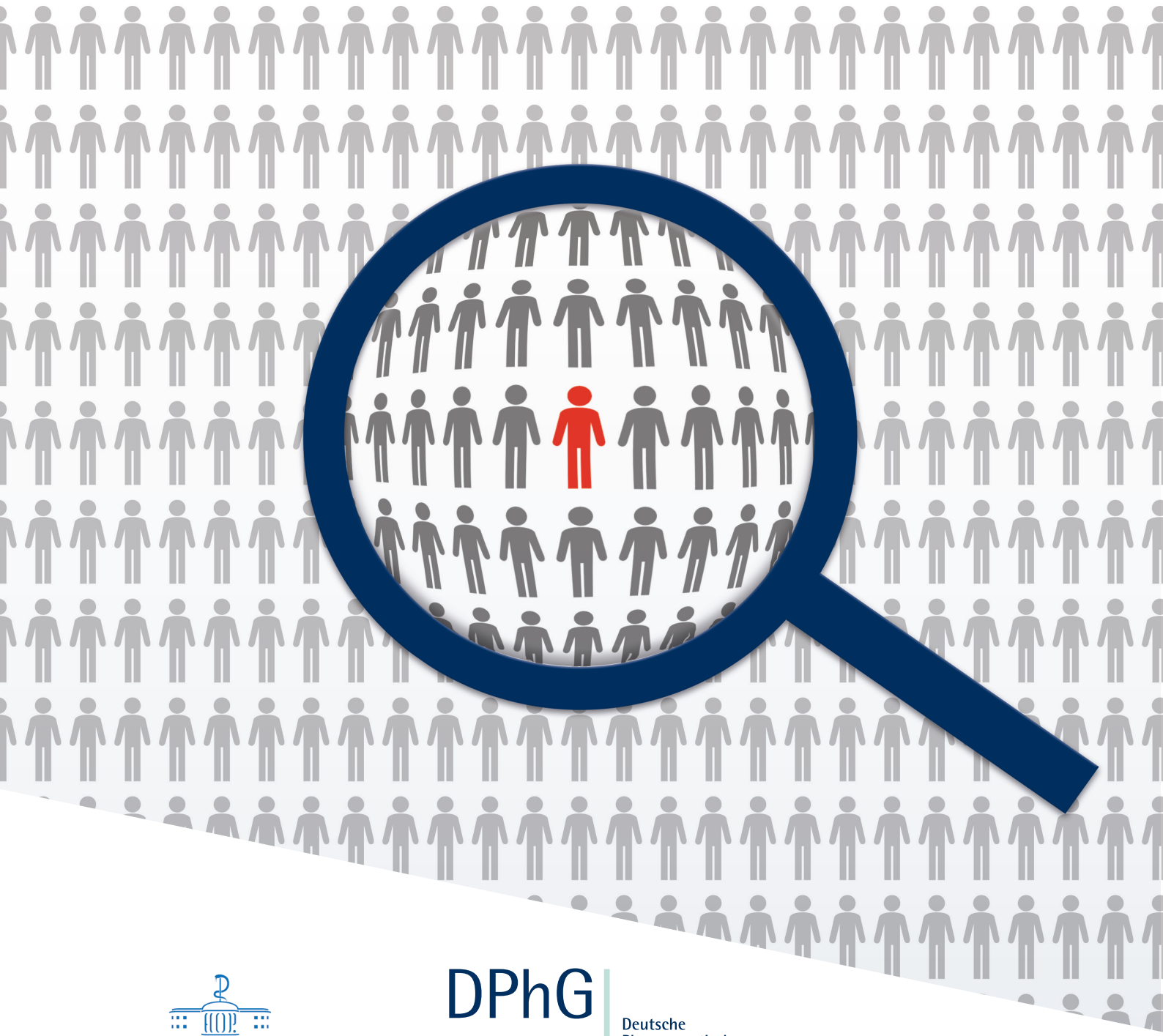
CONCLUDING STATEMENT

RARE DISEASES – AN INTERSECTION BETWEEN GENERAL FRAMEWORKS AND THERAPEUTIC CHALLENGES



HOUSE OF PHARMA

DPhG Deutsche Pharmazeutische Gesellschaft e.V.

Continuing the Successes in Rare Disease Therapy Together

CONCLUDING STATEMENT BASED ON THE EXPERT MEETING HELD ON 28.09.2021 IN FRANKFURT AM MAIN

According to the EU definition, a disease is rare if no more than one person per two thousand of the population suffers from it. Although around 80 percent of these diseases are genetic, many patients are not correctly diagnosed until adulthood, after a long history of illness and having seen a wide variety of doctors with different diagnoses. Rare diseases, of which there are approximately 6,000–8,000 different ones, are often incurable and have lifelong impairments. For more than 95 percent of them, there is still no drug therapy option.

However, the fact that today at least five percent of all rare diseases can be treated with drugs is also thanks to Regulation (EC) No 141/2000 on orphan medicinal products. In the USA, a corresponding regulation, the *Orphan Drug Act*, had already been in force since 1983. Both regulations aim to increase the attractiveness of the highly challenging research and development of drugs for rare diseases for the pharmaceutical industry through economic incentives and regulatory relief. For this reason, the EU regulation grants each company that brings an *orphan drug (OD)* to market approval in the EU a right of market exclusivity for up to ten years after the drug is approved. During this time, no other company will be granted marketing authorisation for a similar drug in the same therapeutic indication – unless it would be more effective or tolerable or would help overcome a supply shortage. The success of Regulation (EC) No 141/2000 is remarkable: while only five OD-like drugs were available in Europe prior to its enactment, over 190 ODs have been approved since.

However, the market availability of ODs varies significantly across EU member states. Of the 47 ODs approved in Europe between 2016 and 2019, only 19 drugs were available on average across all member states, or just 41 percent. Germany ranks at the top with 96 percent, Poland and the Baltic states at the bottom with values between 13 and 2 percent. The reasons for this are multifaceted. They relate to differences in regulatory requirements and healthcare spending, local resources of pharmaceutical companies, and speeds of price and reimbursement negotiations. The inclusion of a drug on insurance reimbursement lists usually determines its availability.

In its Pharmaceutical Strategy for Europe, the European Commission announced that, in addition to Regulation (EC) No 141/2000 on orphan medicinal products, it would also review Regulation (EC) No 1901/2006 on medicinal products for paediatric use to ensure the availability, accessibility and affordability of ODs.

Against this background, the House of Pharma & Healthcare, together with the German Pharmaceutical Society, organised an expert meeting to analyse the status quo of care for patients with rare diseases and to discuss proposals for its improvement – on both a European level and nationally. According to the unanimous opinion of the participating experts, the design of the European pharmaceutical strategy should, with respect to rare diseases, focus primarily on

- Making reliable diagnoses more quickly
- Incentivising research and developing new drugs more effectively
- Coordinating therapy and care more successfully
- Bringing communication and the management of expectations closer together
- Maintaining good access to ODs in Germany and improving access in other EU countries.

Faster diagnosis

Too often, it still takes many painful years before patients with a rare disease receive a proper diagnosis. Advances in laboratory medicine, particularly in whole-genome sequencing, as well as refinements in imaging and bioinformatics, can greatly facilitate the diagnosis of rare diseases. Added to this are the opportunities presented by advancing digitisation and the intelligent networking of medical records. However, the increasing workload in everyday medical practice and hospitals geared towards diagnosis-related groups (DRGs) make diagnosing a rare disease difficult. This is particularly evident in paediatrics, which in the German hospital system is often seen only as an appendix to a hospital system focused on adults. Rare diseases usually manifest in childhood and adolescence.

- The DRG system would need to undergo fundamental reforms for high-performance paediatrics that is able to rapidly identify and treat rare diseases. The importance of the time factor must be better acknowledged.
- More knowledge about rare diseases should be taught in medical and pharmacy studies.
- Newborn screening for rare diseases should be expanded as soon as a reliable detection method is available. A positive example of this is the recently introduced screening for q-associated spinal muscular atrophy (SMA).

- Patient data should be collected on a disease-specific basis in well-functioning and accessible registries.
- Biomaterial databases for rare diseases should be further developed.

More effective drug development

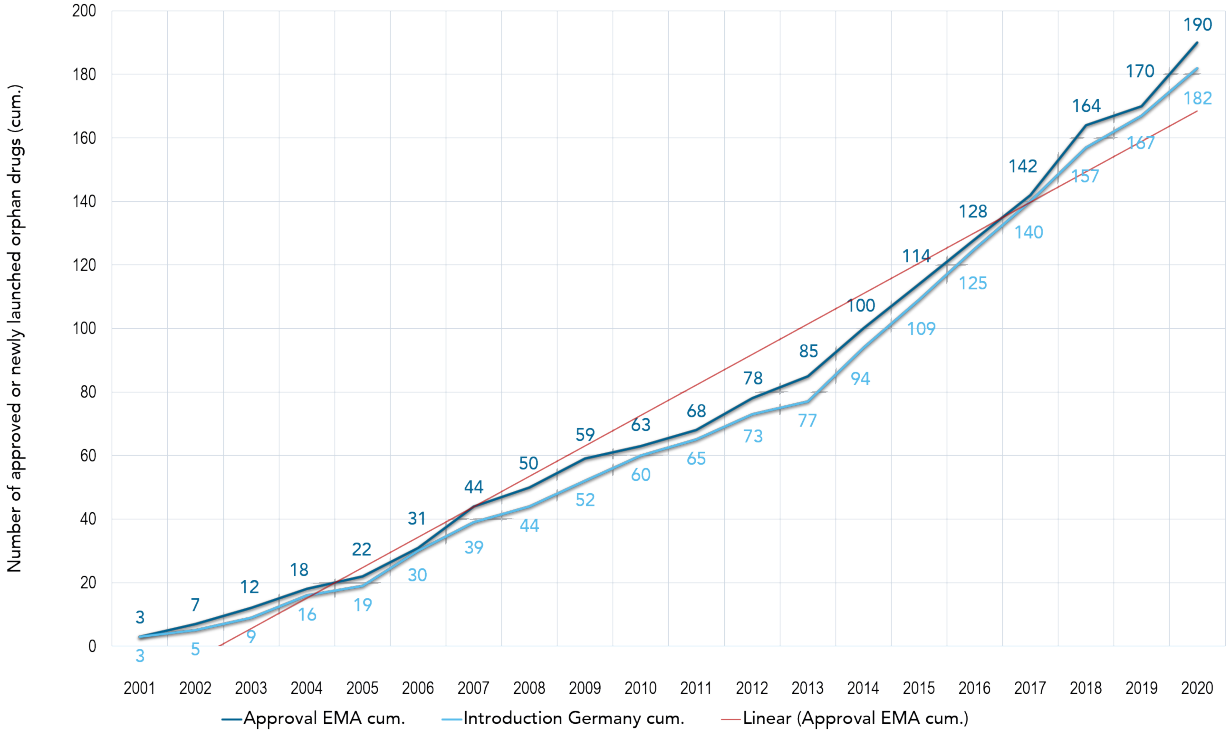
Due to the small number of patients, the development of ODs is a scientific and economic challenge. This is true even for generating a preclinical hypothesis and identifying molecular targets, given the sparse literature and even fewer blood and tissue samples. It applies even more to the design and organisation of randomised controlled clinical trials. Designing trials, establishing indicators of therapeutic success, and recruiting patients is time-consuming and expensive. In order to discover and develop new agents against rare diseases, collaboration between private and public funders in open-science models on a global scale may be an option. One example of this is the *Structural Genomics Consortium (SGC),* founded in 2004, and its associated organisation Agora Open Science Trust. In this model, innovation is protected by *orphan drug* status and market exclusivity rights, but not by patents. Eliminating confidentiality requirements allows for an open and collaborative model with academic partners and the pharmaceutical industry.

- Existing incentives and the research activity they generate must be maintained. Lowering the prevalence threshold or a cumulative prevalence criterion would greatly reduce incentives to innovate.
- In return, companies have a social responsibility to bring to market the ODs they have successfully developed, taking into account regional access conditions.
- Open, pre-competitive collaboration in public-private partnerships can greatly accelerate the development of affordable ODs.
- Innovative financing systems for Ultra Orphans should be developed that allow payers to cover the high one-off or permanent costs.
- Access to care data from the planned research data centre should also be made available to the private sector.

Better coordinated therapy and care

The delayed introduction of new examination and treatment methods (NUB) into the DRG system makes it more difficult to treat rare diseases in the clinic. This issue of an NUB gap is already being addressed by the legislature. In Germany, unlike many other European countries, access to ODs is generally guaranteed. However, the 34 centres for rare diseases are overstretched. A great number of patient inquiries come up against a lack of financial support from payers, i.e. insurance companies. The German Medical Service of the Health Insurance Funds rejects applications for *off-label use* of proven drugs too quickly and apparently without in-depth review. Due to the regulatory framework, *repurposing* of such drugs is costly and barely feasible from an economic standpoint.

- Barriers to access to ODs in the EU should be jointly analysed at country level by all stakeholders in order to then find solutions jointly.
- The clinical network of centres for rare diseases in Germany should be supported more strongly and supplemented by hubs in the outpatient setting.
- *Off-label use* (if there is no approved drug) and repurposing of approved drugs should be facilitated.



Reference: IGES Institut GmbH, Berlin

Communication and the management of expectations

Media coverage of rare diseases and information about breakthroughs in their treatment is not always grounded in fact. On the contrary, it often raises exaggerated expectations. In order to improve this situation in the long term, research-based pharmaceutical companies should maintain a continuous dialogue with medical societies and the relevant patient organisations. With this approach, they can find a common language for proper communication with the public. One aspect of this communication should concern the rapid differential diagnostic advances in cancer medicine. In this field, molecular biology methods now permit fine-grained diagnostics by detecting individual gene patterns, where tumours that were once given uniform names, such as non-small cell lung carcinoma, are presented as multiple individual different tumour entities.

There is no doubt that much has been achieved in dealing with rare diseases over the past 20 years, the experts unanimously concluded. To continue this success in innovation, transparent and long-term predictable framework conditions for research, development, market availability and supply are needed throughout Europe.

The following participants of the expert panel contributed to the preparation of the statement and support the recommendations formulated therein:

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Dr. Sabine Sydow, Berlin
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Dr. Mario Wurglics, Frankfurt a. M.

A representative of the German Federal Ministry of Health attended the expert meeting as an independent observer. Dr. Martina Schüßler-Lenz of the Paul Ehrlich Institute, advised on regulatory and scientific issues.

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