Arzneimittelinformation bei Seltenen Erkrankungen

9. Kongress für Arzneimittelinformation
Workshop

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Global burden of rare diseases

One rare disease only affects few patients

-> 6000- 8000 rare diseases described

-> approx. 300 mio people affected worldwide

-> ~ 30 mio in the EU

-> ~ 3-4 mio in DE

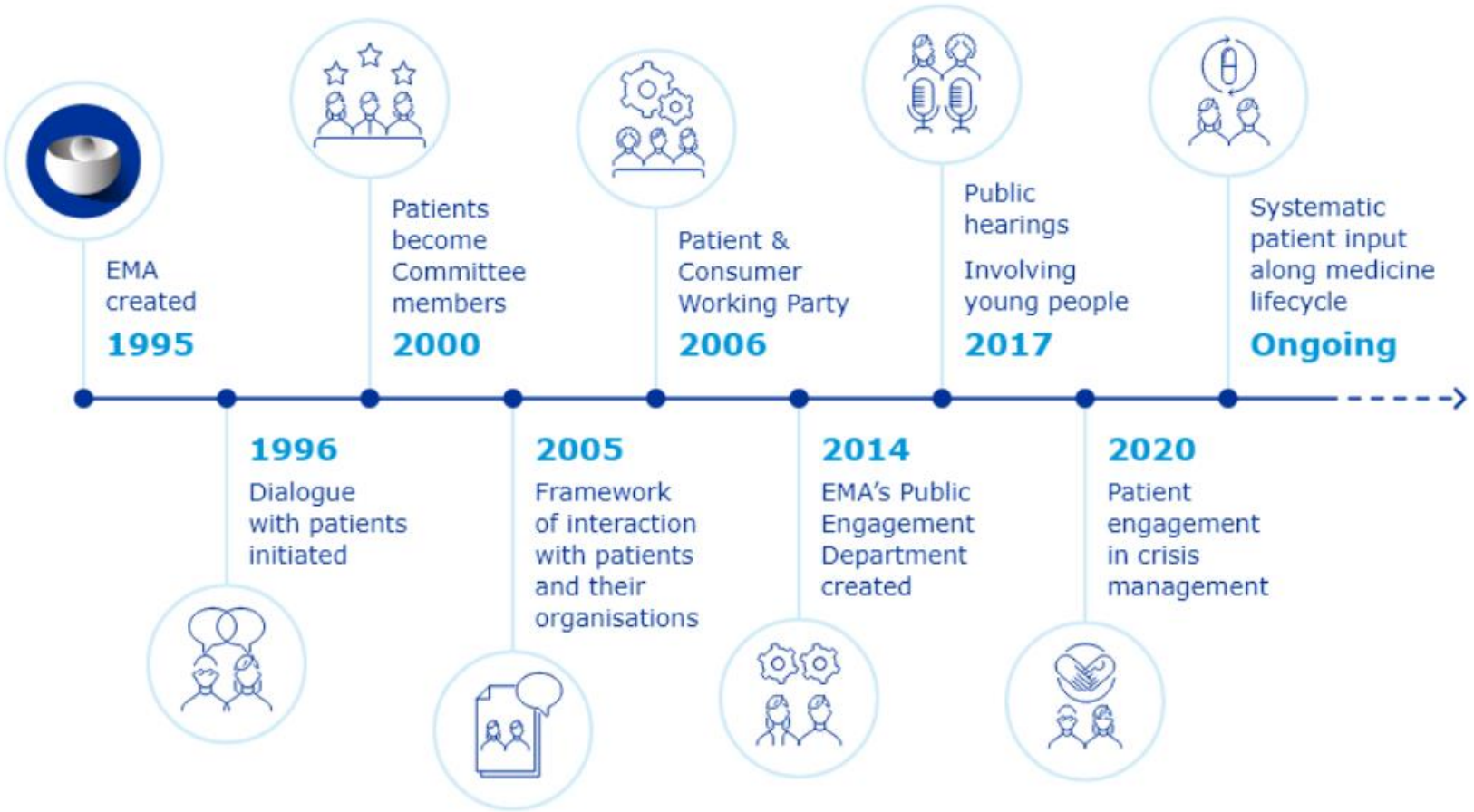
Adachi et al. Int. J. Environ. Res. Public Health 2023, 20, 4732. https://doi.org/10.3390/ijerph20064732

Patient advocacy and expertise

- History of patient advocacy and orphan legislation
- Not only „patient experience“ -> patient expertise!
- Allianz Chronischer Seltener Erkrankungen (ACHSE) https://www.achse-online.de/de/
  - Alliance of national patients organisations
  - Patient engagment and training
  - Information, networking and advocacy
  - Altas für Versorgungseinrichtungen in DE für seltene Erkrankungen https://www.se-atlas.de/map/zse

- EURORDIS – Rare Diseases Europe https://www.eurordis.org/
  - non-profit alliance of patient organisations from 74 countries (Europe + international)
  - information for empowerment from networking to research
  - Policy and (social) care aspects

EMA - interactions with patients and consumers



https://www.ema.europa.eu/en/partners-networks/patients-consumers

Additional information on patient involvement

- Council for International Organizations of Medical Sciences (CIOMS)
- Report of the CIOMS Working group XI Working group XI

DRUG DEVELOPMENT IN RARE DISEASES

Regulatory and legislative setting

Special circumstances...

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

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 rules!

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

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;

Reasoning and historical background of special regulatory frameworks for drug development in rare diseases

- **Experience before introduction of policies**
  - Little innovation in the field of rare diseases (**majority**: genetic diseases affecting children)
  - Even positive signals in rare diseases were not persued further (for marketing authorisation)
  - *Off-label use* common
  - ➢ **Introduction of incentives (typically at least two-stage)**
    1. ***Orphan designation*** (**OD**) for **drug candidates** for a rare disease
       Pre-marketing incentives during development and regulatory interactions
    2. ***Orphan medicinal product*** (**OMP**) still fulfilling orphan criteria at the time of MA
       Post-marketing incentives

Raising and rising awareness
Introduction of orphan policies

- Patient engagement!
  => Orphan policies
  - USA 1983
  - Japan 1993
  - Australien 1997
  - EU 1999
  - …. and counting

⇒ Research and development

⇒ *Licensing*

⇒ *Pricing*

⇒ *Reimbursement* $$$

Chan et al. *Value Health*. 2020; 23(12):1580–1591

Orphan designation (EU)

- **European regulation** to stimulate the **research, development and bringing to the market** of appropriate medicinal products 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)
- Incentives rather than obligations

From EU-regulation to interpretation

Regulation 141/2000 European Parliament and Council

Implementing Regulation 847/2000 European Commission

- Commission Regulation 2018/781 -> similarity
- Q&A related to the assessment of similarity for ATMPs in the context of the orphan legislation (version 2)

Commission Notice on Articles 3,5 and 7 2016**/C 424/03**

Commission GL on Article 8(1) and 8(3) (C(**2008**) 4077)

Commission GL on Article 8(2) (**2008**/C 242/07) (hardly used/to be abolished)

Commission Communication **2003**/C 178/02 – superseeded by **2016/C 424/03**

Commission GL on format and content of applications (2022/C 440/02)

COMP PtC on estimation and reporting of prevalence (2019)

Chronology important!

Why so complicated?

Examples for orphan benefits

Premarketing:

- Regulatory and scientifc advice
- Fee reductions for regulatory procedures
  (waivers esp. Paediatric indications or by type of sponsor, e.g. academics)
- Eligibility for research grants

Postmarketing

- Market exclusivity rights

- *Investor‘s money?*
- *Further national incentives possible, e. g. special status for reimbursment (DE)*
- *Tax reduction?*

Intended

Extra?

Purpose of orphan incentives

Make research and development and bringing of medicinal products for rare diseases to the market

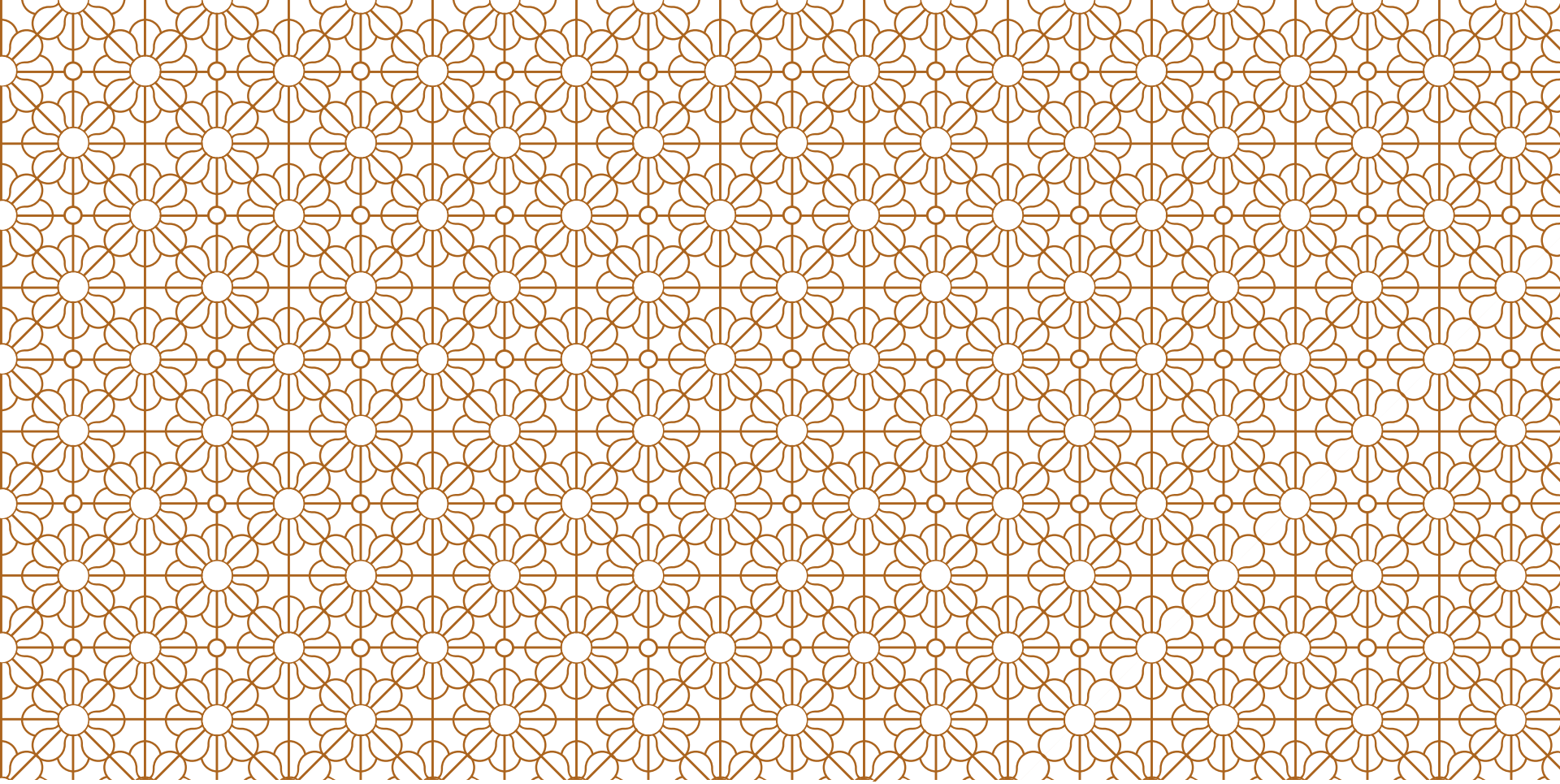
- Streamlined to regulatory/scientific standards
- (Less costly)
- Protected against **direct** competitors

Dilemma: Incentives such as market exclusivity needed for promoting clinical development in rare diseases, but this should not prevent further developments altogether.

* Roberts et al. Therapeutic Innovation & Regulatory Science (2023) *57*:386–395

Orphan criteria international

Criterion	Definition
Rarity	Proportion or absolute figure, thresholds may differ
Condition	According to disease classifications **or other justifications**
Subsetting	Justification for subsetting of broader conditions acceptable? (e.g. in EU **not** for: stage, bio-marker), i.e. acceptability of „targeted therapy“ / personalised medicine
Severity	All diseases or serious conditions, only
Minimal data requirements	Preclinical (in vitro/in vivo) or **clinical** data -> assumptive/robust/stat. significance? Promising development plan
Additional criteria (may be reason for different status!)	• Significant benefit • Structural similarity



ORPHAN DRUG DESIGNATION

EU Regulation

(Current) orphan criteria in the EU

Diagnosis, prevention or treatment of a **rare condition**

§ 3(a) Paragraph 1: affecting 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.

EU

Orphan condition

- Validity of a proposed condition always discussed (artificial “orphanisation” of common diseases to be avoided)
- Typically based on following elements
  - Aetiology (which may include e.g., genetics),
  - Histopathology
  - Pathophysiology
  - Clinical characteristics
  - **Supported** by current internationally accepted classifications systems.
- **Not necessarily congruent** with groupings in treatment guidelines, eligibility to clinical trials, regulatory use within EMA, **over time**….

- https://www.ema.europa.eu/en/documents/other/statement-amended-policy-orphan-designations-inherited-retinal-dystrophies_en.pdf
- Discussion of condition: Wang et al. Orphanet Journal of Rare Diseases (2024) 19:334 https://doi.org/10.1186/s13023-024-03322-7

Medical plausibility

1. A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

(a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition

- Only assessed at initial OD by COMP
  (because at marketing authorisation **favourable B/R established by CHMP**)
- **1/3 in vivo non-clinical data, only**

Tsigkos S, Mariz S, Sheean ME, Larsson K, Magrelli A and Stoyanova-Beninska V (2021) Regulatory Standards in Orphan Medicinal Product Designation in the EU. Front. Med. 8:698534. doi: 10.3389/fmed.2021.698534

Criterion of „return of investment“ 141/2000

Criteria for d

1. A medicinal product shall
medicinal product if its sponso

(a) that it is intended for the diagn ention or treat-
ment of a life-threatening or chro debilitating condi-
tion affecting not more than five thousand persons in
the Community when the ap ation is made, or

that it is intended for the diagnosis, prevention or treat-

(h) all cost and revenue data shall be determined in accordance with generally accepted accounting practices and shall be certified by a registered accountant in the Community;

to justify the necessary investment;

§ 3 (1)
a) 2. paragraph
„return of investment“

-> Barely used (<10 x in almost 25 years)

Criterion of rarity 141/2000

§ 3 (1)
a) 1. paragraph
„prevalence“

Criteria for designatio

1. A medicinal product shall be desig
medicinal product if its sponsor can establi

(a) that it is intended for the diagnosis revention or treatment of a life-threatening or chron ically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or

that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;

Incidence and prevalence

Incidence	Duration of disease (life expectancy)	Prevalence
low	short	low
low	long	(may be) high
high	**short**	**(may be) low**
high	long	high

Prevalence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Points to consider on the estimation and reporting of the prevalence of a condition for orphan designation
Adopted
Reference Number: EMA/COMP/436/01 Rev. 1
English (EN) (148.52 KB - PDF)
First published: 22/03/2002 Last updated: 21/06/2019
View

Criterion of severity

- Prognosis and symptoms/complication/sequelae need to be described
- Usually accepted (very rare exceptions for self-limiting, curable diseases)

Existence of treatment options

Artide 3

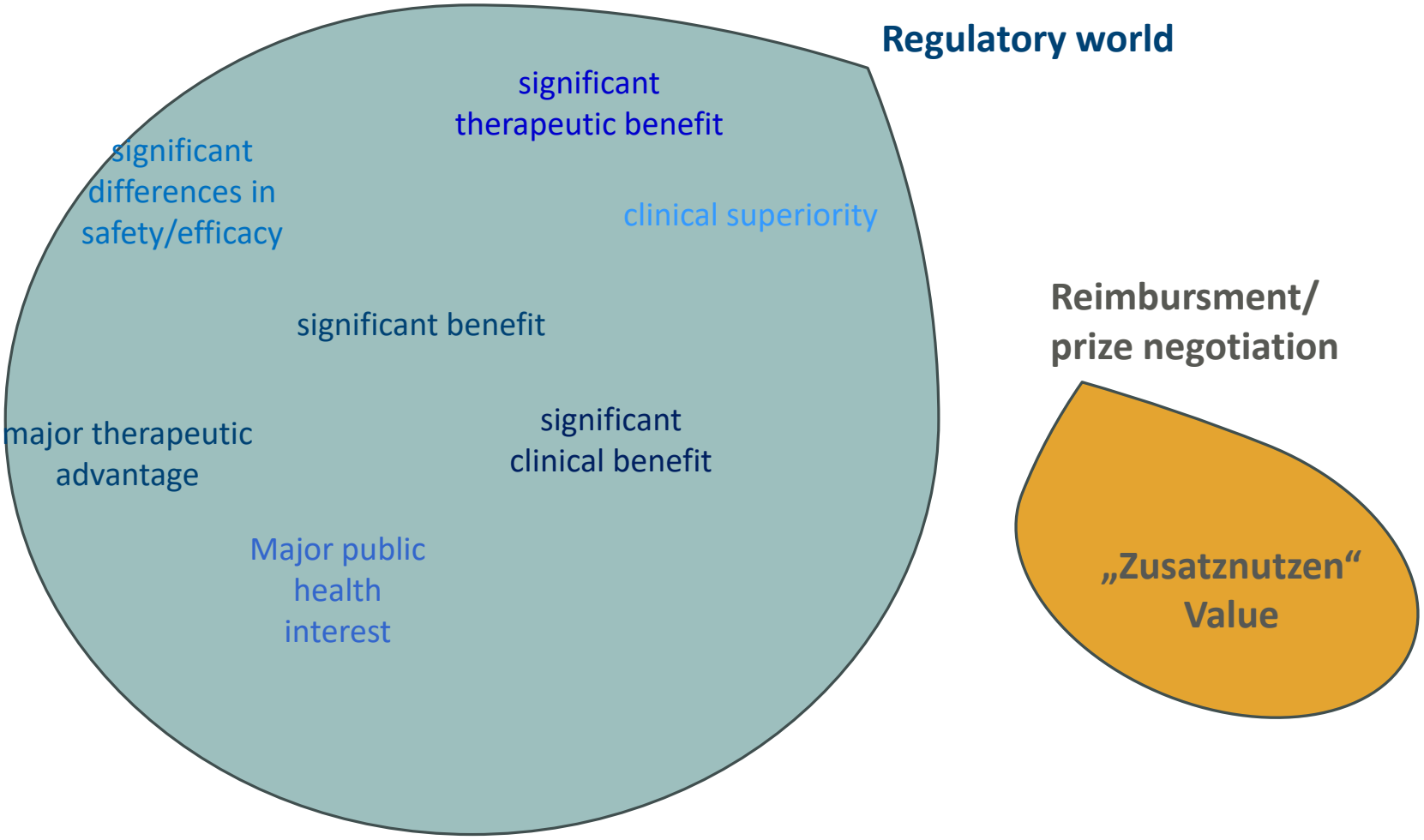
(b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

=> Without satisfactory methods, fulfillment of rarity & severity sufficient for OD

=> **If satisfactory methods exist** -> additional requirement of „relative effectiveness“ (**not required** for marketing authorisation per se)

ELEMENT OF RELATIVE EFFECTIVENESS

Various provisions concerning “benefit”
EMA and beyond



Regulatory setting: Various provisions concerning "benefit" over existing/satisfactory methods

Reg. (EC) 141/2000	Reg.(EC) 1901/2006	Dir. 2001/83/EC	Reg. (EC) 847/2000	Reg. (EC) 726/2004	Reg. (EC) 507/2006	Reg. (EC) 726/2004
Significant benefit	Significant therapeutic benefit	Significant differences in safety and/or efficacy	Clinical superiority	Significant clinical benefit	Major therapeutic advantage	Major public health interest
Orphan designation	PIP/Waiver	New active substance	Break Market exclusivity	+1 year market protection	Conditional marketing authorisation	Accelerated assessment
COMP	PDCO	CHMP	CHMP	CHMP	CHMP	CHMP
P+E	P	E	E	E	E	P

P: Presumed
E: Established

! Different definitions and legal requirements with respect to „comparators" !

Different motivation and aims

Drug regulation

Policy for RD + children or

Provisions in regulatory setting for

- specific products (CMA, EXC, NAS, 8+2+1, break ME)
- innovative approach (accelerated assessment)

➢ Different data over time

➢ Wording similar

➢ **Reimbursment & prizing**

Definition of a „significant benefit“ in the EU orphan framework

a) **Clinically relevant advantage**
   - **Improved efficacy**
   - **(Improved safety)**

b) **Major contribution to patient care**
   - Ease of self-administration (e.g. oral vs iv)
   - Compliance-promoting properties

@MA
To be supported by meaningful benefits for patients, e.g. QoL

→ Guidance and examples in Commission notice – 2016/C 424/03

Fregonese L., et al. Drug Discov Today. 2018 Demonstrating significant benefit of orphan medicines: analysis of 15 years of experience in Europe doi: 10.1016/j.drudis.2017.09.010.

Definition of „satisfactory methods“

Regulation (EC) 847/2000 *„Provide details of the „existing methods“ which **may include** authorised medicinal products, medical devices or other methods of diagnosis, prevention or treatment which are used in the Community“*

Commission notice (2016/C 424/03) *„A MA is granted if the B/R assessment is positive. Therefore, at the time of the grant of a MA in accordance with EU legislation, the authorised medicinal product is considered to be a satisfactory method.“*

- authorised products (national, decentral, central) to be listed comprehensively
- **no off-label use**
- Non-regulated/Non-pharmacological treatments (surgery, radiation, …), if included in guidelines
- ~~Officinal formula, if well-known and general practice in the EU~~ (EC notice 2016)

! **Court case (T-549/19)** Overlap of populations in therapeutic indications critical!

Sheean et al. 2021, Front Med. Defining Satisfactory Methods of Treatment in Rare Diseases When Evaluating Significant Benefit–The EU Regulator's Perspektive doi: 10.3389/fmed.2021.744625

How to demonstrate „significant benefit“

- No prespecified endpoints or design
- Case-by-case approach
- Demonstrating benefit of candidate product (not only discussing lack of efficacy of existing methods)
- New or clearly different patient population benefitting from new treatment (additional line, non-overlapping populations covered in therapeutic indication)
- Improved efficacy (direct or indirect comparison)
- Improved safety difficult to claim based on limited data available at MA
- Major contribution to patient care requires first the demonstration of comparable efficacy/safety and needs to be supported by data

Information on orphan designations

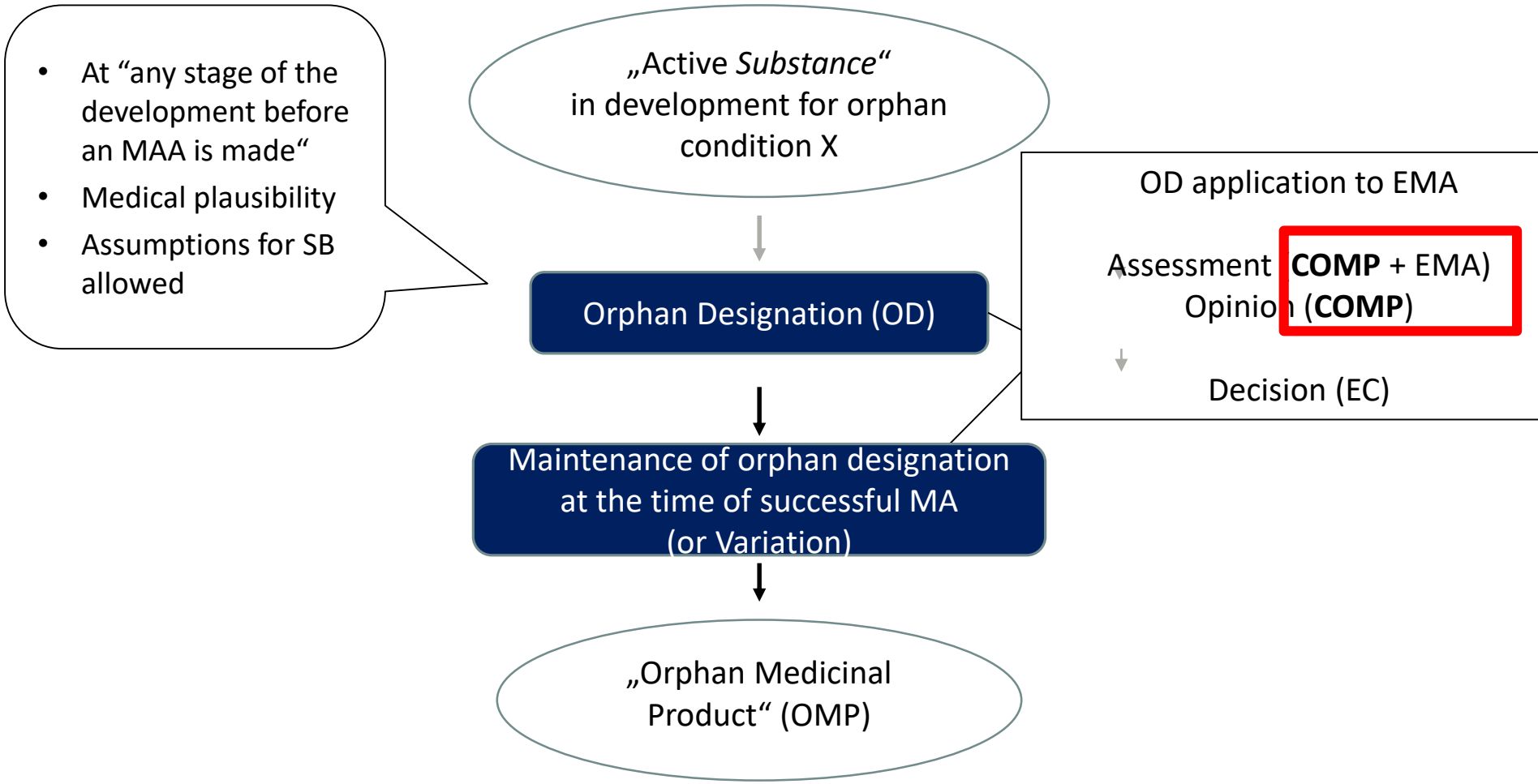
Community register of orphan medicinal products (active/withdrawn or expired/refused) https://ec.europa.eu/health/documents/community-register/html/index_en.htm

IRIS portal: https://iris.ema.europa.eu/odpublicregister/

-> Browsing the sources and asking questions

Procedural information on orphan designation (optional)

Process of orphan designation (OD) in EU



COMP Committee of orphan medicinal products

(At least a) two step process: initial OD

-> „candidate product“ for product development

COMP issues positive opinion

- Active OD (no expiry date, transferrable from sponsors)
- No regular reassessment!
- Eligible for pre-marketing incentives (~12 mio € for fee reductions/year)

COMP not convinced and sponsor withdraws
-> sponsor remains anonymous and may resubmit later again

COMP not convinced and issues negative opinion
-> sponsor may appeal negative opinion/ go to court

(At least a) two step process: *Review of orphan designation at the time of MA*

-> orphan medicinal product (OMP) or non-orphan medicinal product

- Submission of maintenance report with MAA to EMA (~D120)
- Discussion of fulfillment of orphan criteria around opinion on marketing authorisation
- Three possible outcomes:
  - COMP agrees and issues positive opinion
    -> publication of orphan maintenance assessment report (OMAR)
  - COMP disagrees and sponsor withdraws orphan designation
    -> publication of withdrawal OMAR (up to LoQ)
  - COMP disagrees and issues a negative opinion (as OMAR)
  - Sponsor may appeal (delays time to market)
    - If COMP again negative, sponsor may submit law suit

Orphan medicinal product

Positive opinion by COMP:

- OMP with market exclusivity for 10 years **per** underlying OD
- different start dates possible
- **all therapeutic indication** must have (had) OD)

z.B. **Gazyvaro**

Orphan market exclusivity for "Treatment of chronic lymphocytic leukaemia" (based on designation EU/3/12/1054) started on 24 Jul 2014
10 years of market exclusivity
✖ This orphan market exclusivity ended on 24 Jul 2024
Orphan market exclusivity for "Treatment of follicular lymphoma" (based on designation EU/3/15/1504) started on 15 Jun 2016
10 years of market exclusivity
✔ This orphan market exclusivity will expire on 15 Jun 2026

Transparency of COMP decisions

Orphan designations listed in EC-Register

Scientific summary of OD on EMA-homepage
2010 - 2017: Publication of summary of review of OD at the time of MA

EPAR: Reference to (withdrawal of) orphan desigantion at the time of MA

July 2012-2017: Minutes of COMP meetings including details of discussions (listed by orphan condition)

From 2018: Orphan medicines assessment report (OMAR) for OMPs at the time of MA
(including withdrawal assessment report - up to LoQ and negative opinions)

Access to complete COMP reports after marketing authorisation/Variation upon request (EMA/127362/2006)

Market exclusivity

Market exclusivity

Market exclusivity „**earned**“ by the applicant

Protection against **SIMILAR** products by authorities

→ Whenever an OMP is authorised in the **target indication** of a new medicinal product**,**

- **similarity needs to be addressed by subsequent applicants**
- **Applicability of derogations** checked
- Both at validation of MAA and imminently prior to MA!

Similarity

1) Principal molecular structural features

AND

2) Mechanism of action

AND

3) Therapeutic indication

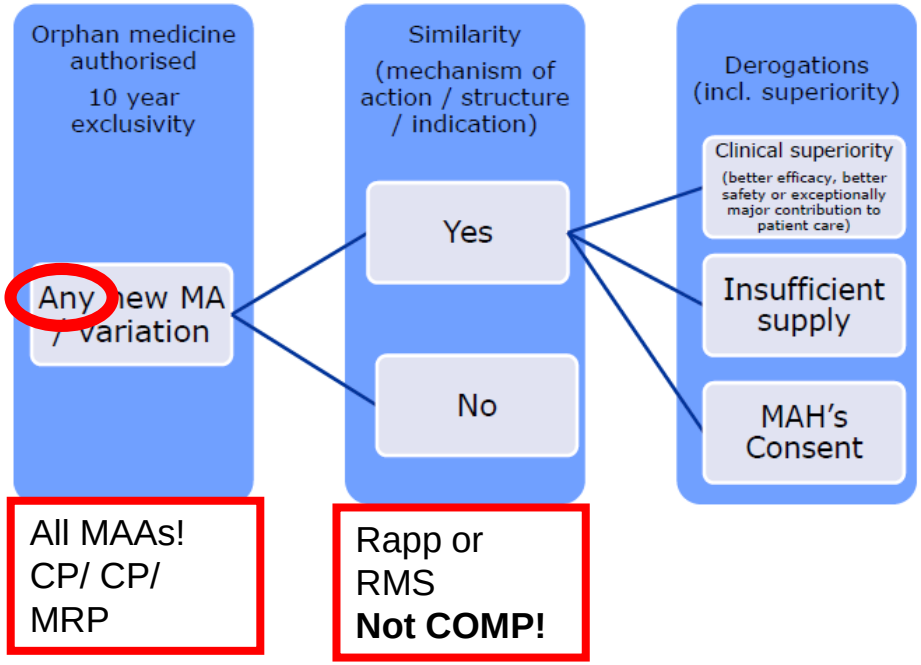
➢ Similarity report to be submitted with MAA (Module 1.7.1)

Table 2 Summary of EU's definitions of similar medicinal product

Synthetics	Synthetic Polynucleotides
• The principal molecular structural features are the relevant structural components of an active substance. They can be the whole or part of the molecule. Whether the principal molecular structural features are the same between two or more molecules will be identified by comparison of their structures	Synthetic polynucleotide substances, single or double stranded, consisting of two or more distinct nucleotides where: • the difference in the nucleotide sequence of the purine and pyrimidine bases or their derivatives is not major, shall be considered similar. Therefore for antisense or interfering nucleotide substances, addition, substitution or deletion of a nucleotide not significantly affecting the kinetics of hybridisation to the target shall normally be considered similar,
• Isomers, mixture of isomers, complexes, esters, ethers, salts, and derivatives of the original active substance, or an active substance that differs from the original active substance only with respect to minor changes in the molecular structure, such as a structural analogue, shall be considered similar	• the difference in structure related to modifications of the ribose or deoxyribose backbone sugars or to the replacement of the backbone sugars by synthetic analogues shall normally result in substances being considered similar. For antisense or interfering nucleotide substances, changes in the (deoxy-)ribose not significantly affecting the kinetics of hybridisation to the target would normally be considered similar
Biological Medicinal Products	**Proteinaceous Substances**
• The principal molecular structural features are the structural components of an active substance that are relevant for the functional characteristics of that substance. The principal molecular structural features may be composed of a therapeutic moiety or a therapeutic moiety in combination with an additional structural element(s) significantly contributing to the functional characteristics of the active substance	• If the difference in structure between them is due to post-translational events (such as different glycosylation patterns) substances shall normally be considered similar. However, exceptionally some post-translational modifications may result in a non-similar substance, if there is significant effect on the functional characteristics of the substance
• Such an additional structural element(s) can be conjugated, fused or linked by other means to the therapeutic moiety or can be an extension of the therapeutic moiety protein backbone by additional amino acids. Substances with structural elements for which similar methods of modification or conjugation technology are used shall normally result in similar substances	• If the difference in the amino acid sequence is not major, substances shall normally be considered similar. Therefore, two pharmacologically related protein substances of the same group (for example, having differences related to e.g. N-terminal methionine, naturally extracted versus rDNA-derived proteins or other minor variants) shall normally be considered similar. However, the addition of a structural element may result in substances being considered non-similar if this significantly affects the functional characteristics of the substance
• Biological active substances that differ from the original biological substance only with respect to minor changes in the molecular structure shall be considered similar	• Monoclonal antibodies binding to the same target epitope shall normally be considered similar. However, two monoclonal antibody conjugates or fusion proteins could be determined to be non-similar if either the Complementary Determining Region sequences of the antibody or the additional structural element of the conjugated monoclonal antibody were different

Roberts et al. Therapeutic Innovation & Regulatory Science (2023) 57:386–395

Similarity assessment



Kozarewicz (EMA, 2014) New Active Substance categorisation and Orphan Similarity- SME workshop: Focus on quality for medicines containing chemical entities
http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2014/04/WC500165443.pdf

Experience with orphan designation in EU

Orphan designations and OMPs in EU (end 2023)

244 initial MAs since 2000 in EU*
50 extensions of indication in
166 orphan conditions

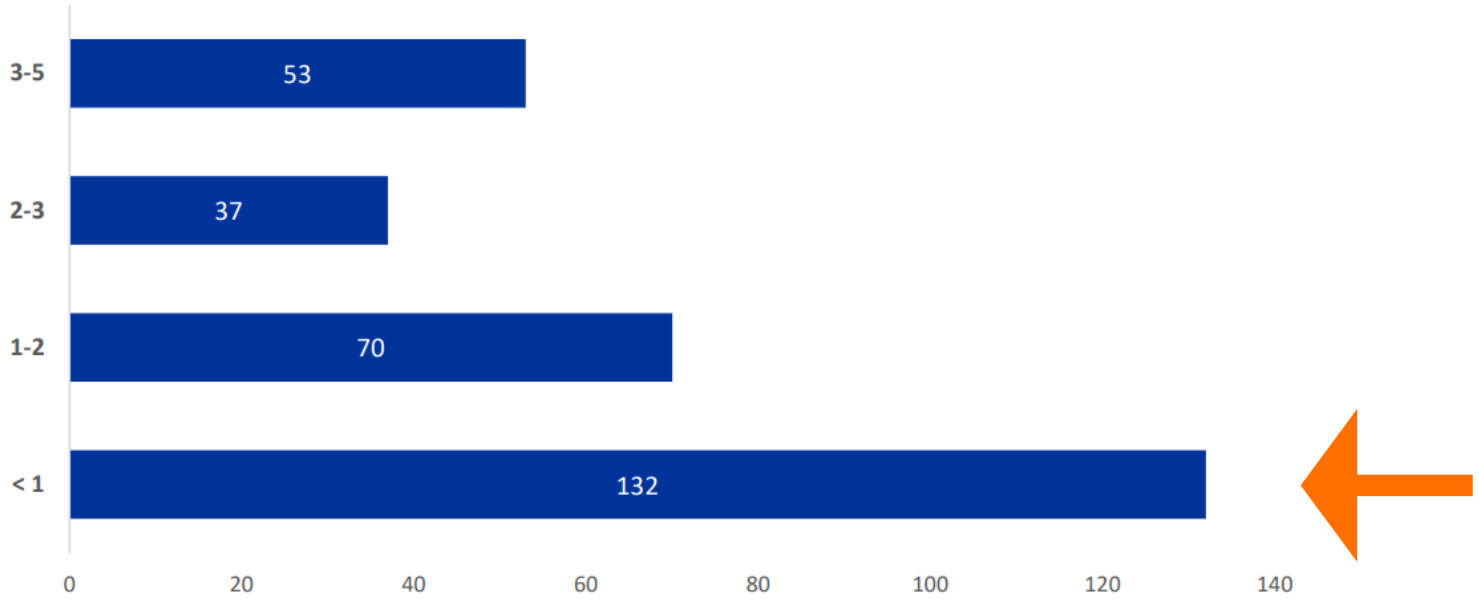
- **>2200 orphan designations in approx. 600 conditions**

6000 – 8000 orphan conditions

*in recent years **more than 1/3** of finalised MAAs/year

https://www.ema.europa.eu/en/documents/leaflet/infographic-orphan-medicines-eu_en.pdf

Prevalence of conditions targeted by OMPs

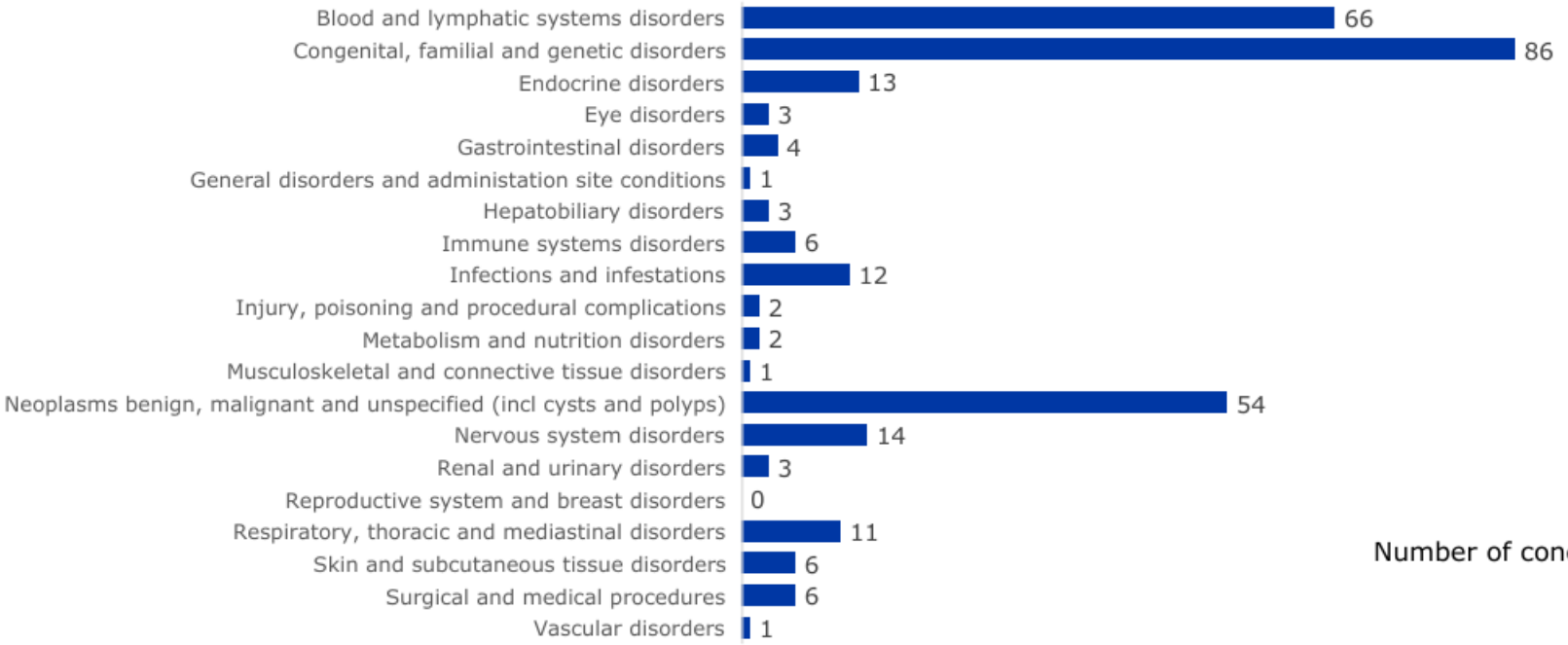


Aus „Orphan Medicinal Product Designation Overview 2000-2023 EMA“

Heterogeneity of OMPs (2000-2023) therapeutic indications (initial MAs + extensions)

ORPHAN MEDICINAL PRODUCT DESIGNATION

Initial orphan marketing authorisations and extension of indication granted to date



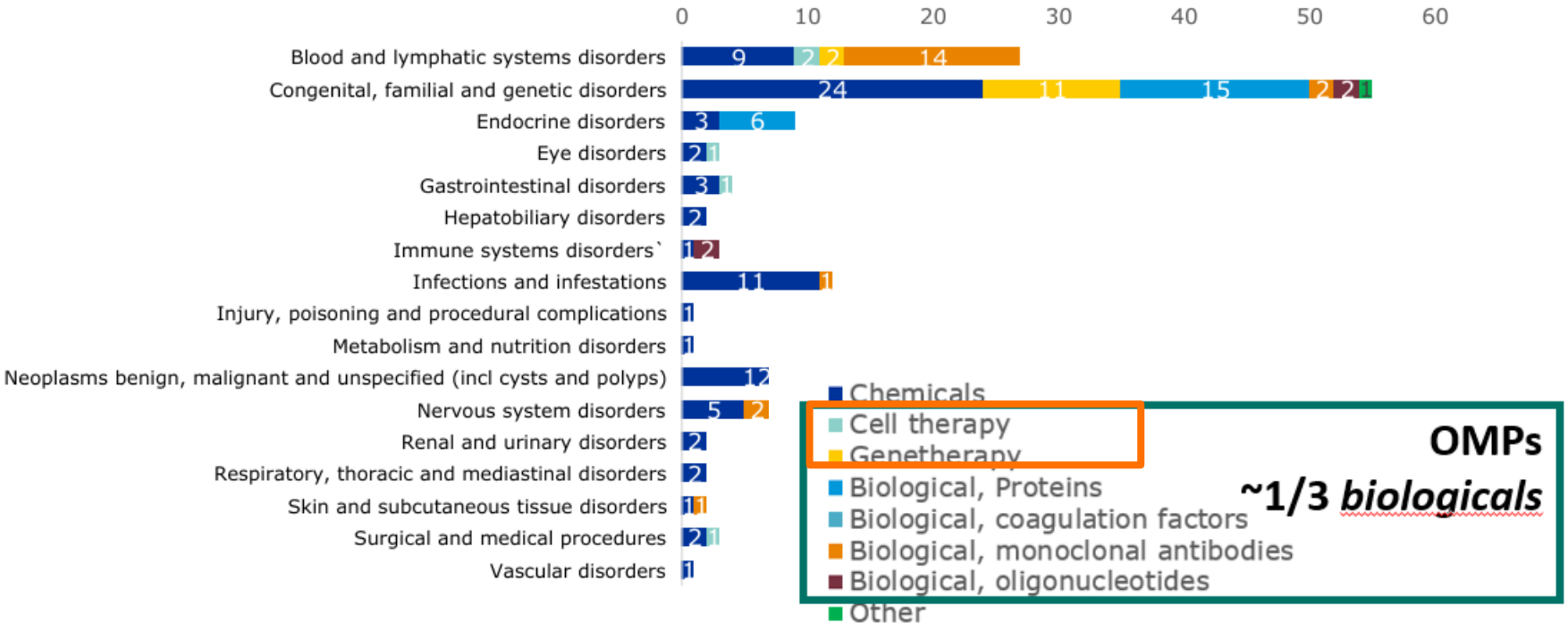
Number of conditions: **166**

Orphan Medicinal Product Designation Overview 2000-2023, EMA

Heterogeneity of OMPs (2000-2023) types of product (initial MA)

ORPHAN MEDICINAL PRODUCT DESIGNATION

Authorisations by type of product



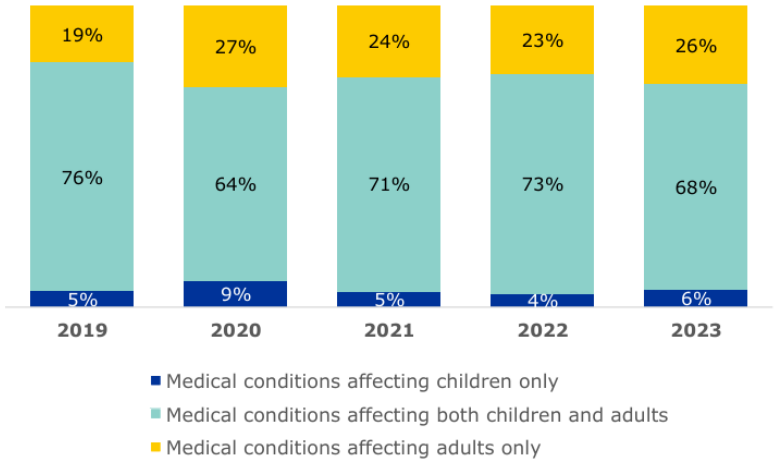
ATMPs: 22 % of initial OD

Orphan Medicinal Product Designation Overview 2000-2023, EMA

Orphan medicinal products for children (only)?

ORPHAN MEDICINAL PRODUCT DESIGNATION

Orphan designations adult/paediatric



EUROPEAN MEDICINES AGENCY

Synergy intended with paediatric regulation (EC) 1901 and 1902/2006:

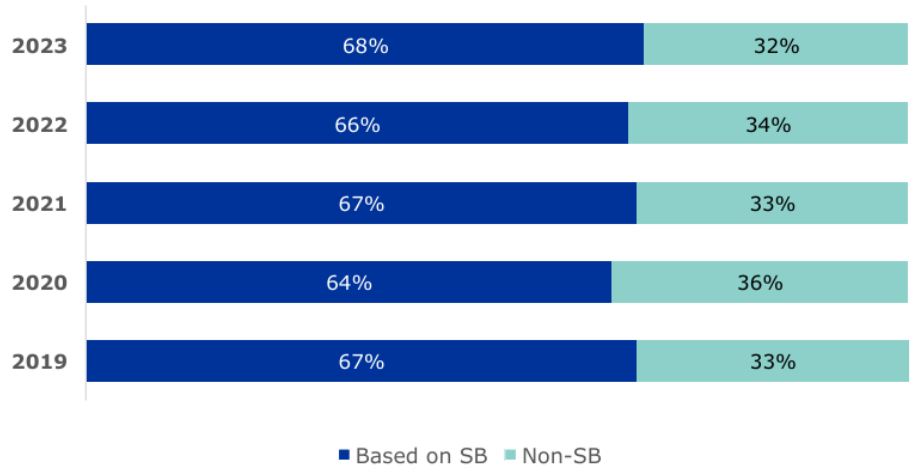
- **10+2** years of market exclusivity when developped according to paediatric investigation plan
- 12 y ME only realised in in less than ~10% of 23 ODs (up to now).

„Orphan Medicinal Product Designation Overview 2000-2023 EMA“

OD for development of first medicinal product for condition?

ORPHAN MEDICINAL PRODUCT DESIGNATION

Designations based on significant benefit (SB)



- More procedures with SB for MA (>75%)
- SB is based on **„clinically relevant advantage“**
  - Better efficacy
  - Improved safety

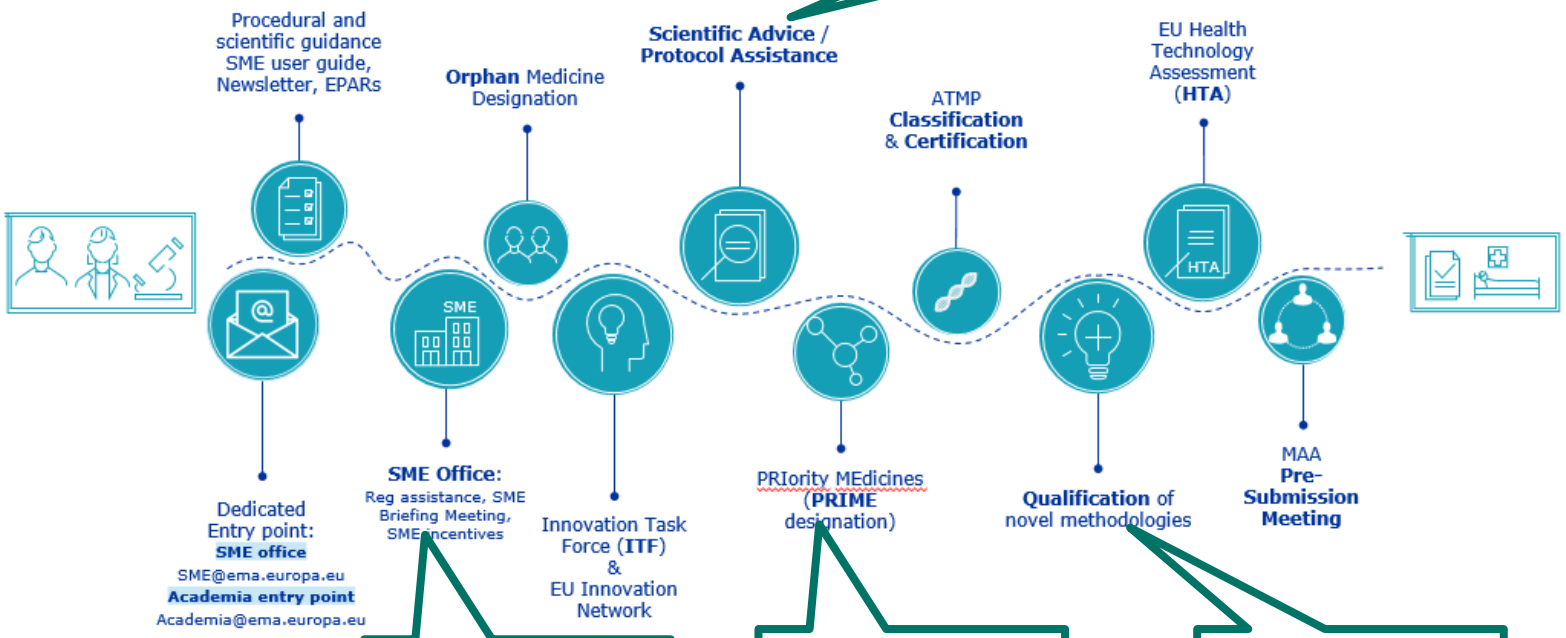
  or on

„major contribution to patient care“

From „Orphan Medicinal Product Designation Overview 2000-2023 EMA“

Support for applicants @ EMA

- Including for academia und *non-for-profit*
- ***Parallel consultation with HTA***



From: Helene Casaert (EMA) Workshop on Support for Orphan Medicine Development

Approx. 30% of applicants

Majority of PRIME products are orphans

Also with respect to registries

Specific problems for OMP with special forms of MA

- Conditional MA or MA under exceptional circumstances
- Pivotal studies often explorative study designs (in small numbers of patients)
- Uncontrolled
- „Surrogate“ or intermediate endpoints
- Follow-up limited

→ Indirect comparisons difficult to interpret

→ Clinical relevance of (intermediate) endpoints not well understood

→MA if benefit/risk balance favourable

→Post-approval requirements for further studies

-> Difficult pricing & reimbursment discussions!

Evidentiary requirements

- **Therapeutic context** important
  Disease specific guidance may be available
  https://www.ema.europa.eu/en/human-regulatory/research-development/**scientific-guidelines/clinical-efficacy-safety-guidelines**
  e.g. ALS, Duchenne, Haemphilia, neoplasms, cystic fibrosis ….
- Scientific advice (**protocol assistance**) highly recommended
- **Prepare and Beware** for reference to (existing) **registries / „RWD“** for increasing efficiency of clinicial trials or post-approval requirements

Naumann-Winter et al. (2022) Licensing of Orphan Medicinal Products-Use of Real-World Data and Other External Data on Efficacy Aspects in MAA Concluded at the EMA Between 2019 and 2021. Front Pharmacol. doi: 10.3389/fphar.2022.920336.

Beyond MA

Data collection beyond MA

-> post-authorisation studies or „specific obligations“*

- safety (PASS) bzw.
- efficacy & safety (PAES)

- Conditional MA or MA under exceptional circumstances *
  approx. 30% of OMPs (2019-2021)

  e.g. **Registries**
  -> EMA Guideline since 2021

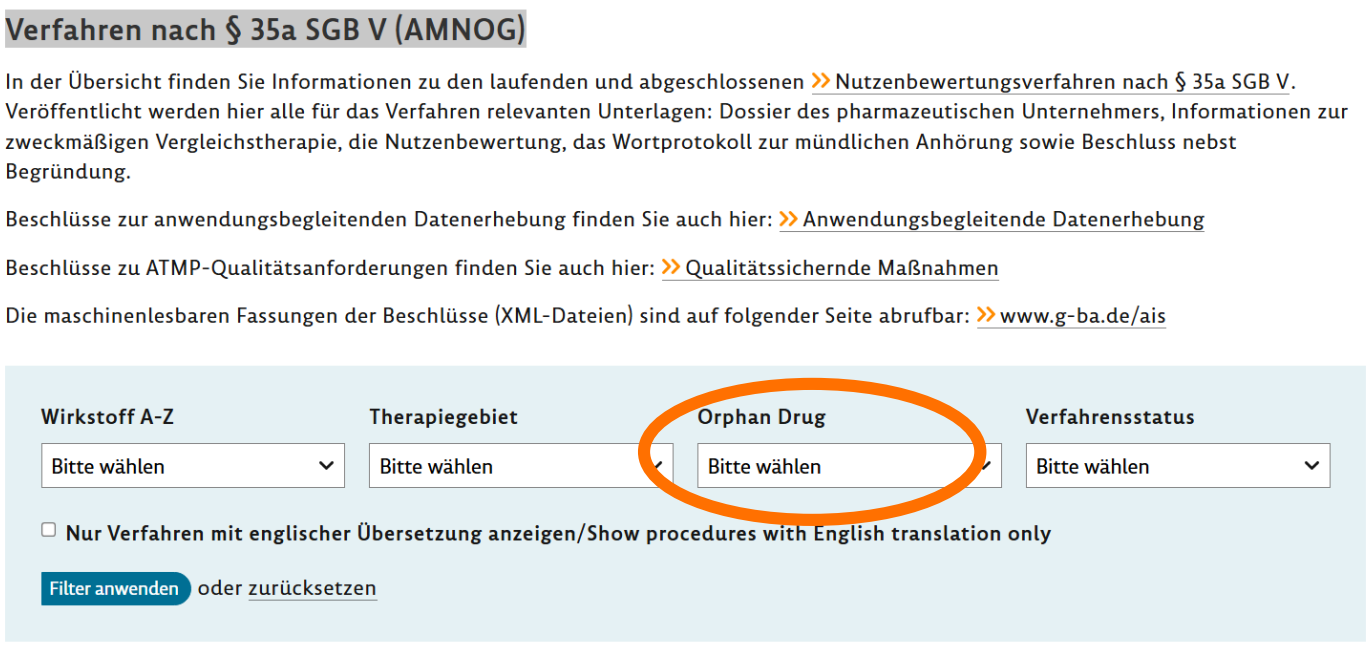
REIMBURSEMENT AND PRICING

Deutschland

Reimbursement and Pricing

Gemeinsamer Bundesausschuss
https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/

Nutzenbewertung nach § 35a SGB V (AMNOG)



Zusatznutzen bei *orphan drugs (limited assessment)*

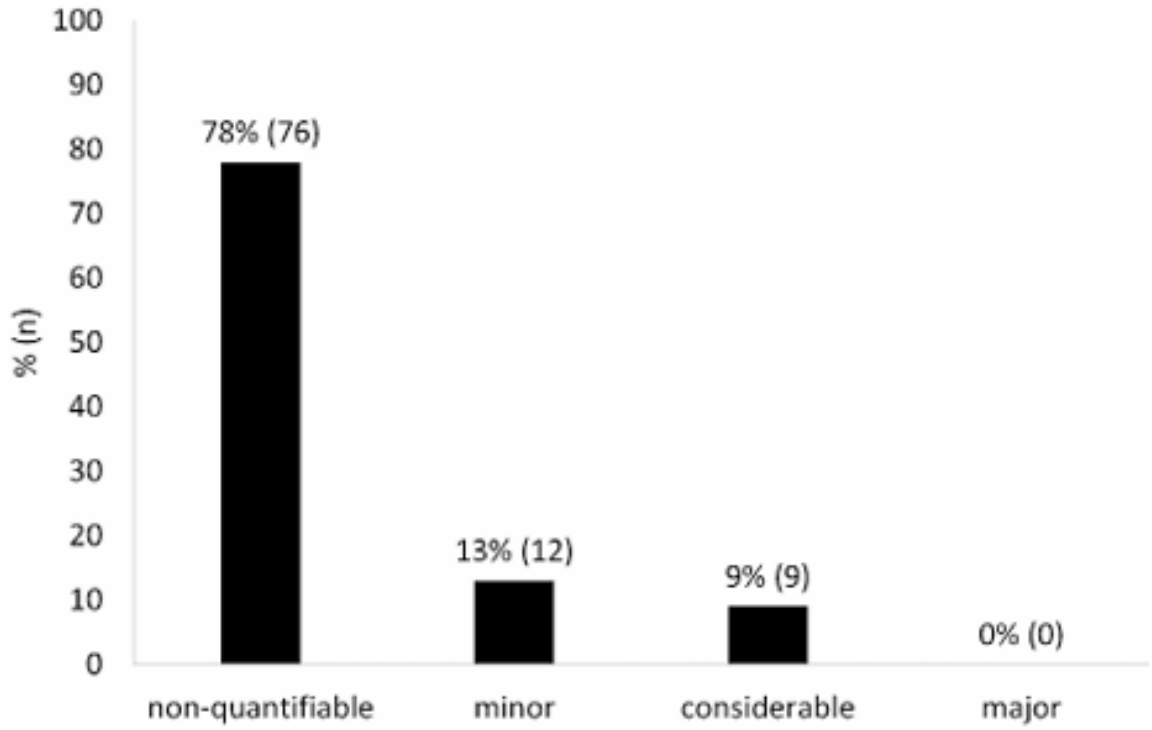


Figure 2. Extent of added benefit in limited assessments of orphan drugs.

Kranz P, et al (2024). Results of HTA assessment of orphan drugs in Germany— lack of added benefit, evidence gaps, and persisting unmet medical needs. International Journal of Technology Assessment in Health Care, 40(1), e68, 1–7 https://doi.org/10.1017/S026646232400062X

Zusatznutzen nach regulärer Nutzenbewertung

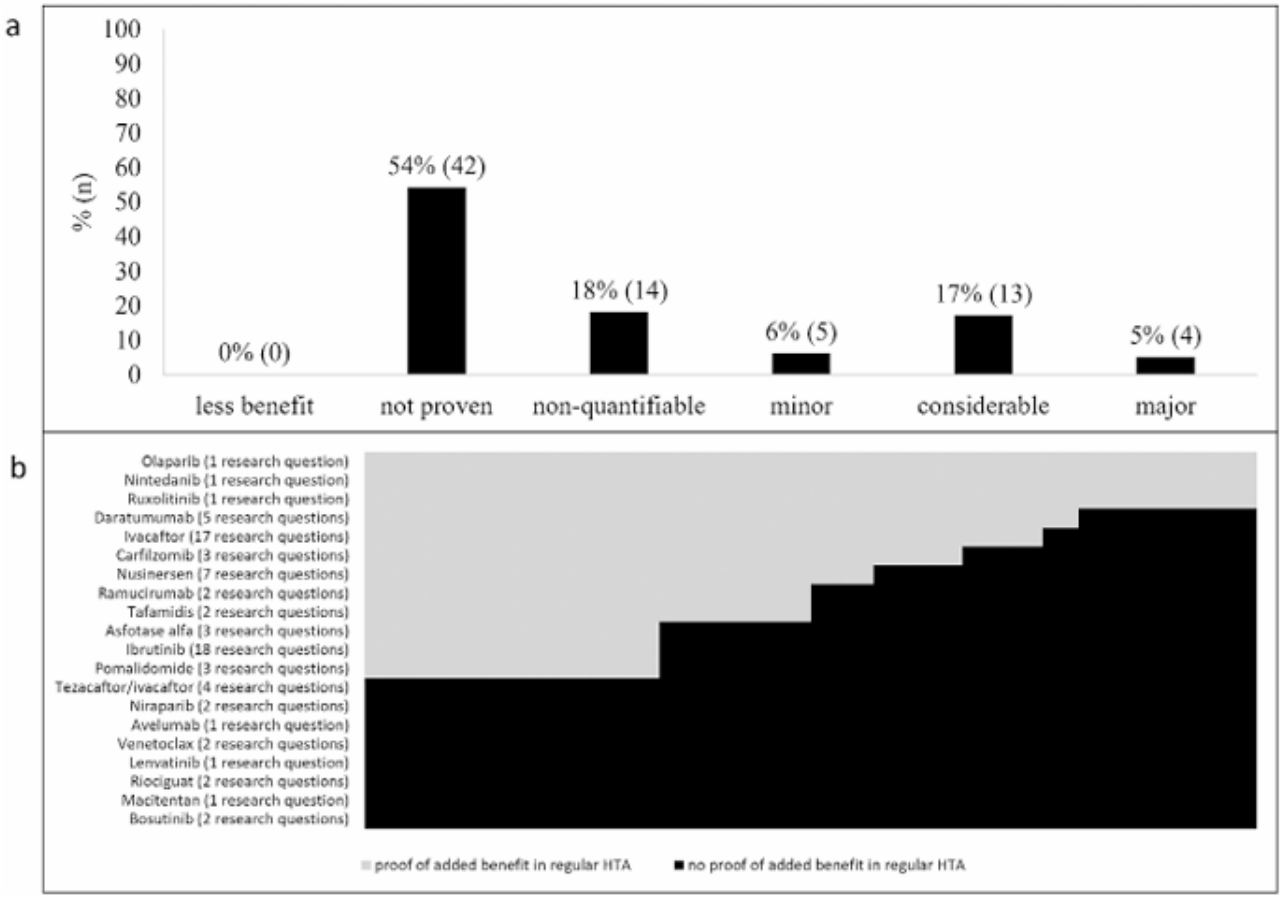
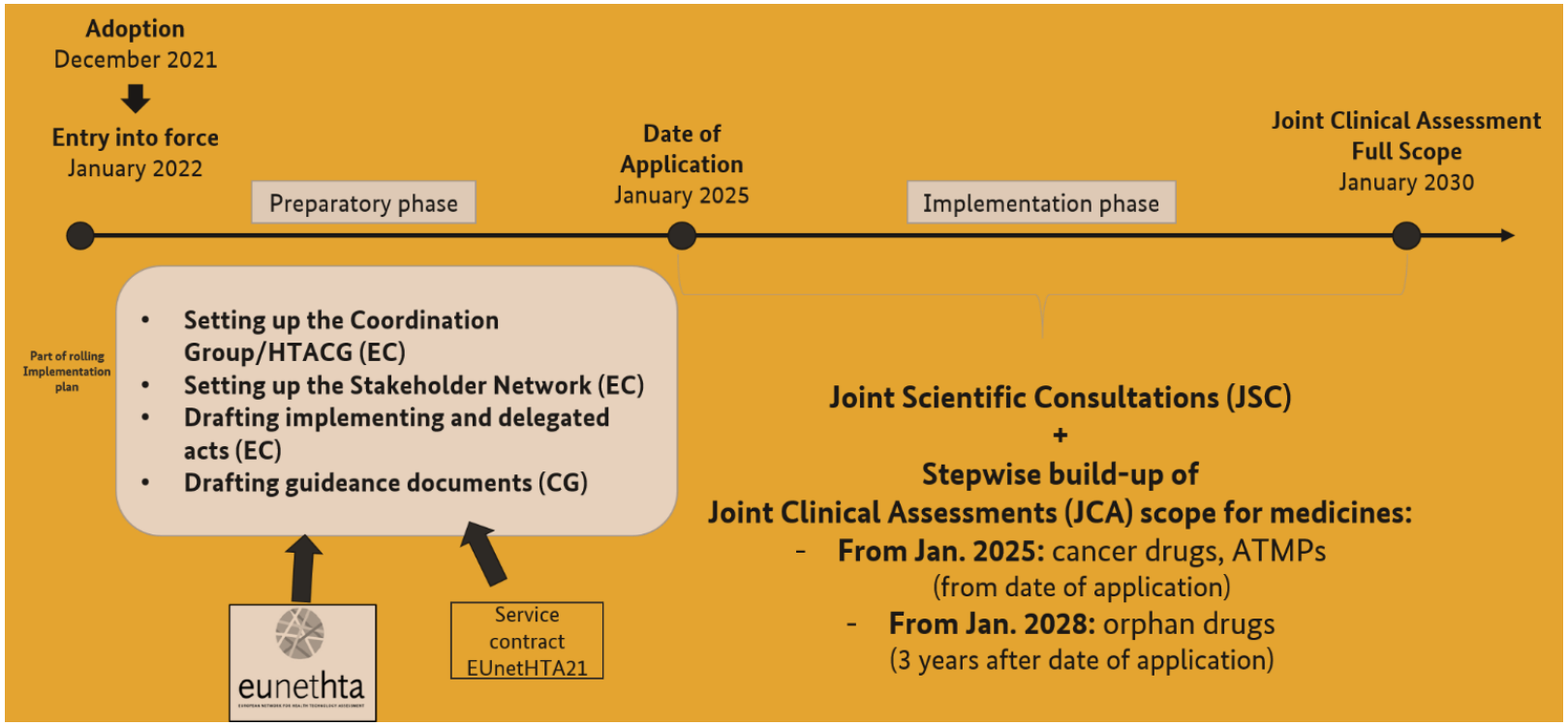


Figure 3. Distribution of ratings of added benefit from regular HTAs of orphan drugs: (a) Summary (b) Individual drugs. Each bar equals 100 percent of the research questions examined. Both graphs are reproduced from the IQWiG working paper (5).

Kranz P, et al (2024). Results of HTA assessment of orphan drugs in Germany— lack of added benefit, evidence gaps, and persisting unmet medical needs. International Journal of Technology Assessment in Health Care, 40(1), e68, 1–7 https://doi.org/10.1017/S026646232400062X

EU HTA regulation



Evaluation of the orphan regulation, impact assessment and proposal for revision

Background on revision of orphan regulation

- **2017**: Evaluation of orphan and paediatric legislation
  https://ec.europa.eu/health/human-use/paediatric-medicines/evaluation_en
  Targeted &Public consultations, Conferences, Workshops & reports
- **2020**: Pharmaceutical strategy and Impact assessment for orphan and paediatric legislations

  Roadmap of inception impact assessment Ref. Ares(2020)7081640 (25/11/2020)

  Public consultation of road map – factual summary available Ref. Ares(2021)6792304 – (04/11/2021)
- **26 April 2023: Proposal for new pharma legislation by EC published**
  https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en
  - **New Directive and new (replacing) Regulation**
- **October 2023 Discussion in European Parliament**
  Opposing modifications by Rapporteurs, outcome yet unclear
  https://healthcarelifesciences.bakermckenzie.com/2023/10/17/eu-pharma-package-ep-rapporteurs-have-opposing-views-on-the-new-pharmaceutical-directive-and-regulation/
  (+links therein)

Evalulation of EU *orphan* regulation (started 2017)

- ~ 300 **new *orphan* indications**
  - mostly **new active substances** (**off label use still common**)
  - **Paradigm change** for some conditions (anti-sense, CAR-T, gene therapy…)
  - **Dynamic research activity** in some indications (parallel development programmes)
  - **AND still neglected** therapeutic fields

⇒ majority of 6000-8000 rare diseases **still without treatment**

⇒ also true for medicines for children **in spite of intended synergy** with paediatric legislation.

Strength and weaknesses of orphan regulation

- Unmet need **not specifically targeted** (e.g. paediatric oncology)
- Unequal access in member states
- Affordability issues
- Fit for scientific progress?
- Room for procedural improvement

Selection of current proposals from regulation with relevance for orphans

- **Modulation of exclusivity period?**
- **Enhanced regulatory/scientific** support (including academia, non-profit)
- More **interactions across different stakeholders** including, e.g. health care professionals, HTA and medical device regulation
- Data collection also within **compassionate use programmes?**
- **Platform trials**
- Reflection of **RWD** in regulatory decision-making -> European Health data space
- More **flexibility** (delegated acts, regulatory sandbox)
- Data protection for **repurposing** (4 years)?
- Transparency on **public funding** received ?

RESEARCH AND DEVELOPMENT

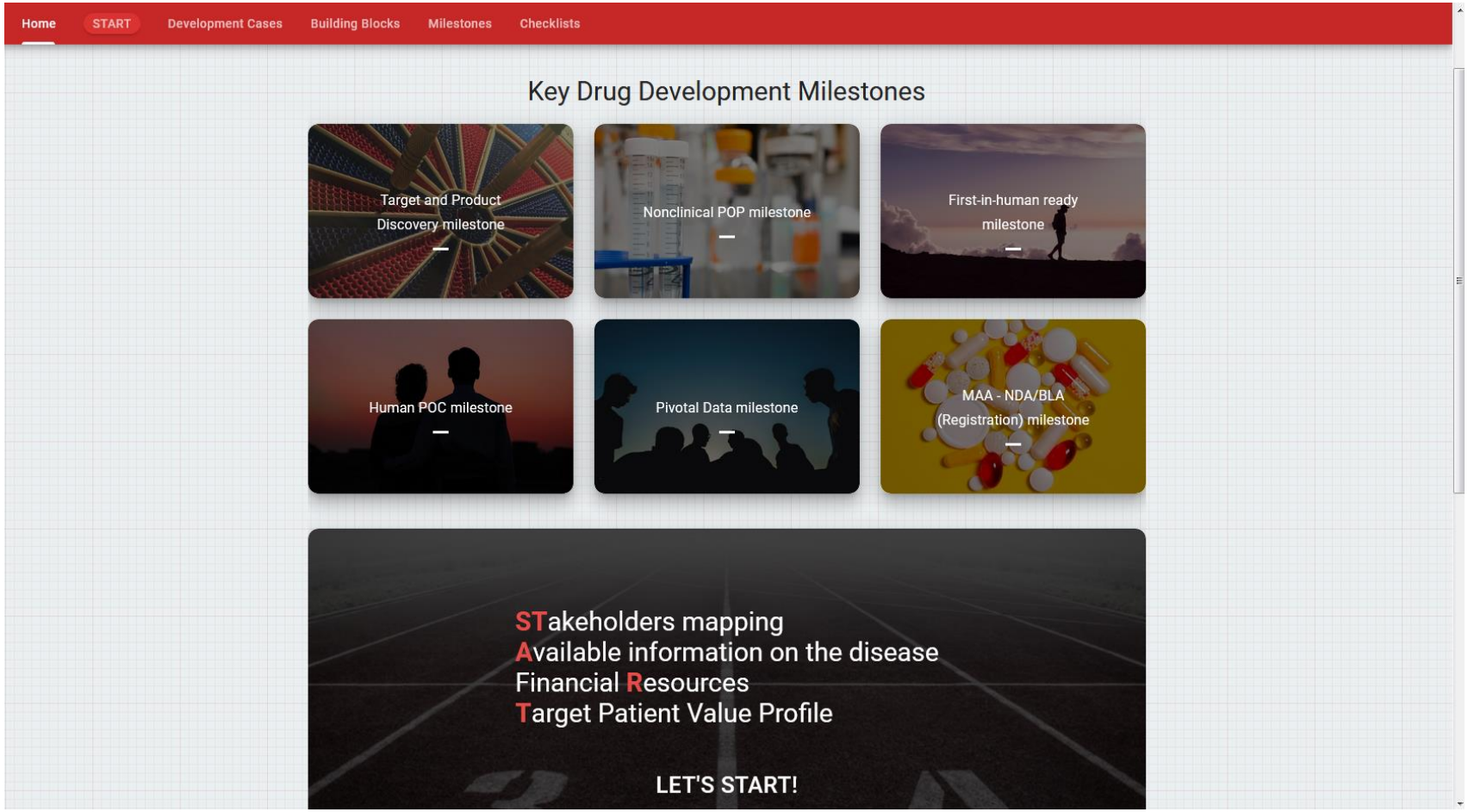
ORPHANET
https://www.orpha.net/de

Knowledge on rare diseases and orphan drugs (classifications, coding, information, specialists….)

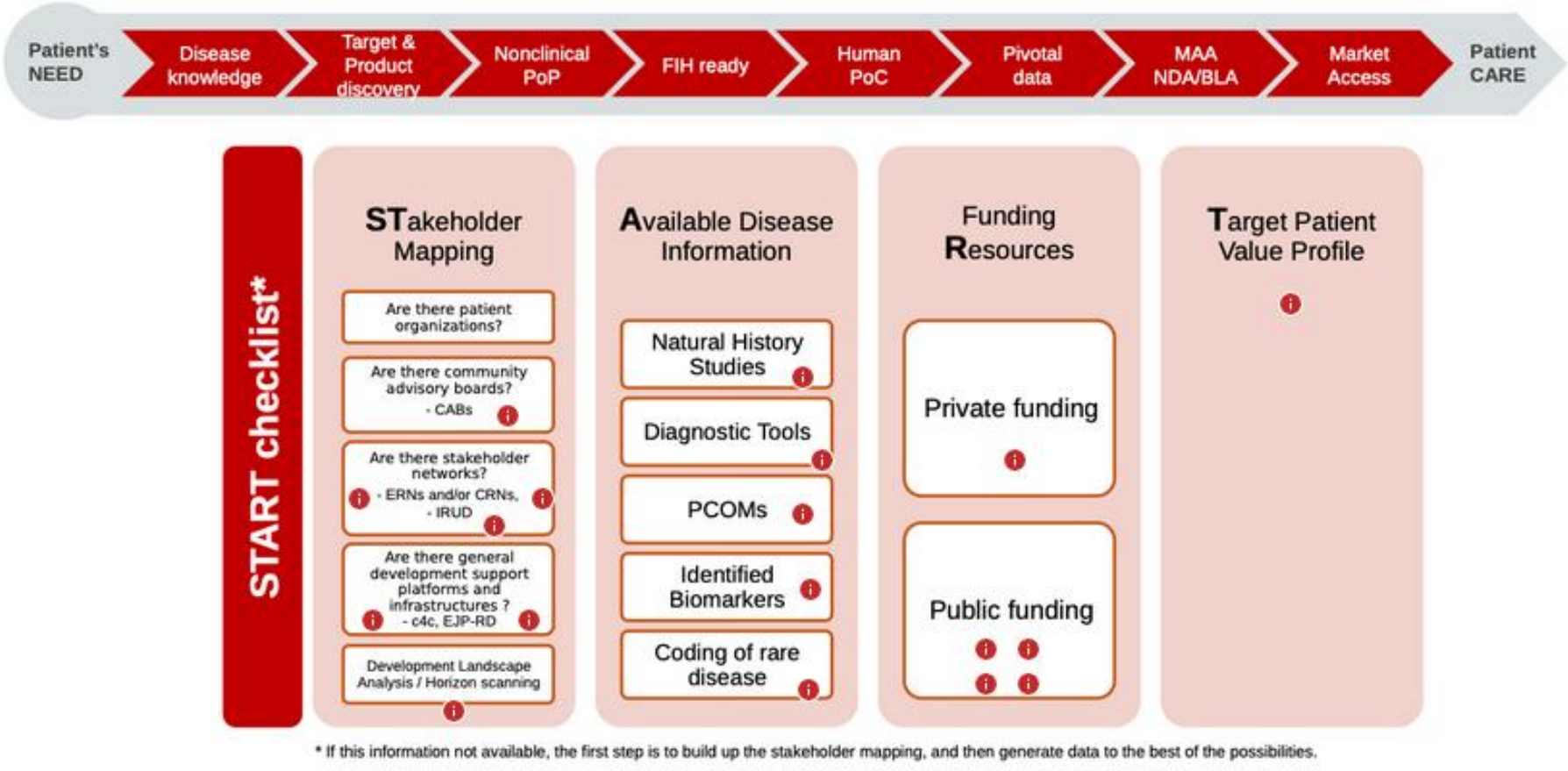
=> Increase visibility of rare diseases also in and for research

RESOURCES FOR DEVELOPPING MEDICINES FOR RARE DISEASES

Public-private partnership: [IRDiRC Orphan drug development guidebook]

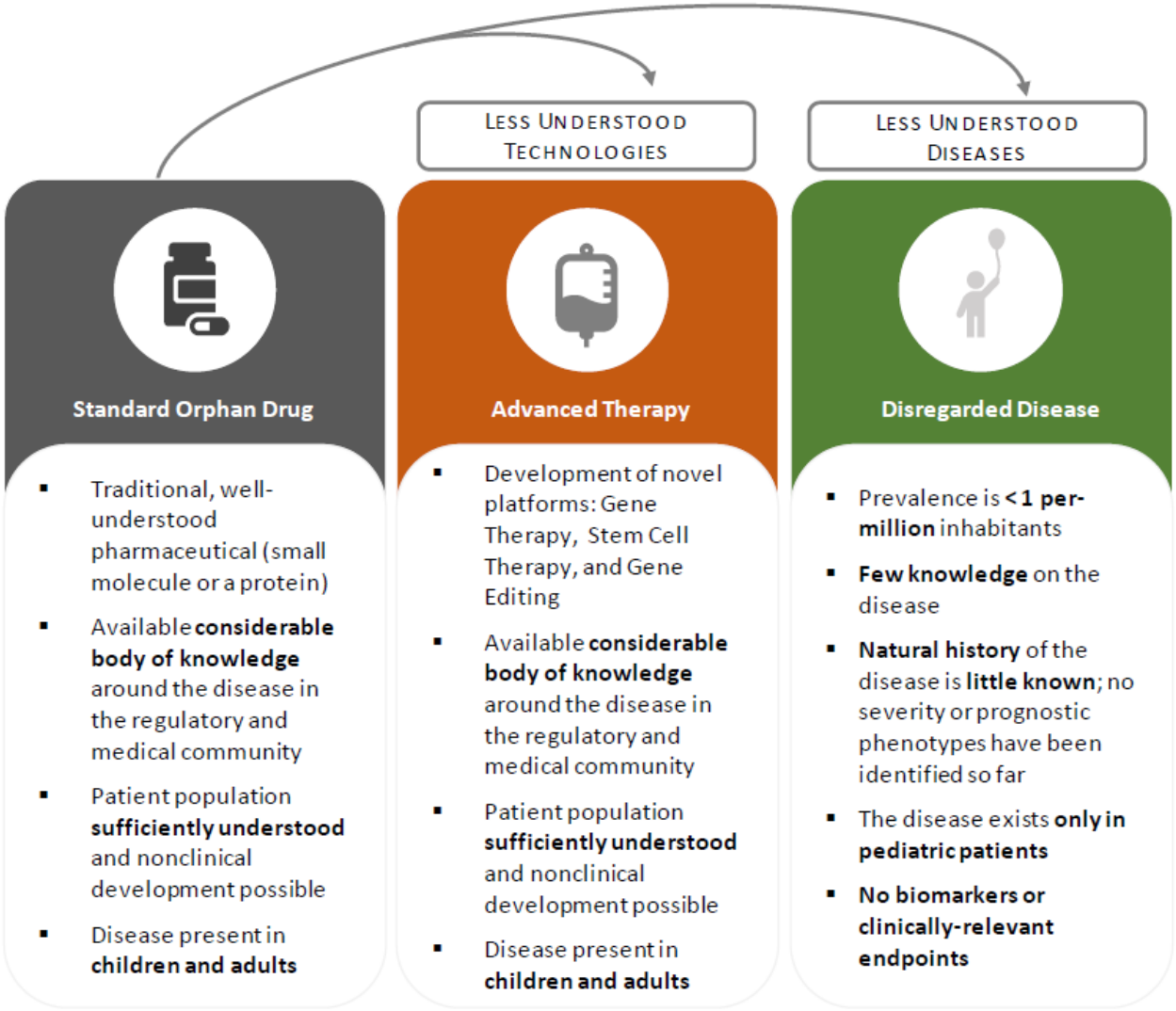


STRUCTURED APPROACH FOR PATIENT-CENTRIC RESEARCH



https://orphandrugguide.org/start

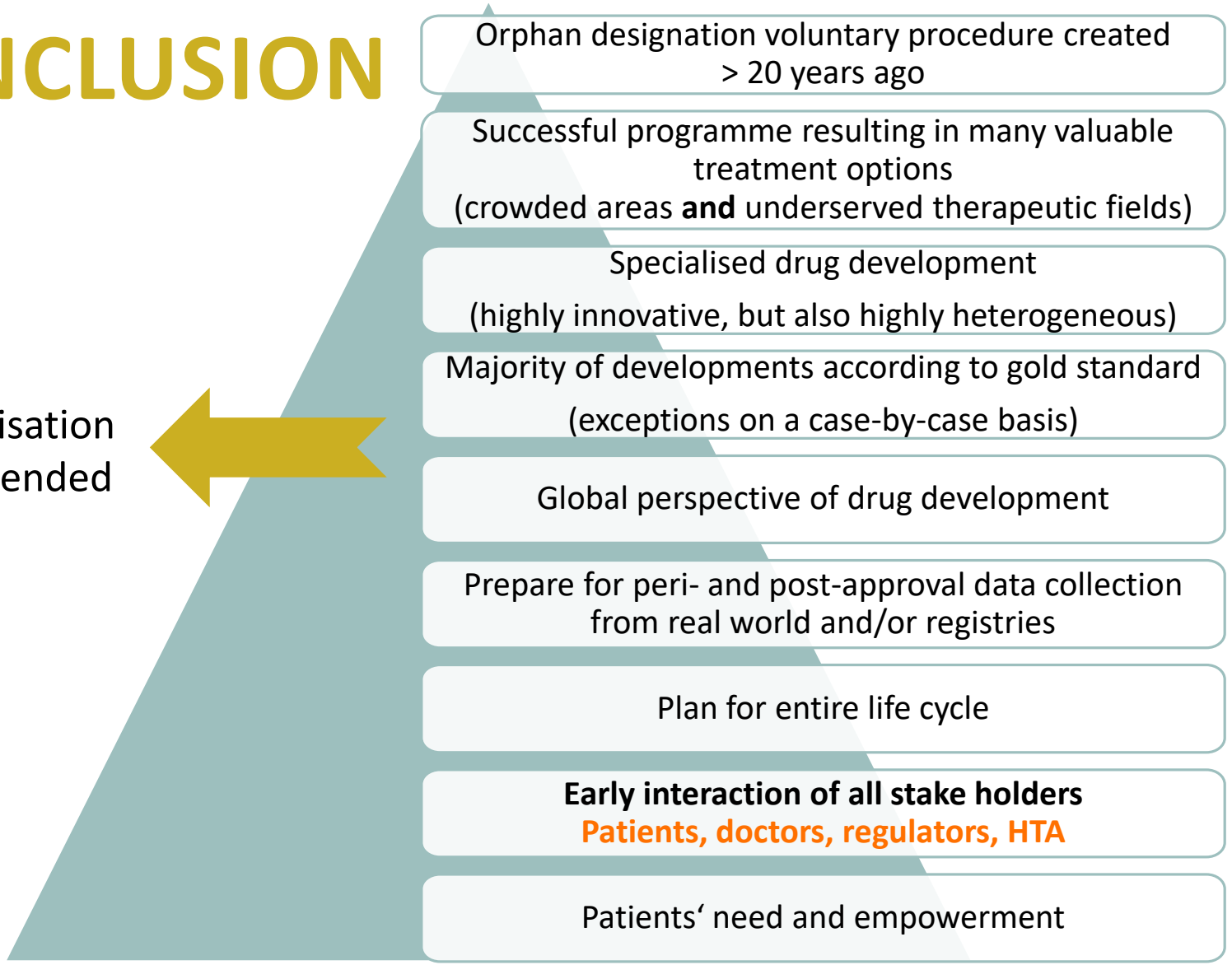
SETTINGS OF RARE DISEASE RESEARCH



http://irdirc.org/wp-content/uploads/2020/03/IRDiRC_ODDG_website.pdf

CONCLUSION

Harmonisation recommended



Thank you for your attention!

Questions?

Useful links

EMA website
https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation-research-development

Procedural advice (with Q&A) (September 2021)
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/*procedural-advice*-orphan-medicinal-product-designation-**guidance-sponsors**_en.pdf

Workshop on regulatory support for orphan medicines (November 2020)
https://www.ema.europa.eu/en/events/workshop-support-orphan-medicines-development

IRIS
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/**iris**-guide-applicants_en.pdf

EC register
https://ec.europa.eu/health/documents/community-register/html/index_en.htm