

vfa/vfa bio Position Paper Orphan Drugs

EXECUTIVE SUMMARY

Orphan drugs are used to treat rare diseases (orphan diseases), of which there are an estimated 6,000 to 8,000. There are currently 112 orphan drugs that have been authorized in the EU (as per December 2018). On top of that, there are 46 further drugs whose orphan drug status was withdrawn on request of the company after their authorization or has expired after 10 years.

The development of orphan drugs has been recognized by the EU as a joint responsibility. On recommendation from the European Council of Health Ministers, in June 2009 the EU member states were called upon to establish national plans for rare diseases by the end of 2013 at the latest. In March 2010 the German Federal Ministry of Health together with the Federal Ministry of Education and Research and the Alliance for Chronic Rare Diseases (ACHSE) subsequently launched the National Action League for People with Rare Diseases (NAMSE). This is 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. NAMSE has elaborated the National Plan of Action for People with Rare Diseases which was presented to the general public in August 2013. Its implementation is currently being accompanied by NAMSE.

The funding measures to date have been shown to be effective: Some 160 orphan drugs have already been approved. The AMNOG is responsible for ensuring that costs remain affordable for the health insurance funds. 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), the body responsible for questions of refunding, as part of market launch of an orphan drug. After the additional benefit has been quantified by the G-BA, the manufacturer has to negotiate the amount refunded for the drug with the National Association of Statutory Health Insurance Funds.

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 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 an advantage for the many patients with rare diseases who can only be given inadequate help at present.

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A) Background, definitions, facts and figures on orphan drugs

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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 6,000 to 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. To be considered a rare disease, there may not be more than five affected persons per 10,000 in the EU; what's more, some 40 percent of all orphan drug acknowledgments relate to diseases that affect less than one person in 10,000.

Serious or life-threatening illnesses from which only relatively few people suffer are often termed orphan diseases (or rare diseases). Medication used to combat them is consequently called orphan drugs. Around four million people in Germany suffer from an orphan disease, in the EU approximately 30 million.

Since people with such 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). 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.

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"). And the European Commission

is currently evaluating legislation for children's medicines and orphan drugs (medicines for special populations).

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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 activities in the first year after authorization: no fees for SME; no reduction for non-SME
- Inspection after authorization: 90% reduction for SME; no reduction for non-SME

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

How do the EU regulations differ from those in the U.S.?

In the U.S., a medication can obtain orphan drug status if no more than 200,000 people in the U.S. are affected by the disease (currently around one patient out of 1,500 persons; in comparison, the figure for the EU is 1 out of 2,000).

The U.S. does not have a restriction to the effect that no satisfactory method of treatment already exists and the products in question have to be drugs or diagnostics, i.e. orphan medical products are also possible there. In addition, the FDA regulations provide the possibility for a 50% tax credit for clinical studies in orphan drug projects. In the USA, market exclusivity for an orphan drug lasts for a period of 7 years (in the EU, due to market access barriers in many countries: 10 years).

Orphan drugs in Europe: status quo

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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 one fifth of the new drugs that are introduced every year.

112 orphan drugs are currently authorized in the EU (as per December 2018). On top of that, there are 46 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 December 2018, some 1,900 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.

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.

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 overcome 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.

Are there differences in the development and authorization of orphan drugs?

The development process for orphan drugs differs from that of other drugs in particular in the clinical phases: For rare diseases, it is often especially difficult to conduct the usually necessary randomized and comparative trials because the patients have 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, tolerability and technical quality must be proven at all times. And compared to the classic authorization process, 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.

An orphan drug status per se does not lead to an accelerated authorization process in which the time for assessment of the documentation is reduced from 210 to 150 days. Instead, the decision of the EMA for such an accelerated authorization process does not depend on the frequency of a disease and is granted only upon special application of the manufacturer and only to those drugs which fill a particularly large gap in treatment. Nor does such an accelerated process mean that the documentation is assessed less meticulously or in less depth. It is rather the case that the application is assessed more quickly because the authority devotes more resources to dealing with it than in other authorization processes.

The PRIME process of the EMA is also independent of the disease's frequency. As part of this program, the EMA – via intensive monitoring of the development – aims to make innovative treatments quickly accessible to patients. To do this, candidates must meet strict requirements: First of all, they should be used in areas with substantial medical need, and second, their initial data from clinical studies should demonstrate significant therapeutic success in patients.

With its Adaptive Pathways approach, EMA is now developing a system in which the approval instruments available so far are put to targeted use (classic approval, approval under exceptional circumstances and conditional approval). This approach provides flexibility, i.e. it is easier to switch among the specified paths of a classic, a conditional approval, or an approval under exceptional circumstances.

Although the orphan drug status per se does not have an influence on approval, a number of different orphan drugs have been approved following a special approval procedure, that is, under exceptional circumstances. In these instances, the applicant must prove that it is not possible to produce study data for the relevant indication to the extent needed for a classic approval. This can be the result of the rarity of the illness, ethical aspects or the status of scientific data.

The approval based on exceptional circumstances must be distinguished from the conditional approval. The latter is initially granted on a temporary basis and is subject to specific obligations. In this case, phase III study data are generally collected and need to be

submitted within a binding period of time; it is assumed, however, that the drug can greatly contribute to patient health before this. Overall, 40 drugs have been conditionally approved and 20 of those are orphan drugs. With a conditional approval, the approval authorities review annually whether the conditions are or will be met. To date, six orphan drugs have received regular approval once their obligations were fulfilled. On the other hand, an approval based on exceptional circumstances will always stay "exceptional" regardless of orphan drug status, because comprehensive clinical data simply cannot be generated.

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Impeded generation of evidence during research and development of orphan drugs

The additional 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 2011 through December 2018, the G-BA certified 61 % 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 and/or the small number of patients.

The requirements for preparing the dossier in the scope of AMNOG are somewhat reduced for orphan drugs compared to drugs without orphan drug status, since the additional benefit is considered proven and at least not quantifiable. And although legislation has thus taken into account the specific features of orphan drugs, the AMNOG standards for orphan drugs seem to have only limited applicability. Once annual gross revenue for an orphan drug exceeds 50 million euros, it is legally treated as other drugs: a regular dossier to its full extent needs to be submitted 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, nothing has changed with regard to available evidence. As part of the reassessment of orphan drugs after they have exceeded the 50-million-euro limit, adjustments are necessary in the AMNOG assessment criteria. In particular, the small patient collective and its effect on the statistical evaluations need to be taken into account.

Why is there an above-proportionate number of orphan drugs in oncology?

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In total, there are around 280 different rare oncological diseases (source: Orphanet). Most of the blood cancer diseases are for example rare diseases. The rare tumor diseases come along with an especially high medical need and correspondingly many research activities. The high number of orphan drugs for patients with rare tumor diseases is particularly due to the advancing molecular knowledge of tumor biology and improved diagnostics. These have led to a better understanding of tumor development as well as of molecular tumor characteristics. It is for this reason that meanwhile some tumor entities could be defined further and could be differentiated from each other on a molecular and therapeutic level, so that today there are narrowly defined oncological indications. In this case, it is imperative to carry out a separate program of clinical testing for each indication as basis for marketing authorization. In doing so, 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")?").

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. 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).

Furthermore, 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, but rejected for drugs used in the treatment of subgroups of patients show that this strict approach is also adopted in practice. In

the case of just about all orphan drugs, the number of patients is well below the limit of 5:10,000.

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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 be personalized orphan drugs. Of the total of 63 personalized drugs currently authorized in Germany, 15 are orphan drugs with active orphan drug status.

In the meantime, orphan drugs are also being developed that are only approved in diseases with certain genetic changes. The EMA has issued a special regulation for these approvals (Commission Notice 2016/C 424/03). It calls for having proof that both the substance is effective in the patient group with a positive biomarker and that this is not the case for biomarker-negative patients.

Is expanding an indication for an orphan drug to a common disease ("Trojans") permissible?

Behind the "Trojan effect" is the conjecture that a company uses authorization for a rare disease to subsequently expand the application area of its drug to common diseases, while retaining the drug's orphan status. However, this is not legally permissible. The active substance of an orphan drug which is to be authorized for a common disease must namely be developed in a separate program to create a drug with its own brand name and separate marketing – naturally without the status of an orphan drug. Or the manufacturer would have to request the withdrawal, or would lose, the orphan drug status for its preparation as soon as it is also to be authorized for a "large" application area. This has already happened in a number of cases. The orphan drug status cannot therefore be transferred to a non-orphan indication.

However, 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 extreme 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.

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B) Orphan drugs in Germany: AMNOG

As for other drugs with new drug substances orphan drugs have to undergo the AMNOG procedure; this includes the quantification 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. In addition, the administrative office of the G-BA assesses the extent of the additional benefit of orphan drugs by itself, as part of which it has the details on epidemiology and the costs of treatment examined by the IQWiG. The G-BA does not make a statement on the extent until the final benefit assessment decision after the hearing procedure.

Does AMNOG also apply to orphan drugs?

Yes. As with other drugs, a manufacturer must submit a dossier containing details on the preparation and the extent of its additional benefit to the G-BA, the body responsible for questions of reimbursement, as part of market launch of an orphan drug. After the extent of the additional benefit has been determined by the G-BA, the manufacturer then has to negotiate a reimbursement rate for the drug with the National Association of Statutory Health Insurance Funds.

This 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 quantifies 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, it is treated under the law like the other drugs: a normal dossier in its full extent must be submitted and an additional benefit assessment in the normal way versus 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.

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Does AMNOG make it easier for drugs with orphan status to be reimbursed?

It is sometimes claimed that orphan drugs are exempted from the reimbursement negotiations prescribed by AMNOG. That is incorrect. Manufacturers also have to negotiate a reimbursement rate for orphan drugs, which applies as of the 13th month after market launch, with the National Association of Statutory Health Insurance Funds. As with all other medicines, these negotiations are also conducted on the basis of the additional benefit dossier submitted by the manufacturer and the respective assessment of the G-BA.

Exemption of or privileged treatment for orphan drugs in the reimbursement negotiations does not exist. Thus, AMNOG by no means makes it easier for orphan drugs to enter the market in Germany.

Is the orphan provision in AMNOG a concession to the industry?

No, the orphan provision is based on the legal requirement that the same matter may not be assessed differently by two different authorities. The G-BA is therefore legally bound by the authorization decisions of the European Commission in that, even if possible through AMNOG, it is usually not allowed to make a different decision on comparable matters (in this case the assessment of additional benefit) than that already taken by the European Commission. Also under this perspective, the 50-million-euro gross revenue mark has to be challenged.

What comparative therapy applies to orphan drugs?

Since the additional benefit of an orphan drug was already proven when it was granted marketing authorization, the comparator used for the authorization trials must be used. Before a specific orphan drug is authorized, there are usually only symptomatic means of treatment and in some cases no therapy whatsoever.

This reasonable rule is annulled by the 50-million-euro gross revenue mark (p.a.), because in this case the G-BA determines an appropriate comparative therapy as a basis to prove the additional benefit of the orphan drug. An additional burden may accrue for orphan drugs through this downstream additional benefit assessment procedure if the authorization trials do not correlate to the conditions of the appropriate comparative therapy as determined by the G-BA retrospectively. In these cases, a methodological problem for proving the additional benefit is being preprogrammed.

Although legislation has taken into account the specific features of orphan drugs and recognized the additional benefits compared to

other drugs, the AMNOG standards for orphan drugs seem to have only limited applicability. As part of the reassessment of orphan drugs after they have exceeded the 50-million-euro limit, adjustments are necessary in the AMNOG assessment criteria. In particular, the small patient collective and its effect on the statistical evaluations as well as the necessity of internationally accepted study designs need to be taken into account. The prevalence criteria remain to be valid independent of the annual sales (the illness remains rare) and, furthermore, exceeding 50 million euros generally doesn't change anything with regard to available evidence.

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What are the sales with orphan drugs in Germany?

Orphan drugs with active status accounted for 3,7 percent of the statutory health insurance scheme's medication expenditures for outpatient care in 2017 in Germany. Approximately 73 percent of orphan drugs result in annual revenues below 10 million euros – thereof more than half below 1 million euros. Overall in 2017, in contrast, there were only five orphan drugs with an active orphan drug status whose annual revenue in the statutory health insurance fund exceeded 50 million euros.

C) Orphan drugs in Germany: 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.

To enable cross-sector care, efforts to overcome possible interface problems (between in-patient and out-patient care) should be undertaken, since interface problems may result in some cases in interruptions to patients' treatment, entailing negative consequences for their state of health. It can be positively outlined that during implementing §39 of Book V of the Social Security Code (SGB V) regarding the discharge management ("Entlassmanagement"), the G-BA obliged the hospitals to secure the continuous drug supply for the patients. The corresponding paragraph of the drug guideline ("Arzneimittel-Richtlinie") regulates that the patient can receive a prescription for the smallest package size when being discharged from hospital in order to bridge the time until out-patient care takes over. This is especially important against the background of the low concentration of centers for rare diseases. In the meantime, details regarding the discharge management have been determined by the extended arbitral body. The corresponding change application of the framework treaty came into effect on October 1st, 2017. It remains to be seen how the framework concretions regarding the discharge management will affect the practical work.

One possible option for adjusted payment for out-patient services is the out-patient specialist medical care ("spezialfachärztliche Versorgung") in accordance with Section 116 b of the German Social Security Code SGB V. This envisages that diagnosis-related items in a scale of charges are negotiated in euros and higher costs –

such as those incurred for patients with rare diseases – are to be paid for in particular by the items in the scale of charges for diagnostics and treatment being calculated separately and being available promptly at the beginning of implementation of the outpatient specialist medical care. At present, however, Section 116b SGB V only lists some very few rare diseases or disease groups in its catalog and so only a fraction of their total number. The ASV catalog should therefore be continuously, promptly and quickly expanded in order to create the framework for optimal patient care and appropriate compensation for care providers.

Another objective under the Plan of Action is to make it easier for patients and medical specialists to access information on rare diseases and to implement strategies that enable faster diagnosis. By establishing a Comprehensive Information Portal about rare diseases in Germany (Zentrales Informationsportal Seltene Erkrankungen - ZIPSE, www.portal-se.de/) knowledge as well as fast access to the correct information shall be made available on a high quality level. This portal is being supplemented by an overview on the standard of care in the field of rare diseases (se-atlas, <https://www.se-atlas.de/>) which is supposed to inform experts as well as the broader public where treatment options and contact persons for certain rare disease can be found. In addition, measures are planned to help intensify research in the field of rare diseases.

Now, it is of utmost importance that NAMSE will continue to exist, ideally with the involvement of the existing players so as to examine, accompany and monitor the prompt implementation of the National Action Plan. 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.

D) 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 6,000 to 8,000 rare diseases and by now approximately 160 approved orphan drugs, there is still a very great deal of work to be done in this area. Therefore, it is crucial that these efforts on a European level are not counteracted through national measures regarding for example cost containment.

The current requirements of the ministerial draft from the Federal Ministry of Health for a law for greater safety in the pharmaceutical

supply (Gesetz für mehr Sicherheit in der Arzneimittelversorgung, GSAV) makes provisions for regulations that are potentially detrimental to the further development of orphan drugs: 1) Expansion of the calculation basis upon reaching the 50 million threshold; 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-clinical studies, 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 prompt 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.