Bundesamt für
Sicherheit im
Gesundheitswesen
BASG

The World of Orphan Medicines

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What we will cover:

- What is a rare disease?
- Incentives for Marketing Authorisations
- New developments
  - Synthetic Controls
  - Endpoints (PRO)
- Practical Examples
- How to approach „Orphan Biosimilars“

What does „rare“ even mean?

In Europe:

- Max five in 10.000 in the EU affected
- ATM 6000 rare diseases characterised
- Ca 190 products authorized for rare diseases

Don't markets regulate this automatically?

From the recitals of Regulation 141/2000 by European Parliament and Council of the EU:

(1) some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the medicinal product; the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions; these medicinal products are called 'orphan';

Same rights for all patients!

patients suffering from rare conditions should be entitled to the same quality of treatment as other patients; it is therefore necessary to stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry; incentives for the development of orphan medicinal products have been available in the United States of America since 1983 and in Japan since 1993;

Criteria for an „Orphan“ medications (EU) EC 141/2000

Diagnosis, prevention or treatment of a rare condition

§ 3(a) Paragraph 1: Prevalence of max. 5 in 10 000
§ 3(a) Paragraph 2: insufficient return of investment

that is life-threatening or chronically debilitating

... e.g. genetic diseases, many cancer types

AND

that there exists **no satisfactory method** of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community

OR

if such method exists, that the medicinal product will be of **significant benefit** to those affected by that condition.

* Rarely used in practice

Source: EMA

Orphan designation

- **European law** to stimulate the **research, development and bringing to the market** of appropriate medications by the pharmaceutical industry

- Application for orphan designation via a voluntary procedure **free of charge** at the Committee for Orphan Medicinal products (COMP) at the European medical agencies (EMA)

Quelle: EMA

Orphan designation – two steps necessary

1) „***Orphan designation***“ (initial OD)
   COMP decides on orphan indications of medicinal products at “any stage of development before **an application for marketing authorisation (MA)** is made“ with assumptions of SB (if applicable) **based on plausible hypotheses.**

2) „***Review of orphan designation***“
   Decides ***before MA* is granted,*** whether product still fulfills orphan criteria to become orphan medicinal product (**OMP**) (higher level of evidence required)

- * Initial MA for each underlying condition or major variations

Quelle: EMA

What benefits does an Orphan designation offer?

Pre-marketing

- Regulatory/scientific advice
- Fee reductions
- Eligibility for research funding by the EC
- Centralised procedure

Post-marketing

- Fee-reductions/exemptions
- 10 (+2 if PIP compliant) year market exclusivity

Quelle: EMA

Who evaluates the designation?

Committee for orphan medicinal products (COMP)

- Scientific and transdisciplinary committee
- 1 member by each member state
- 3 **patient representatives** with full voting rights
- 3 EC-nominated experts
- Makes recommendations to the European Commission

European Commission (EC)

- Official granting of Orphan-Status (not by default in agreement with COMP)
- Community register of orphan medicinal products (active/withdrawn or expired/refused)

Quelle: EMA

The complicated reality of rare diseases

- Insufficiently characterised in literature
- Lack of scientific data
- Often wrong data about natural history
- Very heterogenuous in clinical presentation
- There is no “classic orphan setting”

No assessment of Benefit Risk necessary?

- **YES!** Orphans need to show **pos. Benefit/Risk** like all other medications

- Product, indication or class specific guidelines provide a framework for development but only in some cases

Feasibility vs. Quality of evidence

Mostly < 100 very heterogenous patients in the EU

RCT:

Often no comparator

Often no single Standard of Care

Single Arm trials – challenges for Benefit Risk assessment

Inclusion of RWD (Source? Reliebility?)

Endpoints:

Either no robust endpoint or population to small.

Often different Subsets and/or broad Compositendpoints.

Patient Reported Outcomes (PRO) on the rise

Biomarker as surrogate for efficacy

A setting with a lot of uncertainty

- Marketing Authorisation is more than Benefit Risk
- „Uncertainty“ is an important factor
- Very often what „tips the scale“
- Source for Major Objections
- „Compelling Evidence“ important

Patient Reported Outcomes

- **Patienten Perspective** to B/R and Quality of Life
- **B/R** beyond survival, major morbid events and biomarkers.
- **Often low correlation** with classical endpoints
- Further development of PROs **important goal EMA Stratey 2025**
- Especially important in **Orphan development**, where hard enpoints are also harder to measure (feasibility, sample size, controlls)

PROs continued

- High interest to include PROs and patient preferences in drug development
- Trend "**patient-centred drug-development**" and therefore transparency that should inform regulatory decisions
- **BUT: without specific qualification, use the importance of PROS remains limited**
- **Status Quo?**

Controlled trial? Yes please!

- Even in small collectives, small control groups would be possible
- Reduces „Uncertainty“
- Especially for rare diseases hybrid or synthetix controls might be a way forward
- Controls are modelled partly (or excl.) from RWD
- Source can be registries publications, etc.

External controls - key questions

- Data collection process similar? (RCTS, Cohort Studies, Registries)
- External control population similar ?(age, geographic distribution, performance status, treatment history, sex etc.)
- Outcome definitions match those of clinical trial? (often same outcome defined differently)
- Synthetic control data set reliable and comprehensive? (Sample size, covariates)
- Matching?

Synthetic Controls- Examples

- Cerliponase alfa/Batten disease, to 22 Patienten, 42 external controls were modelled into the control
- Palbociclib, expanded indication to men with HR+, HER2-advanced or metastatic breast cancer on the basis of only external control data
- Also on the rise in non orphan diseases (change in SOC, fragmentation of larger indications)

Recent Examples - Voxelotor

- For treatment of hämolytic anemia in sickle cell disease
- Orphan designation: 2.6 in 10000 („frequent“)

- Surrogate marker: improvement in Hb levels
- 1 PhIII placebo controlled RCT
- Primary endpoint reached
- Uncertainties: PROs no improvement („good Patients“)

Abecma (CAR T-Cells)

- Refractory or relapsed multiple myeloma (3.6 in 10,000)
- multicentre, open label, single-arm clinical trial in 140 adult patients.
- About 67% of patients enrolled in the study responded to the treatment and maintained remission
- BUT: severe adverse reactions and uncertainties regarding RWD
- **Conditional**

IMCIVREE (Setmelanotide)

- Obesity in POMC oder biallelic leptin receptor (LEPR) Defizienz (0.1 in 10,000)

- 2 uncontrolled studies with 21 patients (super small dataset
- Most patients meet 10% weight loss after one year

- „Compelling“
- PASS

Obiltoxaximab

- Anthrax, theoretically 0.001 in 10,000
- Practically: Indication Zero. How do you authorize this?
- Increased survival in animal challenge studies
- Only healthy volunteers treated

But what happens after Market Exclusivity?

- In general medicinal products in rare diseases can be chemical, biologicals, ATMPS …
- Chemicals will be open for Generic and Hybrid applications
- Biologics for the Biosimilar Pathway
- And ATMPs … well, let’s see

An Orphan Biosimilar is also just a Biosimilar

- There is no special regulatory pathway for Orphan Biosimilars
- Any biosimilar application will be a „classical“ Article 10(4)
- However the challenges of the orphan setting remain for the biosimilar developer
- And submissions need to be innovative – and a little bit creative

Biosimilar Development Program (EU)

A stepwise approach to comparability

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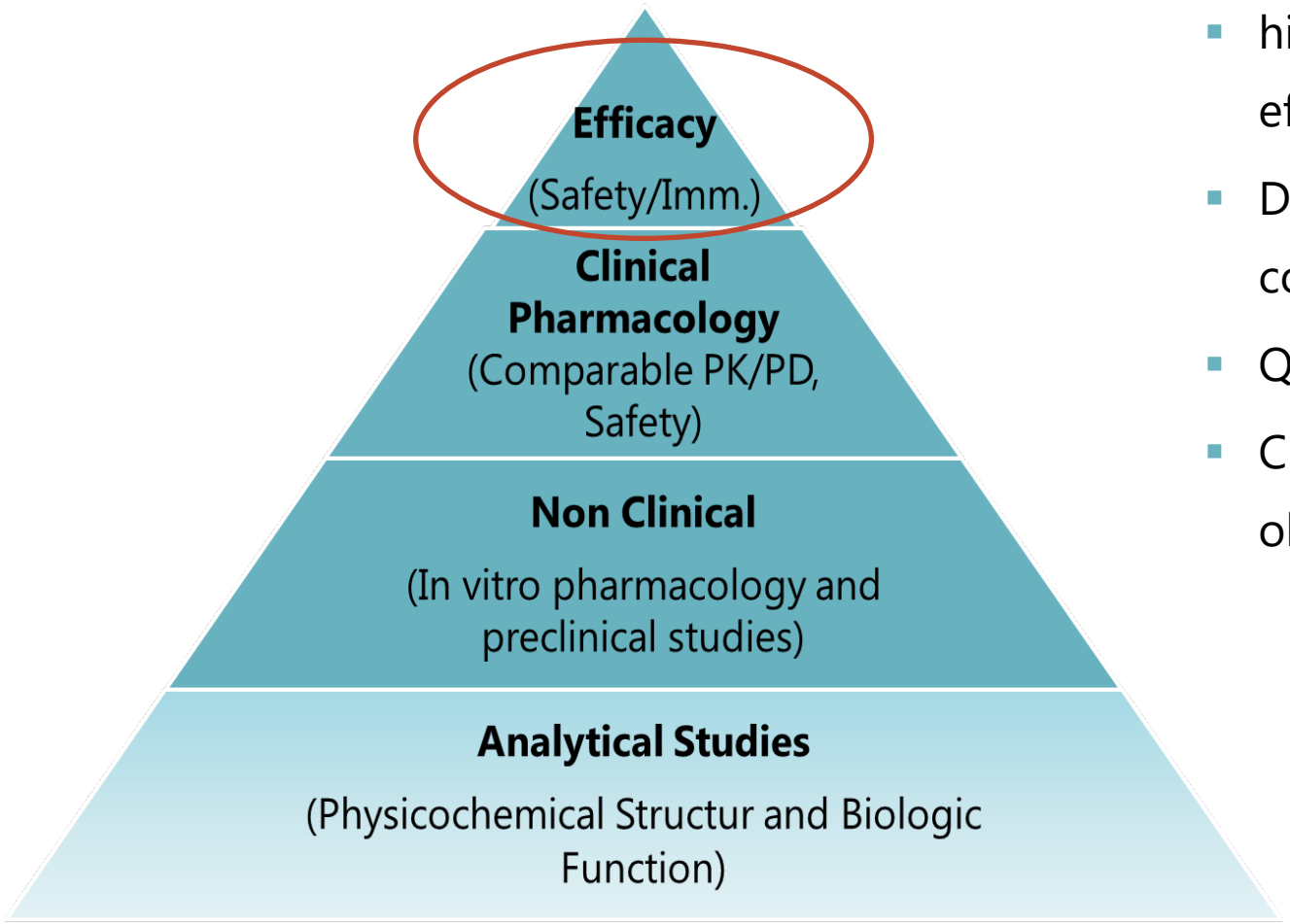

- high standards concerning quality, safety and efficacy.
- Development and Manufacturing more complex compared to generics (small molecule)
- Quality comparability most important
- Clinical comparability: to confirm what has been observed.

To illustrate…

Examples for treatment costs

Tysabri® (natalizumab)	one pack N1	€ 2428.06 (yearly € 29136.72)
Soliris® (eculizumab)	one pack N1	€ 5827,19 (yearly up to € 600.000)
Ocrevus ® (ocrelizumab)	yearly cost	€ ~33000

Biosimilars contribute to keep/make innovative drugs available to a wide range of patients!

Disclaimer: Pricing is not taken into account by regulators

Source: wikipedia, medizinfuchs.de October 2018

Example for „orphan“ Biosimilar?

- We don’t have one … yet!
- Biosimilar Eculizumab is under review
- But how do you show similarity in efficacy and safety in such small groups?

How could clinical similarity work?

- In certain cases, comparative PK/PD studies may be sufficient to demonstrate clinical comparability of the biosimilar and the reference medicinal product
- E.g. PD marker/biomarker is an accepted surrogate marker on the clinical outcome
- Applicants have to come up with a comprehensive way to characterize and compare the clinical profile via PK, functional markers and safety (tailored approach)
- Prerequisite: a **super solid comparability on quality level**

Summary

- There are multiple incentives to develop drugs in rare diseases. (Orphan Designation, Prime, Conditional MA)
- Development remains challenging (Recruitment, Study designs)
- Gap in knowledge on the disease
- PROs and RWD on the rise
- Orphan Biosimilars are just Biosimilars
- A „tailored approach“ with a reduced clinical program could be envisaged.

Thank you!

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