncover any differences in opinion, facilitate solutions and compromises and finally reach a decision or vote. This process is challenging, exciting and very interesting, also because we work with all the novel therapies and concepts developed by companies for the veterinary field, and because we have to handle the referrals where we must take a common EU decision on products for which national member states have expressed diverging views. Striking the right balance between scientific detail and pragmatism, between different cultures, opinions and personalities can be hard work and requires concentration, endurance and good humour to overcome the differences in a friendly atmosphere. The enthusiasm, knowledge and efforts invested by the committee members are impressive and I never stop admiring the capacity and dedication of these busy people. The CVMP also has ten working parties – two of them joint with the Committee for Medicinal Products for Human Use (CHMP) – and we task them to develop guidance and other documents in their relevant scientific or regulatory field. Progressing the committee and specific areas of importance requires strategic thinking, exchanges and reflections to keep the focus and momentum in our work. It is my last year as Chair, and I am grateful to have received the trust and support of the CVMP members and the incredible help of the EMA secretariat over the past five years.
Q: How is the CVMP affected by the increasing requirements for transparency in regulatory processes?

A: The EMA's transparency policy requires that the agendas and minutes of the CVMP's meetings are published and generally we see no problem in that. However, the text is carefully written because companies have legitimate commercial interests in keeping their projects confidential until the marketing authorisation (MA) is granted. We are also very aware that our assessment reports are scrutinised around the world, so they must be clear, consistent and scientifically robust with balanced decisions resting on our legal basis. One of my main priorities is to increase the transparency and predictability of the committee's decisions, because companies should be able to direct their investments to the right studies and projects to ensure their product applications will be successful in the end.

Q: What do you expect from the upcoming new veterinary medicines legislation? How does this impact on the work of the CVMP, and how do you feel it is affecting industry?

A: The European Commission aims for a complete revision of the legislation to ensure that a lot of the administrative burden is relieved from industry, for example by deleting the requirement for periodic safety update reports (PSURs) and renewals. The centralised procedure will be opened to all new products, whether novel, standard or generic, and an enormous initiative has been proposed to harmonise all existing summaries of product characteristics (SPCs) across similar products. On the other hand, limitations in authorisation and use of certain antibiotics, stricter requirements for the 3Rs (reduction, refinement and replacement of animal trials) compliance and decreased involvement of member states in assessment is also part of the proposal. If worked on the human side, I would keep an eye on the development of this piece of legislation.

There is also serious concerns expressed on the sustainability of the system and the workload transferred to the competent authorities, in particular since the resources on the veterinary side are so much less. The new veterinary legislation is an extremely essential tool for us, for the veterinary society, agriculture and for the pharmaceutical companies, and it is of utmost importance that we strike the right balance now.

Q: What is the average length of time it takes the CVMP to assess marketing authorisation applications (MAAs) and approve applications, variations and renewals?

A: The CVMP and the EMA's secretariat always keep to the timelines given in legislation, ie, 210 days for an MAA excluding the clock stop, and we know that predictability of the procedures is necessary for company planning. However, if an application is submitted prematurely with outstanding issues which need further documentation or explanation, then there may be long clock stops in the procedure, so that the applicant can improve the dossier to fulfil the requirements. The better the dossier, the smoother it goes through the assessment process. Therefore I think that more companies should make use of the scientific advice option – and follow the advice they get – because that will definitely reduce the risk for refusal or the request for additional late studies and delays.

Q: What do you see as the biggest challenges facing the CVMP in the next five years? What are your key objectives?

A: The new legislation and the potentially huge workload on the CVMP will be a major challenge. This relates not only to the increased assessment work on new products or on existing products that would be up for harmonisation, but also the impact from changing guidelines, referral procedures and international work.

The topic of antimicrobial resistance has been in focus for many years now and the CVMP has already done a lot in this field, and this will continue to be high on the agenda for many years to come. The environmental risk assessment and the focus on potentially long-term harmful substances is a challenge that is increasing in several EU agencies at present.

Improving availability of products for minor use and minor species (MUMS) in the veterinary field is one of my key objectives, because there is a high need for authorised products for species like ducks, rabbits and goats. The unmet treatment needs relate to several factors, eg, the many different animal species with their individual diseases and production systems, geographical diversity in disease distribution across the EU, the need for adequate food safety and environmental safety and the cost of studies, authorisation and surveillance relative to the expected return on investment for the MA holder. The CVMP will continue to work to extrapolate MRL values to more species where possible, and to designate intended MUMS products to be eligible for reduced data requirements and even for financial incentives, such as free scientific advice and fee reduction if the product is for food-producing species.

Q: What have been the CVMP key successes to date? What have you been most proud of?

A: The transition to a highly efficient, professional scientific committee while keeping up with the increasing workload and complexity of products has been a major achievement over the years. In relation to antimicrobial resistance, the committee and its connected groups have made an enormous contribution to the regulatory input regarding prudent use of antibiotics in veterinary medicine. Over the past five years, more than eight guidelines and reflection papers have been published and more than 20 referrals related to antimicrobial products have been concluded, with increased collaboration established with the Commission, the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA), the World Organisation for Animal Health (OIE), and the World Health Organization (WHO) in this area.

Likewise, I am particularly proud of the successful and respectful cooperation we have developed, involving many different scientists with profound expertise in their fields and competent assessor teams.

The promotion of structured workplans and strategies for projects outside our normal business has made it possible to keep these many projects organised and reaching their goals. For example, the development of the benefit–risk concept for the veterinary field, the injection-site issue, advancing the 3Rs initiative, structuring our input and influence on the international discussions on antimicrobial resistance, and moving towards more proactive management of novel therapies and scientific advice... to name but a few!

Q: What do you think will be the most important issues the CVMP will face in the next five years?

A: Increased global cooperation, the new legislation and prudent use of antimicrobials are easy suggestions. For many other issues, it is difficult to answer because the content of the work with authorisation of new medicines relies on company plans. It requires both in-depth and widespread scientific knowledge from the assessors, who have to be up to date in several academic fields so they can match the level of the industry and deliver a critical and robust assessment. It
Meet the regulators – interview

“I hope that companies will use the option of scientific advice more often, so that dossiers will be complete from day one”

is of course challenging to maintain this position and the European regulatory network has recently started an initiative to coordinate the training of assessors between agencies, which will influence the CVMP as well. It is also my hope that companies will use the option of scientific advice more often, so that dossiers will be complete from day one, the assessment will be straightforward and the applicant will avoid requests for new studies during the procedure.

Q: If you could change one thing about the CVMP tomorrow, what would it be?
A: I would grant CVMP members all the time and support from their home offices that they could dream of! Having said that, it is a privilege to have a job where every week offers new insights and where it is possible to influence the direction of development for veterinary medicinal products in the EU. Even more than that, it is a privilege to work together with so many highly professional people, who are so good at what they do. After each CVMP meeting, I look back over the decisions we have made and the progress during the meeting and it is crystal clear that cooperation improves the outcome. The results that the committee achieves together are much better than the sum of what we could do individually.

Q: On a professional level, who has influenced you most, and why?
A: On a professional level, Professor Christian Friis from the veterinary faculty in Copenhagen was an inspiring (and tough) teacher in pharmacology and toxicology when I was a vet student. I have been lucky to be able to draw on his enormous insight in this field when I started at the CVMP, and through all the years of his long membership on the committee. We have shared many interesting talks and good laughs over the tables at the EMA and I thank him for showing me how to cut straight to the core of the matter.

On a career level, Jytte Lyngvig, the former Director of the Danish Medicines Agency, has been an inspiring leader to follow. I always enjoyed watching her navigate to advance a topic and interacting in groups, where she worked constantly for the benefit of the employees and the responsibilities of our agency. From her I learned that the better the dialogue, the better the chance of a good result – and that even a small agency can play a large role if we help each other through good dialogue.

Q: And finally, on a more personal note, what was the last book you read?
A: The Organized Mind by Daniel J Levitin. He explains the scientific background for how the human brain works in complex situations and how we can help it cope with the information overload in our modern world. It was a gift from my husband and I still wonder if he was trying to tell me something!

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Alternatively the 3-day Medical Devices Introductory Course provides an in-depth understanding of the specialty, which takes place 22–24 June 2016.
PSUR repository – Interactive Q&A session

A webinar hosted by the European Medicines Agency for marketing authorisation holders and industry members outlined the new functionality of the PSUR repository. Reported by Navila Rehman, Principal Consultant, Onix Life Sciences, UK

Introduction
This web-based seminar, entitled “Interactive Q&A Session with MAHs on the New Functionality Provided in Releases v1.03.00 and v1.04.00”, was held by the EMA late last year in London, UK.

The eSubmission Gateway version of the periodic safety update report (PSUR) repository is currently in the process of being enhanced by using an xml delivery file created via the user interface. The use of the xml delivery file has been mandatory since 1 September 2015, and replaces the current file-naming convention. There has been much emphasis on user acceptance testing (UAT) testing by the end-users (marketing authorisation holders (MAHs) and national competent authorities (NCAs). The EMA’s Kristiina Puusaari shared key points, hosted questions for clarification and received suggestions for consideration from industry users.

The PSUR repository is mandated by legislation (Article 107b paragraph 1 and Article 28(2), Regulation 726/2004). It will serve as a secure electronic submission point for all PSURs. The main objective of the PSUR repository is to simplify the PSUR process to benefit industry and to streamline submissions access for EU member states and assessors. The repository will hold the PSUR, PSUR assessment reports and documents supporting the evaluation process and final outcome. The use of the PSUR repository will become mandatory for all PSURs from 13 June 2016, after which PSURs should only be submitted to the repository via the eSubmission Gateway.

The repository will include all PSURs following the PSUR single assessment (PSUSA) and those PSURs which are not part of a single assessment. Where the PSUR is included in a single assessment and covers multiple products with different registration types (eg, format and/or lifecycle), these submissions should still to be sent to the PSUR repository. The repository will replace all individual PSUR submissions to all NCAs, and once the use of the repository is mandatory the only source of the PSUR is the repository. All NCAs will in future retrieve all PSURs, including nationally authorised product (NAP) PSURs, from the repository only.

There has been much emphasis on UAT by industry users, and a summary of the main changes following releases v1.03.00 and v1.04.00 is provided here:

- Multiple electronic common technical document (eCTD) products can now be selected on a single xml delivery file for products with harmonised eCTD lifecycles (mutual recognition/decentralised procedures – MRP’s/DCPs).
- Multiple PSURs for different products contained in the same PSUSA procedure can now be submitted using xml delivery files without failure.
- Non-sequential submissions of PSURs for the same PSUSA procedure can now be submitted.
- A major change to the product selection functionality, where only products containing the relevant active substance(s) is now displayed in the product selection window. This limits the available products to those in scope. There is no more “product short name” search for EU PSUSA, thus removing limitations for generic products and for product search due to language differences.
- Ability to indicate “associated” submissions – ie, to be used when one single PSUR covers multiple products with individual eCTD lifecycles. This functionality allows “deduplication” of submissions for NCA reviewers.
- A new mandatory field has been introduced with the addition of MAH contact email address.

The webinar served to answer questions raised by industry during the training sessions on the creation of the xml delivery file and to whom the PSUR is to be submitted prior to the mandatory use. Key points covered are summarised below.

Product selection
The MAH should check the EU reference date (EURD) list which confirms the PSUSA number of the procedure. This PSUSA ID holds the metadata, for example the member state, details of the rapporteur, submission deadline, international nonproprietary name (INN) and active substance. Prior to the creation of the xml delivery file, it is the responsibility of each MAH to ensure that their product is up to date in Article 57. This should be done well in advance of any PSUSA procedure and must be done prior to the procedure data lock point (DLP).

The key function of the user interface is to select all the products for which the PSUR is being submitted. The product listing and product information is read directly from Article 57. The majority of products are displayed through real-time view to Article 57 (with overnight update for any changes). In cases where the product cannot be found, it is likely that the entry into Article 57 is incorrect or missing. The EMA must be contacted well in advance of the submission deadline to ensure the products are included in the procedure scope.

Occasionally some products might not be available and EMA (PSUR repository team) may advise selecting only the available products and indicate in the cover letter that some products are missing. Where the package has already been submitted to the relevant NCAs and the cover letter cannot therefore be updated, the PSUR repository team will inform the product team, including the Pharmacovigilance Committee (PRAC) Representative/lead member state of the technical issue so that the missing products are included in the procedure scope, even though not stated in the xml delivery file. In such circumstances, the MAH should ensure they are able to provide proof of the submission (common European submission portal (CESP) receipt) to the relevant NCAs.

In cases where the product is entirely missing, this may be due to incorrect legal basis. The majority of PSURs for generics, well-established use, homeopathic and herbal medicines products do not have to be submitted as they are exempt, but in some cases there may be an obligation where certain active substances are involved. The EURD list should be checked to see whether there is a requirement to submit Article 10(a), 10a, 14 or 16a products. It is imperative that the Article 57 database is therefore up to date.
Table 1: PSUR submission prior to mandatory use.

<table>
<thead>
<tr>
<th>CAPs:</th>
<th>To all member states in which the medicinal product has been authorised</th>
<th>To the lead member state appointed for the procedure (even if the product is not authorised in that member state)</th>
<th>To the PRAC rapporteur, i.e., the person named in the EURD list</th>
<th>To the EMA via eSubmission Gateway/Web Client including xml delivery/file created in the PSUR repository user interface</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed CAP/NAP&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td>PSUSA procedure:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSUSA procedure:</td>
<td>Yes&lt;sup&gt;(b)&lt;/sup&gt;</td>
<td>N/A</td>
<td>Yes&lt;sup&gt;(b)&lt;/sup&gt;</td>
<td>Optional, but strongly recommended before the mandatory use</td>
</tr>
<tr>
<td>(a)NAPs include products authorised via mutual recognition procedure (MRP), decentralised procedure (DCP) and national procedure.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b)The submissions should be sent as per the “Requirements on submissions for periodic safety update reports” to national competent authorities (NCAs) for products authorised via national procedures, MRP and DCP (NAPs).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Where the MAH creates the xml delivery file with an incorrect or additional product(s), the EMA procedure assistant/procedure managers must be informed so they can ensure that the correct scope is reflected.

**Grouping of associated submissions**

The EMA encourages harmonising the product lifecycles across all products, to reduce the number of duplicate submissions. Grouping of associated submissions will indicate to the NCAs that certain submissions contain the same PSUR, thus reducing NCA workloads as they will not need to download all submissions, but only those that are relevant to them. Where a single PSUR document has been prepared by the MAH covering multiple different products that have their own eCTD or mixed eCTD/non-eCTD electronic submission (NeeS) lifecycles, and with the correct use of the “group ID” functionality in the creation of the delivery file, the NCA will be able to see that the submissions contain the exact same document. For example, in the simplest case the MAH may have a duplicate centrally authorised product (CAP) in eCTD format; in this case a submission for each product will need to be made but the MAH will be able to indicate in the xml delivery files that the two submissions contain the same PSUR document or response document. Therefore the functionality can be used for both the initial and supplementary information. However, it is important to note that the same group ID must not be used for supplementary information as this does not contain the same information/documents as the initial PSUR. Therefore a new group ID should be generated.

The MAH should be aware that even though different formats can be associated to each other, the submission still needs to be sent separately. An eCTD and NeeS submission must not be included in the same submission package. Multiple different xml delivery files and multiple different packages will still need to be submitted.

The group ID functionality would rarely be used for multiple associated NeeS submissions. It is possible to create one single xml delivery file covering all different NeeS products and indicate the sequence number for each NCA.

**Submission deadline**

One of the validation business rules concerns the legally binding submission deadline. Should the MAH pass the deadline then the user interface will no longer offer the MAH the PSUSA. It is imperative to ensure timely submission as mandated by the legislation and as stated in the EURD list. If the submission deadline is missed, for any reason, and the xml delivery file cannot be created, the MAH should contact the EMA to check if the product can still be included in the procedure. Under exceptional circumstances, the EMA can prepare a delivery file and provide this via email to enable the submission to be...
There is no change to this practice. When supplementary information is submitted after the PRAC adoption; this is currently provided via Eudralink and does not include updated product information (PI) which is requested sequences from the MAHs, such as responses, comments, etc. This includes all follow-up submissions. As a future enhancement, could you append the product name/unique identifier to the delivery XML file for it to clearly show which submission it is associated with? Can I submit to the PSUR repository on behalf of my local representatives? Regarding the cover letter, are local affiliates able to submit their own cover letters? Or does this mean that the cover letter submitted through the repository should then be circulated locally for all submissions? Is there a possibility to see how many countable units have to submit a PSUR to calculate the fee for each MAH? When a risk management plan (RMP) is part of the PSUR submission, will RMP be accepted/rejected? And how will the applicant learn of its status? Is the EMA providing any portal or link for MAHs to check upcoming MAH submissions? Table 2: Key questions raised during the meeting and clarifications by the EMA on the PSUR repository.

<table>
<thead>
<tr>
<th>Question</th>
<th>EMA response</th>
</tr>
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<tbody>
<tr>
<td>We had an experience while dispatching an MRP submission. We created delivery file with all the countries’ details, nut when we received acknowledgement, it showed only first-country details. Is this a normal acknowledgement? Is the EMA looking to modify it?</td>
<td>This has been raised to the technical development team, however as the Gateway acknowledgments and the PSUR repository delivery files are different and generated by different systems, this will need to be carefully considered.</td>
</tr>
<tr>
<td>As a future enhancement, could you append the product name/unique identifier to the delivery XML file for it to clearly show which submission it is associated with?</td>
<td>This has been logged as a “new change request” to the system. All new change requests will be prioritised by the PSUR Repository Advisory Group (PRAG) and implemented in future releases if considered necessary/useful.</td>
</tr>
<tr>
<td>Can I submit to the PSUR repository on behalf of my local representatives?</td>
<td>Many companies/MAHs like to centralise the sending of submissions, including PSURs – the eSubmission Gateway/Web Client and the PSUR repository allow submissions on behalf of other MAHs/local representatives. There are no restrictions in place on the submissions on behalf of another MAH or submissions by a consultancy or CRO [contract research organisation]. Supplementary information submissions/submissions of responses can be made directly by the local offices even if the “initial” PSUR was submitted by a third party.</td>
</tr>
<tr>
<td>Is there a possibility to see how many countable units have to submit a PSUR to calculate the fee for each MAH?</td>
<td>For information on pharmacovigilance fees and the advice note, please review the section “Calculating the fee” on the “pharmacovigilance fees payable to the EMA” website. Also view the Q&amp;A on the pharmacovigilance fees, and if you have any specific fee-related questions you can submit them to the EMA using the “EMA Fees Query Form”.</td>
</tr>
<tr>
<td>When a risk management plan (RMP) is part of the PSUR submission, will RMP be accepted/rejected? And how will the applicant learn of its status?</td>
<td>RMPs should not be submitted as a part of PSUR submission. The PSUSA covers only the PSURs, and if an RMP is included in the submission it might be overlooked/ignored and it will not be assessed. This might lead to issues, as the RMP submission has not been considered received. We strongly recommend submitting all RMP submissions as separate lifecycle sequences. RMPs are allowed to be submitted for some CAPs.</td>
</tr>
</tbody>
</table>

made. In such cases the MAH should provide the following:

- The procedure number (eg, PSUSA/00001234/201509)
- Submission format (eCTD or NeeS)
- The list of product names/presentations/strengths to be included, ie, the Annex I
- Sequence number(s)
- Applicant (senders) routing ID
- Contact email address.

Supplementary information

Any PSUR-related submission after the initial PSUR submission for which a “success acknowledgement” has been received should be submitted as “supplementary information”. This includes all follow-up sequences from the MAHs, such as responses, comments, etc. This does not include updated product information (PI) which is requested after the PRAC adoption; this is currently provided via EudraLink and there is no change to this practice. When supplementary information is selected it is possible to select the PSUSA procedure number from the PSUR repository interface for which the submission deadline has passed.

Submission of PSURs prior to mandatory use

During the transitional period and prior to mandatory use, there is no change to the existing rules for submission to the NCA for both pure single NAPs and products included in PSUSA procedure. It is important to note that once the mandatory use begins on 13 June 2016 there should be no submissions to the NCAs. All PSURs should be submitted to the PSUR repository only. Table 1 summarises to whom the submission is to be submitted to prior to mandatory use. Furthermore, to check whether the product is included in CAP/NAP or NAP/NAP PSUSA procedure, the information is available in the last two columns of the right-hand side of the EURD list (see Figure 1) under column headings “CAP” and “NAP”. If the column for CAP is empty, as in the top row of the example, your procedure is NAP/NAP. If both
columns are filled, as the middle row in the example, your procedure is mixed. The procedure contains CAPs only where CAP field is filled.

**Key tips**

To avoid submission problems, key tips include the following:

- Where the product cannot be found from the dropdown menu, check the entry in Article 57 database and add/edit Article 57 database. If there are errors in the product information/name/numbers, log in to Article 57 to make changes/updates.
- Always double-check that the correct EMEA/H/C number in six-digit format has been entered for all CAP products. This number is visible in the “EMEA Product/MRP/DCP number” field. If the number is missing or in incorrect format, this should be added/amended.
- Check that the correct senders routing ID is entered in the xml delivery file. If the applicant (senders) routing ID is incorrect/missing, no receipts or acknowledgements will be sent from the system.
- Do not rename the delivery file.
- Ensure the xml delivery file is in the correct place in the folder structure. This file should be placed at the root level folder. There should not be any additional empty folders at the top level.
- Submissions should be compressed before transmission as a zip file. When creating the zip, ensure that the submission folder (e.g., 0017), the xml delivery file and, if applicable, the working documents folder are in a root folder and then create the zip.
- Only one package and delivery file should be included per zip file. The zip file can be renamed in accordance with the guidance provided in “Annex 3 PSUR filenames for repository submissions when using the xml approach”. File names are not validated for PSUR repository submissions via the Gateway/Web Client.
- Do not add NeeS submissions inside eCTD zip file or on the same delivery file and vice versa.
- Use the “Advanced Mode” for all transmissions via the Web Client, as well as for submissions smaller than 10MB to receive the “Acknowledgements from the eSubmission Gateway / Web Client”. A summary of key questions raised during the webinar, along with EMA responses, is provided in Table 2.

**Summary**

The UAT for release v.1.05.00 had no further change requests and identified defects have been resolved. The release therefore remains on target for the end of December 2015 and “go-live” in January 2016.

The release of v.1.06.00 is scheduled for Q2 2016 and will be the last planned release prior to the mandatory use of the repository on 13 June 2016. The EMA has strongly recommended that submissions should already be provided to the repository even though the use is not yet mandatory. This gives all parties an opportunity to experience the use of the repository prior to the mandatory use, and also gives an opportunity to detect any further technical/business process issues that can be rectified in time before the mandatory use.

It was clear from this webinar that much work has been done on the PSUR repository and that there will be many benefits to industry in providing a single submission point of PSURs. The emphasis being that eventually there will no longer be the need to submit individually to each NCA where the product is authorised.

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- A brief abstract of 100–200 words should be provided at the top of the article, together with key words which summarise the main theme(s) of the paper.
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The Vancouver style of referencing should be used (see examples below). References to journal articles, books and monographs should be listed as follows:


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References to websites and online databases should be as follows:

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- The full title of the document cited as a journal article
- The date of the document’s publication or last revision (if known)
- The full web address (URL)
- The date the author(s) visited the website, in parentheses, eg. (accessed 1 January 2016).

Reference numbers should be inserted in superscript at the appropriate places in the body text, with the full citations in a separate section entitled “References” at the end of the article.

Footnotes should not be used. It is usually possible to incorporate the information in the body text, or as a reference at the end of the article.