Orphan medicinal products –
A European process overview

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Abstract
Since the inception of EC Regulation 141/2000, there has been a steady increase in the number of orphan medicinal products (OMPs) available in today's EU markets. This article looks at how regulatory innovation has enabled these products to reach the patient in an accelerated fashion, while delivering robust safety and efficacy standards. It also aims to provide a glimpse of advances to current legislation aimed at not only strengthening public trust in the EU regulatory systems, but also improving patient access to medicines especially for the rarest of diseases.

Introduction
With the advances in biopharmaceutical research and development (R&D), enormous progress has been made with the enhancement of preventative, diagnostic and treatment measures of a great number of diseases. Despite these advances, a number of diseases remain untreated, or are still persistent around the world. Thanks to better technology and improved infrastructure, some of these diseases have become manageable and “under check”. There are however, diseases that are uncommon, many of which have debilitating and/or life-threatening effects. These diseases generally affect relatively few people in a wide population and are commonly referred to as orphan (rare) diseases.

For a disease to be designated as orphan, the following criteria must be met:

1. Seriousness of the disease/condition
2. The rarity of the condition (affecting no more than five in 10,000 people in the EU) or evidence of insufficient return in investment
3. Seriousness of the disease/condition
4. The existence of alternative methods of prevention, diagnosis or treatment
5. The rarity of the condition

The orphan designation is not to be granted at any stage in the medicine’s development. Opinions for designations are based on the following criteria:

1. The rarity of the condition (affecting no more than five in 10,000 people in the EU) or evidence of insufficient return in investment
2. Seriousness of the disease/condition
3. The existence of alternative methods of prevention, diagnosis or treatment
4. The rarity of the condition
5. Seriousness of the disease/condition

The medicinal products are under investigational review, thus positive opinions on orphan drug designations are formed only on the basis of potential activity (ie, the product’s eligibility for an MAA via a positive benefit–risk balance, efficacy, good risk management plan (RMP), etc). An orphan designation does not obviate the need for a marketing authorisation. Therefore, all drugs designated as “orphans” must demonstrate satisfactory quality, safety and efficacy and undergo regulatory review before they can be granted a marketing authorisation (MA).

Because the numbers of test subjects are extremely low, data to be included in the dossier for the analysis and evaluation of the MAA of orphan products are not readily available. Careful planning is encouraged to ensure harmonised and uniform data are presented for analysis and evaluation by the Committee for Human Medicinal Products (CHMP) during this phase. As part of the incentives engineered to aid in the R&D of orphan medicines, the European Medicines Agency (EMA) has provided scientific advice for orphan-designated products to ensure any proposed deviations from regular procedures are discussed and decided on with EU regulators during the medicine’s development. Sponsors should submit annual development reports summarising the status of the development of the medicine, including reviews of all ongoing clinical trials, preview of proposed investigations, and a list of anticipated or current problems in the process, difficulties in testing and potential changes that may have an impact on the medicine’s orphan designation.

The EU, under the umbrella of a single government entity, introduced the orphan Regulation – EC Regulation 141/2000 – in 1999. The Regulation has steadily gathered momentum and has helped introduce incentive systems or procedures with the primary purpose of promoting and encouraging orphan drug development.

Though patients still face delays in access to the improved treatments, these incentives have helped raise the availability of OMPs from eight in 2000 to 107 in 2011, 148 in 2012 and more than 150 in today’s EU markets.

From an EU perspective, OMPs are designated by the European Commission on receipt of a positive opinion from the selected regulatory body – the Committee for Orphan Medicinal Products (COMP) – via a process commonly known as orphan drug designation (ODD). ODD can be granted at any stage in the medicine’s development. Opinions for designations are based on the following criteria:

1. The rarity of the condition (affecting no more than five in 10,000 people in the EU) or evidence of insufficient return in investment
2. Seriousness of the disease/condition
3. The existence of alternative methods of prevention, diagnosis or treatment
4. The rarity of the condition
5. Seriousness of the disease/condition
Focus – Orphan drugs

Marketing submissions and authorisations

The submission strategy for any given product is dependent on the nature of the product, target indication(s), history of the product and the marketing plan. MAAs for orphan products are filed using the centralised procedure. Of note is the fact that though hundreds of orphan designations are approved per year, only a small number of these products make it to the market.

A list of orphan-designated products authorised (date of EC Decision) in the EU from 2006–2013 is provided in Table 1 and illustrated in Figure 1.

OMPs by virtue of their use in the treatment of rare diseases can be eligible for EU licensing flexibilities while still under the centralised procedure. It is important to note however that these licensing flexibilities are not solely for OMPs, but due to their unique position (used in the diagnosis and treatment of rare diseases – predominantly unmet medical conditions), they are normally prioritised and/or meet most of the eligibility criteria in such licensing flexibilities. OMP sponsors are encouraged to seek EMA advice prior to submission on the justification for applying for an MA under any of these licensing flexibilities. Scientific advice can be sought on the limitations imposed by the rarity of the disease and the collection of comprehensive data on safety and efficacy, but not on the ethical issues that arise from collecting such data.

Accelerated assessment

The objective of accelerated assessment is to help speed up the development and availability of drugs that treat serious diseases; demonstrating that they are of “major public health interest, in particular from the viewpoint of therapeutic innovation” (Article 14(9) of Regulation (EC) 726/2004). The criteria for requesting submission for accelerated assessment are as follows:

- Justification that the medicinal product is of major public health interest
- Demonstration of therapeutic innovation
- Submission of a Letter of Intent by prior notification (allow around 70 days or more prior to MAA)

Table 1: Orphan medicines authorised in the EU between 2006 and 2013.

<table>
<thead>
<tr>
<th>Medicinal product (brand name)</th>
<th>Approval year</th>
<th>Approval type</th>
<th>Medicinal product (brand name)</th>
<th>Approval year</th>
<th>Approval type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exjade</td>
<td>2006</td>
<td>Regular approval</td>
<td>Mepact</td>
<td>2009</td>
<td>Regular approval</td>
</tr>
<tr>
<td>Evoltra</td>
<td>2006</td>
<td>Exceptional approval</td>
<td>Mozobil</td>
<td>2009</td>
<td>Regular approval</td>
</tr>
<tr>
<td>Myozyme</td>
<td>2006</td>
<td>Regular approval</td>
<td>Nplate</td>
<td>2009</td>
<td>Regular approval</td>
</tr>
<tr>
<td>Naglazyme</td>
<td>2006</td>
<td>Regular approval</td>
<td>Peyona</td>
<td>2009</td>
<td>Regular approval</td>
</tr>
<tr>
<td>Nexavar</td>
<td>2006</td>
<td>Regular approval</td>
<td>Arzera</td>
<td>2010</td>
<td>Conditional approval</td>
</tr>
<tr>
<td>Savene</td>
<td>2006</td>
<td>Regular approval</td>
<td>Tepadina</td>
<td>2010</td>
<td>Regular approval</td>
</tr>
<tr>
<td>Sprycel</td>
<td>2006</td>
<td>Regular approval</td>
<td>Vpriv</td>
<td>2010</td>
<td>Accelerated approval</td>
</tr>
<tr>
<td>Atriance</td>
<td>2007</td>
<td>Exceptional approval</td>
<td>Esbriet</td>
<td>2011</td>
<td>Regular approval</td>
</tr>
<tr>
<td>Cystadane</td>
<td>2007</td>
<td>Regular approval</td>
<td>Plenadren</td>
<td>2011</td>
<td>Regular approval</td>
</tr>
<tr>
<td>Diacomit</td>
<td>2007</td>
<td>Conditional approval</td>
<td>Tobi Podhalar</td>
<td>2011</td>
<td>Regular approval</td>
</tr>
<tr>
<td>Elaprase</td>
<td>2007</td>
<td>Exceptional approval</td>
<td>Votubia</td>
<td>2011</td>
<td>Conditional approval</td>
</tr>
<tr>
<td>Glolan</td>
<td>2007</td>
<td>Regular approval</td>
<td>Vyndaqel</td>
<td>2011</td>
<td>Exceptional approval</td>
</tr>
<tr>
<td>Inrelex</td>
<td>2007</td>
<td>Exceptional approval</td>
<td>Aducetris</td>
<td>2012</td>
<td>Conditional approval</td>
</tr>
<tr>
<td>Inovelon</td>
<td>2007</td>
<td>Regular approval</td>
<td>Bronchitol</td>
<td>2012</td>
<td>Regular approval</td>
</tr>
<tr>
<td>Revlimid</td>
<td>2007</td>
<td>Regular approval</td>
<td>Dacogen</td>
<td>2012</td>
<td>Regular approval</td>
</tr>
<tr>
<td>Siklos</td>
<td>2007</td>
<td>Regular approval</td>
<td>Glybera</td>
<td>2012</td>
<td>Exceptional approval</td>
</tr>
<tr>
<td>Soliris</td>
<td>2007</td>
<td>Accelerated approval</td>
<td>Jakavi</td>
<td>2012</td>
<td>Regular approval</td>
</tr>
<tr>
<td>Tasigna</td>
<td>2007</td>
<td>Regular approval</td>
<td>Kalydeco</td>
<td>2012</td>
<td>Accelerated approval</td>
</tr>
<tr>
<td>Torisel</td>
<td>2007</td>
<td>Regular approval</td>
<td>Nexobrid</td>
<td>2012</td>
<td>Regular approval</td>
</tr>
<tr>
<td>Yondelis</td>
<td>2007</td>
<td>Exceptional approval</td>
<td>Revestive</td>
<td>2012</td>
<td>Regular approval</td>
</tr>
<tr>
<td>Ceplene</td>
<td>2008</td>
<td>Exceptional approval</td>
<td>Signifor</td>
<td>2012</td>
<td>Regular approval</td>
</tr>
<tr>
<td>Firazyr</td>
<td>2008</td>
<td>Accelerated approval</td>
<td>Xaluprine</td>
<td>2012</td>
<td>Regular approval</td>
</tr>
<tr>
<td>Kuvan</td>
<td>2008</td>
<td>Regular approval</td>
<td>Bosulif</td>
<td>2013</td>
<td>Conditional approval</td>
</tr>
<tr>
<td>Thalidomide Celgene</td>
<td>2008</td>
<td>Regular approval</td>
<td>Defitelio</td>
<td>2013</td>
<td>Exceptional approval</td>
</tr>
<tr>
<td>Vidaza</td>
<td>2008</td>
<td>Regular approval</td>
<td>Iclusig</td>
<td>2013</td>
<td>Accelerated approval</td>
</tr>
<tr>
<td>Volibris</td>
<td>2008</td>
<td>Regular approval</td>
<td>Imnovid</td>
<td>2013</td>
<td>Regular approval</td>
</tr>
<tr>
<td>Cayston</td>
<td>2009</td>
<td>Conditional approval</td>
<td>Orphacol</td>
<td>2013</td>
<td>Exceptional approval</td>
</tr>
<tr>
<td>Firdapse</td>
<td>2009</td>
<td>Exceptional approval</td>
<td>Procysbi</td>
<td>2013</td>
<td>Regular approval</td>
</tr>
</tbody>
</table>
Focus – Orphan drugs

Request for accelerated assessment prior to submission of MAA (at least ten working days)

- Demonstration that the OMP is the first available treatment and/or has an advantage over an existing treatment, ie:
  - Show superior effectiveness
    - Evidence of improved efficacy via direct comparative clinical trial results
    - Evidence of improved safety (ie, no important reduction to benefit)
    - Major contribution to patient care, such as new model/route of administration; treatment alternative; different response from other treatments
  - Avoid the serious side-effects of previously available treatments
  - Improve the diagnostic capabilities (early diagnosis most often leads to improved outcomes).

The CHMP conducts an accelerated assessment in a maximum of 150 days. If it identifies major objections during the assessment, the CHMP can revert to the normal timetable for the centralised procedure, which allows a maximum of 210 days (Article 6 (3) of EC Regulation 726/2004).

A good example of how OMPs can gain an advantage with accelerated assessment is referenced with the drugs Soliris® (eculizumab) (indicated for the treatment of patients with paroxysmal nocturnal haemoglobinuria) and Kalydeco® (ivacaftor) (indicated for the treatment of cystic fibrosis patients age six years and older who have gating mutation in the CFTR gene [cystic fibrosis transmembrane conductance regulator gene]). Both medicinal products received orphan drug designation and the sponsors submitted a Letter of Intent for accelerated assessment which was agreed on by the CHMP prior to the start of the MA procedure. Soliris was approved within 147 days in April 2007, making it the first medicinal product approved under such conditions and along the same lines; Kalydeco was approved within 150 days in May 2012.

Conditional marketing authorisations

The objective of conditional marketing authorisations (CMAs) is to ensure medicines are available to patients with “unmet medical needs” (eg, emergency threats, orphan medicines). An MA is granted on the basis of incomplete assessment under very strict obligations which would be reviewed annually by the Agency – EC 726/2004 (Article 14(7)). The product is authorised to be marketed on the grounds that it is highly probable the sponsor (applicant) will be in a position to provide a comprehensive clinical report within a short timeframe.

The conditional approval addresses situations where an urgent need exists, and a medicinal product in development promises significant health benefits but the full safety/efficacy testing has not been completed. The EMA’s approval of such drugs under the conditional authorisation helps to speed up the product’s availability in the market.

The criteria for the granting of a CMA are as follows:
- The benefit–risk ratio must be positive
- “Unmet medical needs” (ie, conditions for which there are no available satisfactory methods for diagnosis, prevention or treatment or the product is of significantly major therapeutic advantage than a similarly listed product (EC 507/2006 Article 4)) must be fulfilled
- High likelihood that comprehensive clinical data will be provided within an agreed timeframe
- Additional data are required, but the benefit(s) to public health of immediate availability must outweigh the risk(s).

The sponsor is committed to fulfill post-marketing obligations (conduct new studies to help substantiate a positive benefit–risk ratio, collection of pharmacovigilance data and periodic safety update reports (PSURs), etc) to obtain a definitive authorisation, based on full safety research and testing, or the product may be withdrawn from the market.

It is recommended that the product sponsor should notify the EMA of its intentions to request a CMA as part of its “Letter of Intent”.

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**Figure 1: Types of OMP approvals between 2006 and 2013.**

<table>
<thead>
<tr>
<th>Accelerated approval</th>
<th>Conditional approval</th>
<th>Exceptional approval</th>
<th>Regular approval</th>
<th>Regular approval [hybrid]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5</td>
<td>6</td>
<td>11</td>
<td>32</td>
</tr>
</tbody>
</table>

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A level of transparency is required for these criteria to be effectively implemented. As such, the list of obligations for a CMA must be made publicly accessible, as well as the timeline for meeting each obligation; the labelling and patient information should also reflect the “conditional nature” of the MA approval – this may include the inclusion of the “black triangle” to ensure healthcare professionals are aware that an advanced monitoring system is required for such medicinal products. There are also financial penalties imposed in cases of infringement of the specific obligations.

The CMA is valid for a year but, can be renewed provided the marketing authorisation holder (MAH) applies for renewal of the MA before its expiry. During this renewal process, the benefit–risk ratio will be reassessed to ensure it remains positive. Also, the status of the specific obligations is reviewed, as well as the set timeframes for meeting these obligations. On fulfilment of all specific obligations, the CMA may convert to a “normal” MA.

Medicinal products such as Diacomit® (stiripentol) (indicated for the treatment of severe myclonic epilepsy in infancy) and Arzerra® (ofatumumab) (indicated for the treatment of chronic lymphocytic leukaemia) are good examples of how OMPs can be approved under the CMA. Both medicines satisfy the “unmet medical needs” criterion by virtue of their orphan designation coupled with the lack of other approved treatment options (in the case of Arzerra). Furthermore, following consultations with the sponsors, the CHMP was of the opinion that both product sponsors were in a position to provide the comprehensive clinical data over an agreed timeframe. Sponsors of Arzerra for example, provided comprehensive clinical data from ongoing Phase III randomised, controlled clinical studies in earlier disease settings. Other conditions set out by the CHMP involve assessment of the high response rate and control of the disease in the refractory setting, as well as observational studies in a Phase IV trial. Similarly, both products exhibited acceptable safety profiles, resulting in a positive benefit–risk ratio. Therefore the CHMP, having considered the data submitted, was of the opinion that the benefit(s) of the immediate availability of both medicinal products outweighed the inherent risk(s). The respective MAHs provided a letter of undertaking in compliance with the guidelines and thus ensured that any imposed obligations or follow-up measures will be met within the proposed timetable.

Authorisation under exceptional circumstances

The objective of authorisation under exceptional circumstances is to make medicines available for the treatment of patients with chronic or seriously debilitating diseases or whose disease is considered life-threatening where there is a lack of satisfactory treatment by an authorised medicinal product for those diseases. Usually, there is a lack of comprehensive data on the efficacy and safety of the medicinal product largely because the sponsor is unable to provide comprehensive evidence due to the rarity of the disease for which it is indicated.

Medicines are authorised under exceptional circumstances on the condition that the sponsor introduces “specific procedures”, with particular emphasis on the safety of the product. It is important to note that an approval under exceptional circumstance would not be granted if the CHMP deems that a conditional approval is more appropriate.

Unlike the CMA, where marketing approval is granted in the absence of comprehensive data in the likelihood that the sponsor is poised to provide such data within an agreed timeframe, the approval under exceptional circumstances circumvents the inadequacy of the product sponsor to provide comprehensive data by setting out obligations aimed at the provision of safety and efficacy information on the product’s intended use. Hence, it may not be likely that a full dossier can be submitted. On rare occasions however, where a full dossier has become available and no specific obligations remain, a normal MA could be granted.

The legal basis for granting a MA under exceptional circumstances states that the “authorisation may be granted only for objective, verifiable reasons and must be based on one of the grounds set out in Annex I to Directive 2001/83/EC.”14 The sponsor must show (with justifiable reasons) that comprehensive data on the safety and efficacy under normal conditions cannot be provided due to:
- Rarity of the indication – the sponsor must provide evidence that the disease is encountered so rarely (eg, mention an orphan designation)
- Present state of scientific knowledge – the sponsor must describe the level of scientific knowledge required to carry out the trials and provide evidence that it cannot develop such knowledge presently
- Ethical issues – the sponsor must show that it would be contrary to generally accepted principles of medical ethics to collect such information. An independent ethics committee (EC) may be consulted by the EMA to verify the ethical issues.

The product sponsor is advised to put forward a proposal for a programme of study in particular concerning the safety of the medicinal product. This could include detailed pharmacovigilance activities, an RMP, prescription or conditions of use, transparency in the product information (ie, the packaging leaflet must show that the information available for the concerned medicinal product is incomplete in certain “specified” areas).

The MA under exceptional circumstances is valid for five years on a renewable basis, but is subject to an annual re-assessment of the benefit–risk ratio by the CHMP.

The CHMP during the assessment phase reviews the information provided and will determine if there are sufficient grounds for the approval of the medicinal product under exceptional circumstances. Once agreed on, the CHMP reviews the proposed “specific procedures” to address not only the impact of the proposed risk minimisation activities on the benefit–risk ratio but also to determine if further studies can better inform on aspects that are important to the safe and effective use of the medicinal product.

Examples of how orphan medicines have gained marketing authorisation under exceptional circumstances have been reviewed with the drugs Evoltra® (clofarabine) (indicated for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and when no other treatment is expected to work), Yondelis® (trabectedin) (indicated for the treatment of patients with ovarian neoplasms and patients with advanced soft tissue sarcoma after failure of anthracycline and ifosfamide, or who are unsuited to receive these agents) and Atriance® (nelarabine) (indicated for the treatment of patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens).

The product sponsors provided verifiable evidence which supported the inability to submit comprehensive data on the clinical efficacy and safety of the products due to the rarity of the condition and/or the small size of the population of affected patients. The CHMP, after consultation with the sponsors, recommended that post-marketing safety data must be provided (sponsors to encourage diligent reporting of any adverse reactions relating to the use of the medicinal products, conduct further Phase III trials to determine safety and efficacy,
maintenance of a good RMP as well as good pharmacovigilance), as well as the provision of specific obligations (eg, sponsors to provide a “user’s information pack with recommendations for safe use of the drug” for doctors and other health care professionals).

The CHMP acknowledges that intensive additional monitoring is required for these products on assessment of the dossier provided, as there were many uncertainties as a result of the limited size of the safety database and the lack of controlled efficacy trials to demonstrate the products’ overall effect, but was of the opinion that the benefit–risk ratios of the medicinal products were favourable – thus granting an MA under exceptional circumstances. As part of the exceptional approval, the CHMP imposed additional risk minimisation activities (for example, the sponsors of Evoltra implemented specific strategies to minimise cardiac and renal toxicity which includes the provision of user information packs with recommendations for safe use of the drugs). The Evoltra sponsor was also urged to encourage prescribers to participate in voluntary adverse reporting systems in order to collect relevant information about patient and disease characteristics and treatment for all registered patients as well as information on any serious drug-related events. Yondelis and Atriance were further assessed on the grounds laid out in Article 3 of Regulation EC 847/2000 and both were considered not similar to other medicinal products authorised with the same therapeutic indication.

Compassionate use policy

By virtue of their development for the treatment of very rare and seriously debilitating diseases, OMPs may qualify under the compassionate use policy, and can be used as treatment options that allow the use of unauthorised medicines in patients.

The compassionate use policy aims to facilitate the access of new medicinal products currently under development to patient groups with seriously debilitating and/or very rare (life-threatening) diseases. Such products must be eligible for marketing authorisation through the centralised procedure or must be undergoing clinical trials – EC 726/2004 (Article 83 (2)).

The execution of this policy is to be adapted by individual EU member states (MS) per their national legislations (for example, the Early Access to Medicines Scheme in the UK). There is an option for the MS to seek CHMP opinion with respect to the conditions for use, target patient population, the conditions for distribution and on the eligibility of the product for MAA via the centralised procedure, provided a request for recommendations is made to the CHMP. This aims to improve transparency and collaborations between MS in terms of treatment availability, favour a common approach across the EU, as well as facilitate and improve the access of patient to compassionate use programmes within the EU.

The criteria for eligibility under the compassionate use programme as laid out in Article 83 of Regulation (EC) 726/2004 are as follows:

- The medicinal product must only be available to “patients with chronically or seriously debilitating disease, or a life-threatening disease, and who cannot be treated satisfactorily by an authorised medicinal product” in the EU
- The programme must be for a “group of patients”
- The medicinal product should be eligible for a centralised MA or, alternatively, is undergoing clinical trials.

The compassionate use programme in any given MS will be discontinued when the product becomes commercially available (ie, the product has been granted an MA).

The EMA is responsible for keeping an up-to-date list of the positive opinions given for compassionate use in a public register. Medicinal products such as Daclatasvir and IV Zanamivir are examples of medicines that are available for compassionate use. Further details of these and other guidelines on Compassion Use Programmes are available via the EMA website.

A new era for OMPs in the EU

The implementation of the EU Orphan Medicinal Product Regulation has not only raised awareness of the daily issues faced by patients, carers and healthcare providers in managing rare diseases, but has also proven to be successful for the pharmaceutical industry. Sponsors of OMPs have benefited from a range of incentives (market exclusivity of ten years, fee reductions, protocol assistance, etc) and consequently there have been increased numbers of OMPs made available to patients with rare diseases.

After more than 12 years of the implementation of OMP Regulation, steady progress has been made in not only increasing the availability of orphan medicines, but also in ways to make these medicines easily accessible to patients worldwide. Bruno Sepodes, COMP Chair, explains that “the work of the COMP is evolving and constantly adapting to better serve and address patients’ needs, the growing scientific knowledge on rare diseases, and the regulatory framework”.

In line with the successful collaboration between the EMA’s COMP and the US FDA – which promoted orphan drug development via the parallel submission process, leading to around 62% of applications submitted in parallel in 2012 – the COMP has expanded its collaborations with international bodies like Japanese regulatory authorities, Health Canada and, most recently, the Australian Therapeutic Goods Administration (TGA). These collaborations will promote worksharing between the regulatory authorities and, most importantly, impact positively on accelerating access to new medicines for patients with rare diseases both in the EU and worldwide.

Furthermore, the COMP has formed a partnership with various health technology assessment (HTA) bodies in Europe. The aim of this collaboration is to improve understanding of orphan designations and the processes of getting orphan medicines to market. This could help define ways to share information relating to patient care for rare disease patients as well as provide financial sustainability for healthcare systems.

Most importantly, the COMP has been keen to strengthen patient interactions in areas like contributions to patient care, assessment of significant benefits, improvement of quality of life, new formulations, etc. As such, expert patients and recognised patient organisations like the EURODIS Rare Diseases Europe can be sought by the COMP for their opinions relating to the areas mentioned above and ultimately help in addressing issues relating to patients’ needs. The COMP should prioritise patient opinions with respect to the improvement of the quality of life and this should form a basis of a justification for an orphan drug.

Room for improvement

The EMA is addressing some issues that are still outstanding:

- Improved access for patients to new medicines. A pilot programme (adaptive pathways, formerly known as adaptive licensing) has been started by the EMA, and companies are invited to participate with a submission of ongoing medicine development programmes for consideration. The process would start with an early authorisation of a medicine in a restricted patient population,
followed by repeated phases of evidence gathering and revisions of the MA to expand access to the medicine. It builds on current regulatory programmes that allow collection of real-life data and development of RMPs like the compassionate use programme, MAs under exceptional circumstances, conditional authorisation, etc. The goal of this pilot programme, according to Hans-Georg Eichler, EMA Senior Medical Officer, is to “maximise the positive impact of new medicines on public health by balancing timely access for patients with the need to provide adequate evolving information on their benefits and risks” This would not only combat the rigidity of guidance requirements which sometimes prevail over the unmet needs of life-threatening and severely rare diseases, but also serve as a justification for the improvement of the quality of life which ultimately is one of the key objectives of the orphan regulation.

Accessibility and affordability. An orphan medicine that has been granted an MA is in most cases the only available option for the treatment of a given indication. As such, there is a high value placed on orphan medicines by the product sponsors. Glybera (a gene therapy) for example, costs more than €1 million per year per patient. Making orphan medicines accessible should go hand in hand with making them affordable – an orphan drug is of little use if one of these two factors is missing. The EMA with its collaboration with the HTA bodies should look at pricing and reimbursements more closely. Medicines should not only make a clinical case but also a value case. This is because, though the clinical case on the efficacy and safety for medicines can be measured via scientific breakthoughs and clinical trials, there is no current benchmark for measuring value, and each medicinal product must make an important case for added value. All stakeholders who have a role in determining patient access, including the EMA, industry, HTA bodies and patient organisations should be involved at the start of a medicinal product’s lifecycle to promote transparency and fairness. Arguments can be made for the excessive pricing of orphan medicines with respect to the recuperation of development costs and business gain as well as with the notion that without these drugs, the cost of caring for people with rare disease could be much more than the cost of the orphan medicine. A safe and effective medicinal product should be “value-worthy” or its availability can be hampered. It is worth mentioning again that should an MS show with supporting evidence that an OMP is excessively profitable after five years, the said orphan medicine could loose its ten-year marketing exclusivity.

Provide a parameter for direct patient involvement. The EMA is looking to identify how to minimise side-effects and provide cost-effective measures via collaborations with expert patients and with patient organisations like EURODIS. Discussions with patient groups would aim to integrate their views and opinions in areas such as new formulations, new routes of administration, treatment modality, etc. Patients or a recognised patient group should be involved at the start of the orphan medicine’s lifecycle, and their opinions should be considered when discussing specific options of development, assessment, licensing, reimbursement, post-market surveillance, monitoring and the utilisation pathways of any given OMP.

Summary
Since the inception of EC Regulation 141/2000 there has been a steady increase in the number of OMPs available in today’s EU markets. The success of this orphan drug regulation lies not just in the number of medicinal products available for the treatment of rare diseases (due to the implementation of the incentives including protocol assistance, marketing exclusivity, etc), but more so in the promotion of public awareness of these rare, and in some cases life-threatening, diseases.

Despite these groundbreaking advances in the management, diagnosis, and treatment of rare diseases, limitations like the rigid regulatory framework have made it difficult to make therapeutically important drugs available at an earlier time. To resolve this, the EMA has introduced licensing flexibilities (like the compassionate use programme, conditional approval, etc) to ensure these medicinal products are accessible to patients earlier than might otherwise be the case and by doing so, ensure there is an available form of treatment for disease conditions which are encountered so rarely that there is often no alternative therapeutic solution. The key is to balance the eradication of unmet medical needs with strong assurances that the safety and efficacy standards of any such medicines are not compromised. Therefore, all medicinal products developed for the treatment of rare conditions must primarily be evaluated and given an orphan designation by the COMP, show evidence of therapeutic innovation and must meet accepted standards of safety and efficacy during the CHMP assessment before they can be made available to patients.

To achieve such constant high standards, transparency is crucial, and the EMA’s collaboration with international regulatory bodies, the HTA bodies and especially with expert patients and patient organisations must be strengthened to promote fair pricing and ensure an OMP is affordable to the patients who need them. Hence, the ultimate goal to improve the quality of life of rare disease patients should be prioritised when assessing a medicinal product for its use in the treatment and/or management of an orphan disease.

References
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