vfa / vfa bio Position Paper

# Orphan Drugs

Orphan drugs are used to treat rare diseases (orphan diseases), of which there are an estimated 8,000. Around four million people in Germany suffer from an orphan disease, in the EU approximately 30 million. There are currently 134 orphan drugs that have been authorized in the EU (as per April 2022). On top of that, there are 66 further drugs whose orphan drug status was withdrawn on request of the company after their authorization or has expired after 10 years.

## Executive Summary

The EC Regulation on Orphan Medicinal Products (no. 141/2000) took effect on January 2000, and has had a major impact since then. 200 orphan drugs have already been approved. Before 2000, hardly more than one drug for the treatment of a rare disease may have reached the market per year. Thus, a restriction of funding measures included in this regulation for the development of more orphan drugs in the EU should be avoided by all means. This would ultimately lead to fewer R&D activities in this field with high medical needs without providing better access to orphan drugs in EU countries.

As with other drugs, a manufacturer must submit a dossier containing details on the preparation and the extent of its additional benefit to the Federal Joint Committee (G-BA), as part of market launch of an orphan drug in Germany. After the additional benefit has been assessed by the G-BA, the manufacturer has to negotiate the amount refunded for the drug with the National Association of Statutory Health Insurance Funds.

In June 2009, EU member states were asked to develop national plans for rare diseases. In August 2013, the corresponding National Plan of Action was published by the National Action League for People with Rare Diseases (NAMSE) in Germany. NAMSE is consistent with a proposal by vfa bio for a body of experts from all fields whose mandate would extend beyond the terms of the German parliament. NAMSE permanently assists with the implementation of the National Plan of Action and strives to improve the care received by individuals with rare diseases.

Given the large number of orphan diseases and because of the huge medical need for new therapeutic options especially for people with rare diseases, there is still a very great deal of work to be done in this area. vfa and vfa bio are strongly committed to rigorously promoting the development of new therapies for orphan diseases throughout the whole value chain.

## 1. Background, definitions, facts and figures on orphan drugs

### 1.1 What are orphan drugs and why do they exist?

Orphan drugs are used to treat rare diseases (orphan diseases), of which there are an estimated 8,000. The term orphan diseases comes from the fact that they used to be pretty much neglected because they are so rare, i.e. they are treated like orphans. Around four million people in Germany suffer from an orphan disease, in the EU approximately 30 million.

In order for a drug in development to be granted orphan drug status by the EU, the disease concerned must be life-threatening or severe and rare. In the EU, there may be no more than five affected persons per 10,000; what's more, some

40 percent of all orphan drug designations concern diseases that affect less than one person in 10,000. Moreover, there must be the lack of a satisfactory treatment option for the rare disease. Or there must be a significant benefit expected from the drug compared to an already available preparation. In addition: Orphan drug status is denied for a drug developed for patients with a rare subtype of a more common disease.

Since people with rare diseases should have the same right as other patients to be treated with authorized medicines, policymakers have initiated measures to encourage activities in this field. That is necessary to give drug manufacturers and developers the prospect, even in small markets, of covering their research and development, production and marketing costs and allow them to make a profit appropriate to the economic risks.

The EC Regulation on orphan medicinal products (No. 141/2000) came into effect on January 22, 2000. It includes provisions such as: The status "orphan medicinal product" can be designated on the basis of epidemiological criteria (not more than five affected persons per 10,000 in the EU) or of economic criteria (there is no chance for the development costs to be recouped).

In November 2016, the European Commission has published the "Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (2016/C 424/03)" which specifically addresses the following aspects: clarification of the definition of "significant benefit", encouraging the development of orphan drugs for communicable diseases (e.g. Ebola), handling when two orphan drug applications are pending in parallel for approval, reassessment of the orphan criteria when a sponsor extends the use of its product after marketing authorization, clarifications on processing the transfer of orphan designations between sponsors. In July 2016, the European Commission has published a draft concept paper "Concept of 'similar medicinal product' in the context of the orphan legislation: adaptation to technical progress").
The European Commission has also recently evaluated EU legislation regarding medications for children and rare diseases. As part of this work, the commission issued an inception impact assessment (IIA) on the question of revising the EU regulation on children and rare diseases in November 2020. This assessment outlines potential ways to increasingly focus R&D activities on areas where no treatment options exist as well as to eliminate unequal access of EU member states. A legislative proposal from the European Commission is expected in Q4/2022.

The EC Regulation on Orphan Medicinal Products has had a major impact since taking effect: 200 orphan drugs have already been approved. Before 2000, hardly more than one drug for the treatment of a rare disease may have reached the market per year. Thus, a restriction of funding measures outlined in the EU Regulation on Orphan Drugs for the development of more orphan drugs in the EU should by all means be avoided. Because this would ultimately lead to fewer R&D activities in this field with high medical need without providing better access to orphan drugs in EU countries.

**European orphan drug legislation encourages the development of drugs for rare diseases through:**

- **10 years market exclusivity**
  In this period, marketing authorization for similar medicinal products for the same therapeutic indication are only granted if they are more effective, are tolerated better or help overcome a supply bottleneck.
- **Complete (SME*) or partial (non-SME) exemption from EMA fees**
  However, these financial incentives are small in relation to the high expenditures for research and development of drugs.
  – Consulting during development: no fees for SME; 75% reduction for non-pediatric-related assistance and no fees for pediatric-related assistance for non-SME
  – Pre-authorization inspection: no fees for SME and non-SME
  – EMA authorization fees: no fees for SME; 10% reduction for non-SME
  – Fees for post-authorization activities of the EMA, including annual fees, during the first year after marketing authorization: no fees for SME; no reduction for non-SME

*SME = small and medium-sized enterprises (http://ec.europa.eu/growth/smes/business-friendly-environment/sme-definition_de)

### 1.2 Orphan drugs: status quo

Since the year 2000, pharmaceutical companies have increasingly developed drugs for rare diseases (see www.vfa.de/orphans). Over the past ten years they have accounted for an average of nearly 30 percent of the new drugs that are introduced every year.

134 orphan drugs are currently authorized in the EU (as per April 2022). On top of that, there are 66 further drugs whose orphan drug status was withdrawn on request of the company after their authorization or has expired after 10 years. Almost all these drugs are still on the market and are therefore available to treat patients with rare diseases. Considerable progress has thus been achieved in the past years. Nevertheless, there are authorized orphan drugs for only about 2 percent of rare diseases.

By April 2022, some 2,450 further development projects have been designated the orphan drug status. These projects will result in further authorized drugs in the coming years, despite the fact that – due to the generally high risk of failure in drug development – only a small number of them will attain marketing authorization.

### 1.3 Who decides whether a drug is designated as an orphan drug and what criteria have to be met?

The Committee for Orphan Medicinal Products (COMP), a special body at the European Medicines Agency (EMA), decides on applications for designation of an orphan drug status. A subsequent recommendation to authorize the orphan drug following a positive assessment of its quality, efficacy and safety is issued – as is the case with other drugs – in a centralized process by the Committee for Medicinal Products for Human Use (CHMP) at the EMA; a binding authorization is then granted by the European Commission.

The Regulation on orphan medicinal products (No. 141/2000/EC) includes in particular the following provisions: Recognition of the status of “orphan medicinal product” for drugs to combat diseases with not more than five affected persons per 10,000 in the EU; the disease must be life-threatening or serious and there must not already be an existing satisfactory method of treatment for it. These two criteria must be proven by the applicant by means of appropriate documentation. The application for designation of orphan drug status can be submitted at any time during development

of such a drug before authorization of it has been applied for.

### 1.4 How is a medicine designated the orphan drug status? When and how is it examined?

A drug is designated as an orphan medicinal product only if the disease is rare and if the drug is expected to be of significant therapeutic benefit for the affected patients, compared with already available forms of treatment provided that those exist. This is examined again by the COMP directly before authorization is granted. If the disease is no longer rare or if the additional benefit does not exist or no longer exists for the affected patients when the drug is to be authorized, the orphan drug status is withdrawn before granting authorization.

If an orphan drug is authorized, exclusive marketing rights to it in the EU are granted for ten years. This is intended to prevent the market, which is already small as it is, becoming even smaller as a result of competitors with similar medicines. Further similar orphan drugs in a disease area are only authorized in this 10-year period of time if they are more effective or tolerated better (or help over-come a supply bottleneck), i.e. when they provide an additional benefit for the affected patients. That means the exclusive marketing rights do not offer the manufacturer an absolute guarantee, but rather a relative guarantee that it will be able to sell its products in what is only a small market segment for a rare disease for a limited period of time.

At the end of the fifth year on the market and at the request of a member state, the EMA can review whether the drug still meets the requirements for being designated as an orphan. If this is no longer the case, the status – along with the exclusive marketing rights – is withdrawn. This case, however, did not occur up to now.

### 1.5 Are there specifics in the development and authorization of orphan drugs?

The development of drugs for treating rare diseases – whether or not they have orphan drug status – differs from that of other drugs, especially in the clinical phases: For rare diseases, it is especially difficult to conduct the usually necessary randomized and comparative trials because the patients have often to be found from all around the world. Because the diseases are rare, the trials can only be performed with far fewer patients. It is often assumed in this context that a lower number of patients ought to mean that the trials are quicker and less expensive than ones with more patients. However, whether this actually reduces development times and means less cost and effort differs from case to case and depends on the type of illness, its rarity and the logistics required for carrying out clinical trials. That is because getting the few patients to the small number of clinical trial centers and including them in a trial for a lengthy period of time may well be very time-consuming and therefore costly. The comparatively limited number of patients in these clinical trials may also hinder certain trial designs or restrict the applicability of special statistical methods for the evaluation of clinical trials. The applicant and EMA therefore hold scientific advice meetings to develop suitable study designs that take the special features of small patient numbers and requirements regarding data for safety and efficacy into consideration.

The orphan drug status per se does not enable simpler or faster authorization. The requirements for clinical testing and authorization of drugs do not depend on the frequency of a disease: The drug's efficacy, safety and technical quality must be proven at all times. And orphan drugs must show that they have a benefit over comparator therapies – if already available – before they are designated as orphan drug and before they are allowed to keep the orphan drug status at the time of approval.

Irrespective of this, the EMA has established special approval pathways in order to approve innovative drugs in areas of particularly high medical need – for both common and rare diseases – faster than in the classic procedure:

- **Approval under exceptional circumstances**: In the case of approval under exceptional circumstances, the applicant must demonstrate that it is not possible to provide study data for the respective indication to the same extent as for a classic approval. This may be the case for

rare and for common diseases and may be the result of ethical aspects or the status of scientific knowledge.

- **Conditional approval** is initially granted on a temporary basis and is subject to specific obligations, is independent of the frequency of a disease and is granted if the drug can make a major contribution to patient health. The regulatory authority will then review annually whether the conditions have been or are being met. Overall, 76 drugs have been conditionally approved and 38 of those are orphan drugs (as of April 2022). So far, 10 orphan drugs have been granted regular approval after the conditions were met – approval for one of them has now been revoked. In addition, three other orphan drugs with conditional approval have meanwhile been withdrawn from the market.

**Orphan drug approvals from 2015-2021**

- 68% of all orphans passed through the standard approval process
- 32% were processed through a special approval pathway: 25% were conditionally approved (subject to specific obligations), 7% were approved under exceptional circumstances

Irrespective of conditional approvals or approvals under exceptional circumstances, the EMA can conduct an accelerated assessment, which is also independent of the frequency of a disease. This accelerated approval process can be used for drugs that fill a particularly large gap in treatment. The authority then provides faster testing in the standard approval process, which shortens the regulatory processing time from 210 to 150 days. During the period 2015-2021, this affected 22% of orphan drug approvals.

### 1.6 Impeded generation of evidence during research and development of orphan drugs

The significant benefit of orphan drugs is attested with its approval recommendation by the EMA and approval by the European Commission. Nevertheless, like all drugs with new active substances, orphan drugs are subject to the additional benefit assessment within the scope of the AMNOG procedure. From January 2011 through January 2022, the G-BA certified 59 % of orphan drugs as having a “non-quantifiable additional benefit” – compared to just 4 % of drugs without orphan drug status. A non-quantifiable additional benefit means that this medication has an additional benefit over the appropriate comparator, but this cannot be assessed as being minor, considerable or major.

Why this discrepancy? With regard to the additional benefit assessment, both the dossier template as well as the IQWiG Rapid Report use randomized controlled studies as an assessment basis for quantification of the additional benefit. However, studies of this type are often difficult or not at all to be conducted for rare diseases due to ethical aspects, because often other therapeutic options are not available, and/or the small number of patients.

Once annual gross revenue for an orphan drug exceeds 50 million euros, its significant benefit is no longer considered proven. The drug is then legally treated as other drugs and triggers an additional benefit assessment over the appropriate comparator specified by the G-BA. In this context, the 50-million-euro limit is arbitrary, since the sales figure is independent of the prevalence criteria (the illness remains rare) and, furthermore, usually nothing has changed with regard to available evidence. As part of this reassessment, adjustments are necessary in the AMNOG assessment criteria. In particular, the small patient number and its effect on the statistical evaluations need to be taken into account.

Furthermore, an additional hurdle can rise in this extra benefit assessment (when an orphan drugs exceeds 50 million euros) if the clinical trials used for marketing authorization do not correspond to the appropriate comparator as specified by the G-BA subsequently. In these cases, a methodological problem for proving the additional benefit is preassigned.

### 1.7 Why are there many orphan drugs in oncology?

In total, there are more than 200 different oncological diseases – many of which are rare. Most of the blood cancer diseases are for example rare diseases. Tumor diseases come along with an especially high medical need and correspondingly many research activities. The multitude of orphan drugs for patients with rare tumor diseases is particularly due to the advancing molecular knowledge of tumor biology and improved diagnostics which have led to a better understanding of tumor development as well as of molecular tumor characteristics. In any case, it is imperative to carry out a separate program of clinical testing for each oncological indication as basis for marketing authorization. Due to regulations by the EMA and the European Commission an artificial break down of large indications into smaller ones is legally not possible (see “Are there “artificial” rare diseases as a result of “orphaning” (“slicing”)?”).

### 1.8 Are there “artificial” rare diseases as a result of “orphaning” (“slicing”)?

Behind this question is the occasionally voiced suspicion that the industry makes “rare” diseases out of common ones by creating more or less arbitrary indication subsets (“slicing”). In this connection, personalized medicine is often also mentioned in the same breath as orphan drugs, especially whenever a company succeeds in developing a personalized drug that is suitable for persons in a smallish group of patients within a relatively frequently occurring disease. Contrary to general opinion, however, the European Commission does not designate an orphan drug status to such a drug and instead categorically excludes slicing, i.e. splitting an indication into smaller subindications that can be “orphaned”. The relevant document (EMA/COMP/15893 /2009) reads verbatim: “This is imperative to prevent the slicing of common conditions into invalid subsets. It is important that sponsors […] are aware that this is an important issue that will be reviewed by the Committee.” (see also ENTR/6283/00 Rev 4).

Personalized medicine is completely independent of the frequency of an illness and thus does not generate new orphan drugs. Drugs from personalized or stratified medicine can only be designated orphan drug status by the European Commission if the general indication were already below the orphan limit of 5 patients to 10,000 persons (such as is the case with cystic fibrosis). A number of cases where orphan drug status has been applied for the treatment of subgroups of patients but was rejected show that this strict approach is also adopted in practice.

Nevertheless, there are also some orphan drugs in personalized medicine. If research and development reveals that a personalized approach works for a rare disease, that benefit must not be withheld from the affected patients. That means there can and will also furthermore be personalized orphan drugs. Of the total of 98 personalized drugs currently authorized in Germany, 23 are orphan drugs with active orphan drug status (as per April 2022).

Orphan drug status can also be assigned to medications used to treat diseases involving certain genetic changes. The European Commission has issued a special regulation for this purpose (Commission Notice 2016/C 424/03). Under this notice, it must be demonstrated that a medication would be effective among biomarker-positive patients, but not for biomarker-negative patients. This is similar to the requirement for medications that have a positive effect only in tumors with certain mutations, regardless of the organ system involved – a tumor-agnostic medication. To receive orphan drug status, a medication must be shown to be ineffective in patients with frequently occurring diseases like breast and colon cancer without the mutation’s presence.

### 1.9 Is it possible for one orphan drug to be used for several rare diseases?

It is possible for an orphan drug to be able to be used for multiple rare diseases and, for all the indications together, to exceed the criterion of rarity that applies to a single indication. Up to now, this has been an exception. The exclusive marketing rights only apply in the indication for which the orphan drug status was granted. If the preparation is authorized for a further indication, it is by no means the case that the company automatically obtains the orphan drug status for that

indication. Instead, proof that the requirements for this status are met for the new indication must be furnished again. The new indication is also always based on relevant research and development work without which authorization is not possible.

If development of drugs for rare diseases is to be encouraged, development for individual indications and not for the products must be promoted. That is the only way of achieving the goal of improving the supply of medicines to people who suffer from rare diseases. The only thing that counts for patients is that there are preparations that help them. Whether these preparations are also authorized for other indications is completely irrelevant to these patients.

## 2. Orphan drugs in Germany

As for other drugs with new drug substances orphan drugs have to undergo the AMNOG procedure; this includes the assessment of the additional benefit through the G-BA as well as the subsequent negotiations regarding reimbursement rates. In contrast to other drugs however, the additional benefit of orphan drugs is already rated as evidenced because the orphan drug status is confirmed by the European Commission within the approval process.

However, the AMNOG took into account the special situation of orphan drugs from the very beginning. These drugs must already demonstrate during the approval process that they have a significant benefit over comparator therapies – if such therapies exist at all – in order to keep their orphan drug status. Their additional benefit is therefore considered proven under the AMNOG.

This AMNOG process for orphan drugs differs in two points from that for other drugs: 1) The orphan drug status is linked to the proof of additional benefit which is reviewed before authorization is given at the European level and which is rated therefore as evidenced. 2) The G-BA assesses the additional benefit on its own; the IQWiG is not voicing a recommendation before. The appropriate evidence from the authorization trials is used for this.

However, once the orphan drug exceeds annual gross revenue of 50 million euros, its additional benefit is no longer considered proven und it is treated under the law like the other drugs. The company must submit a normal dossier in its full extent to the G-BA. Subsequently, an additional entire benefit assessment in comparison to the appropriate comparative therapy as determined by the G-BA is being performed, followed by reimbursement negotiations. Consequently, it may even happen that an orphan drug is subjected to the AMNOG process twice in quick succession: first of all, in the “orphan variant,” then – once its annual gross revenue passes the 50-million-euro mark – in the normal form. In this context, the 50-million-euro limit is arbitrary, since the sales figure is independent of the prevalence criteria (the illness remains rare) and, furthermore, nothing has changed with regard to available evidence.

Since the introduction of the AMNOG in 2011, the share of drug expenditures of the total expenditures of the statutory health insurance has remained almost constant at around 16%. Due to the low number of patients, the prices for orphan drugs are usually higher than those for drugs for common diseases. However, this is put into perspective because only a few people are affected by a rare disease. In addition, due to the special challenges involved, the cost of research and development for orphan drugs is at least as high as for drugs for the treatment of common diseases. And of course, also patients with rare diseases have a right to adequate therapy.

## 3. NAMSE and the National Plan of Action

The European Council of Health Ministers adopted the Council’s proposed recommendation in June 2009 (2009/C 151/02). The EU member states were required to adopt national plans for people suffering from rare diseases by the end of 2013 at the latest.

In 2010, the German Federal Ministry of Health together with the Federal Ministry of Education and Research and the Alliance for Chronic Rare Diseases (ACHSE) launched the National Action League for People with Rare Diseases (NAMSE)

with the aim to achieve lasting and substantial improvements in diagnostics, therapy and research in relation to rare diseases. The coalition has 28 partners, all of whom are national and professional associations of the key players in the health system. Their objective is to analyze and tackle existing deficits in the field of rare diseases. vfa and vfa bio expressly welcome these activities and, as partners in the NAMSE coalition, actively contribute expertise from the industry from many projects relating to the treatment of rare diseases.

In August 2013, the National Plan of Action for People with Rare Diseases was presented to the public. The Plan of Action contains 52 proposed measures in the fields of care/centers/networks, research, diagnosis, registers, information management, patient orientation, implementation and further development.

One focus of the Plan of Action is the formation of nationally recognized centers of expertise. As a result, patients are to be able to obtain medical services representing the best-possible care for their specific disease faster, more efficaciously and as close to their place of residence as possible. To enable that, structures that promote collaboration between specialists and sharing of know-how nationally and internationally have to be created. Further treatment is then to be integrated in quality-assured care by general practitioners and specialists and near to patients' place of residence. As part of this, patients with rare diseases should receive already authorized orphan drugs quickly and unbureaucratically. Communication between the center and general practitioner, as well as appropriate quality management, must be ensured for this.

Following first-time prescription at the center, there might be difficulties in subsequent prescription of medication in out-patient care by the doctor treating the patient further. Therefore, when orphan drugs are prescribed, there should be more extensive regulations on recognizing such prescriptions as a special aspect of practice nationwide ("Praxisbesonderheit"; in connection with the requirement of a close coordination between the center and the general medical practitioner), so that in this case such a prescription is being classified as extra-budgetary treatment. This is not envisaged in the National Plan of Action; there is merely the proposal to examine in the medium term whether measures to flank the supply of drugs to people with rare diseases are necessary after implementation of the center model in the field of rare diseases.

Now, it is of utmost importance that NAMSE will continue to exist to examine, accompany and monitor the prompt implementation of the National Plan of Action. This would be consistent with the proposal by vfa bio for a German committee of experts on rare diseases as a permanent body that continues to exist beyond the life of a parliament and is made up of experts from all fields.

More information on the National Plan of Action for People with Rare Diseases and on the coalition partners, as well as a link for downloading the National Plan of Action, can be found at: www.namse.de/english.

## 4. Outlook

An important step forward was made with the European Regulation in 2000 to foster the development of orphan drugs also in the European Union. Given that there are an estimated 8,000 rare diseases and 200 approved orphan drugs, there is still a very great deal of work to be done in this area. A restriction of funding measures included in this regulation for the development of more orphan drugs in the EU should be avoided by all means. This would ultimately lead to fewer R&D activities in this field with high medical needs without providing better access to orphan drugs in EU countries.

Furthermore, it is crucial that these efforts on a European level are not counteracted through national measures regarding for example cost containment. The law for greater safety in the pharmaceutical supply (Gesetz für mehr Sicherheit in der Arzneimittelversorgung, GSAV) which became effective in August 2019 encompasses regulations that are potentially detrimental to the further development of orphan drugs: 1) Expansion of the calculation basis upon reaching the 50 million threshold through inclusion of sales from the

hospital setting; 2) The power of the G-BA to call for studies accompanying application and limiting the prescription of orphan drugs to those specialist physicians/hospitals taking part in these accompanying study. Because the IQWiG and G-BA have so far not shown willingness to take into appropriate consideration the more difficult conditions for generating evidence with rare diseases and have also regularly rejected non-randomized studies, the AMNOG assessment will have to change. Otherwise, there is a risk that orphan drugs now established for patient care will increasingly be left behind in the additional benefit assessment and could ultimately no longer be available for patient care. With regard to the overarching goal of improving the situation of people with rare diseases, the point of view of the vfa is that tightening of the current regulations for orphan drugs and any restriction of patient access should be dispensed with.

Instead, further developments in the field of orphan drugs should be encouraged, especially with regard to current national efforts to improve the standard of care for people with rare diseases in Germany. The German government therefore sent out a right and important signal by founding NAMSE in 2010. Now it is important to examine, accompany and monitor the implementation of the National Plan of Action for People with Rare Diseases which was published in August 2013.

The next important step will now be to establish nationally recognized centers of expertise so that patients obtain medical services representing the best-possible care for their specific disease faster and more efficaciously. Further treatment is then to be integrated in quality-assured care by general practitioners and specialists and near to patients' place of residence. Furthermore, NAMSE must be transitioned into a sustainable structure.

The need for new treatment options is especially high for people with rare diseases. vfa and vfa bio are strongly committed to rigorously promoting the development of new therapies for orphan diseases throughout the value chain. That requires a cohesive policy integrating research, health and economic policy. That would consistently support political measures to encourage research and development of orphan drugs and above all would be of benefit for the many patients with rare diseases who can only be given inadequate help at present.

As stated in its coalition agreement, the goal of the German coalition government is a new beginning for innovation and investment. The German government supports a preventive, crisis-proof and modern healthcare system that utilizes the opportunities offered by biotechnology and medical procedures. The fight against rare diseases is explicitly identified here. Now it is a matter of setting the right course!

As of: 05.2022