Processes to Evaluate the Safety and Efficacy of Drugs for Rare Diseases or Conditions in the United States and the European Union

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Industry Perspectives on the Application of Regulatory Flexibilities

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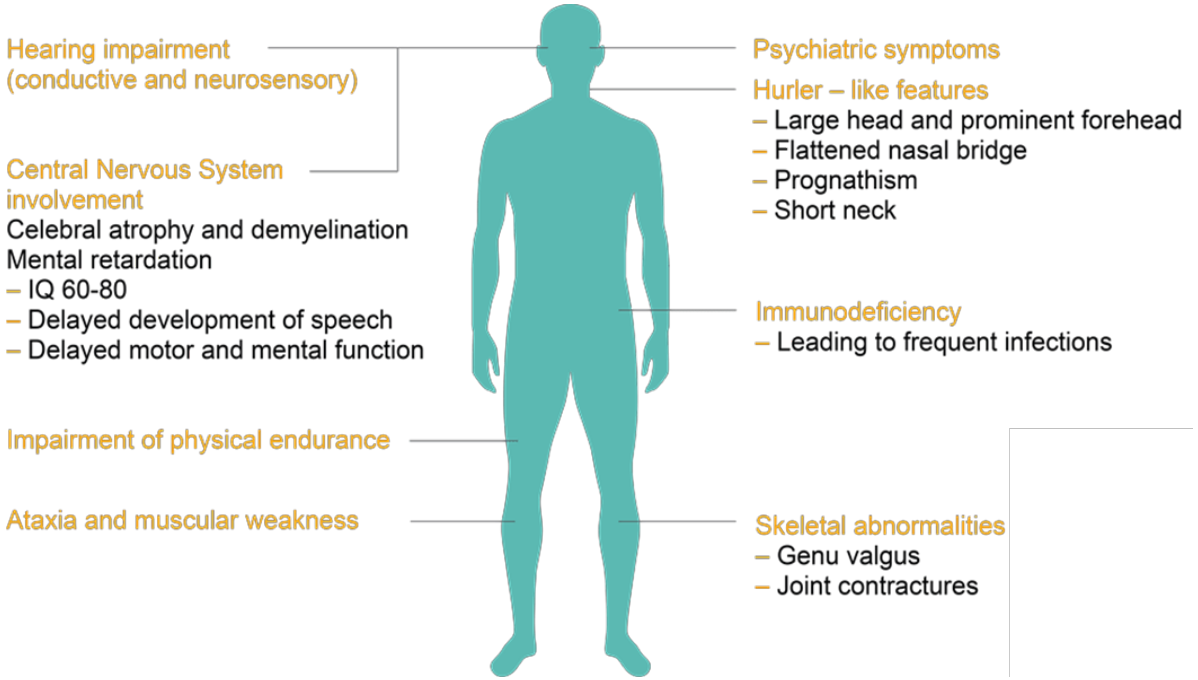
A paradigmatic case of ultra-rare disease: alpha-mannosidosis

Basic facts about the disease

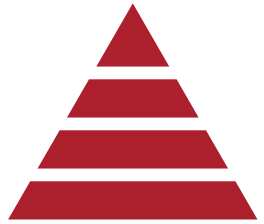
- Single gene defect (MAN2B)
- Glycoproteinosis
- Lysosomal accumulation of oligo-saccharides → systemic manifestations
- ~ 200 private mutations
- Ultra-rare: prevalence < 1/M (identified patients: <150 in EU, < 50 in US)
- Missing knowledge:
  - genotype-phenotype correlation,
  - natural evolution data
  - clinical endpoints and biomarkers

- Insidiously progressive disease leading to disabling decline
- Highly heterogeneous disease
- Continuous spectrum of manifestations & severity



How are rare diseases different?

No critical mass

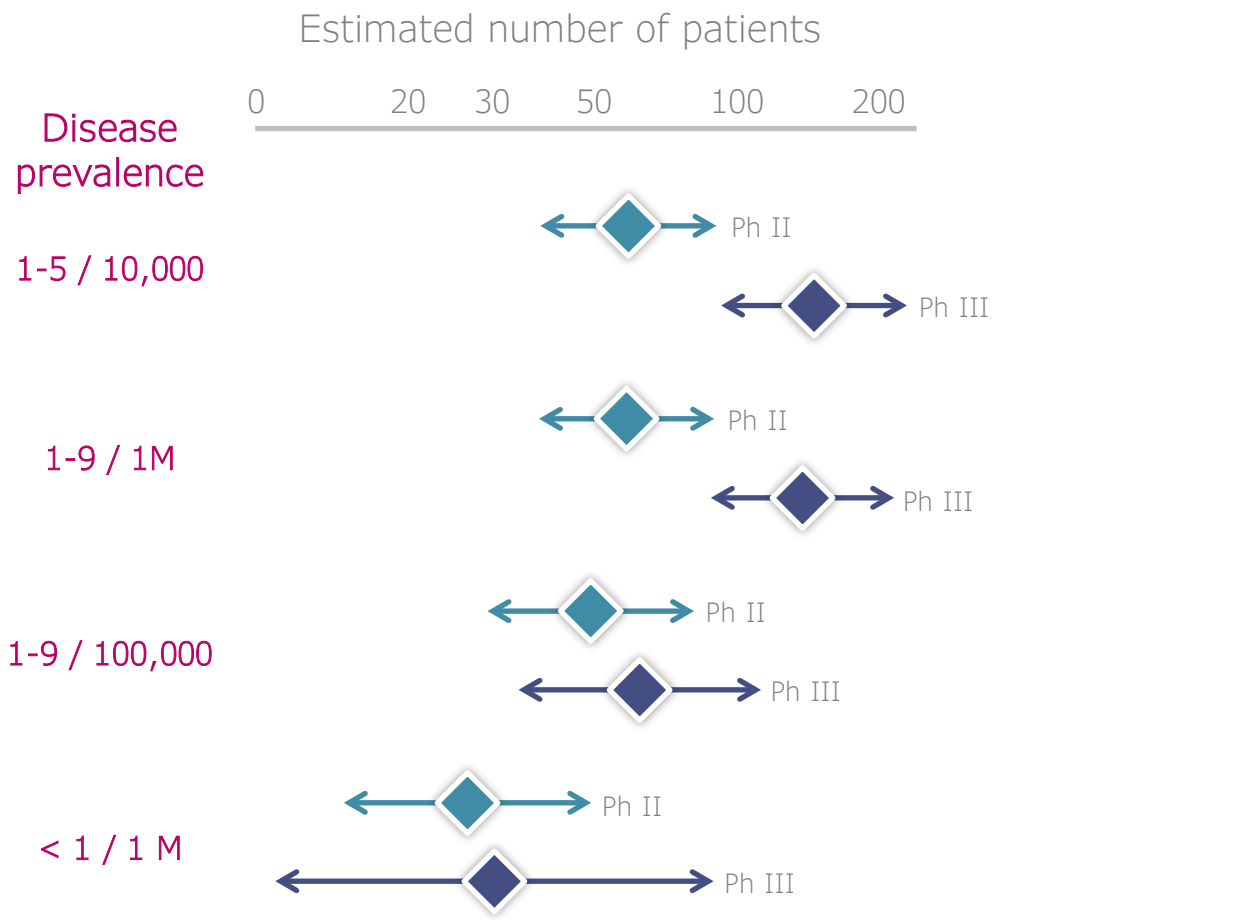


Limited knowledge base

Effect of prevalence and phase of study on trial size

- Aggregated analysis of registered clinical trials for rare diseases
- Trials from ClinialTrials.gov; diseases from Orphadata
- 1567 trials (0.8% of total)
  - 1.2% - prev <1/1,000,000
  - 8.0% - prev 1–9/1,000,000
  - 50.5% - prev 1–9/100,000
  - 40.3% - prev 1–5/10,000

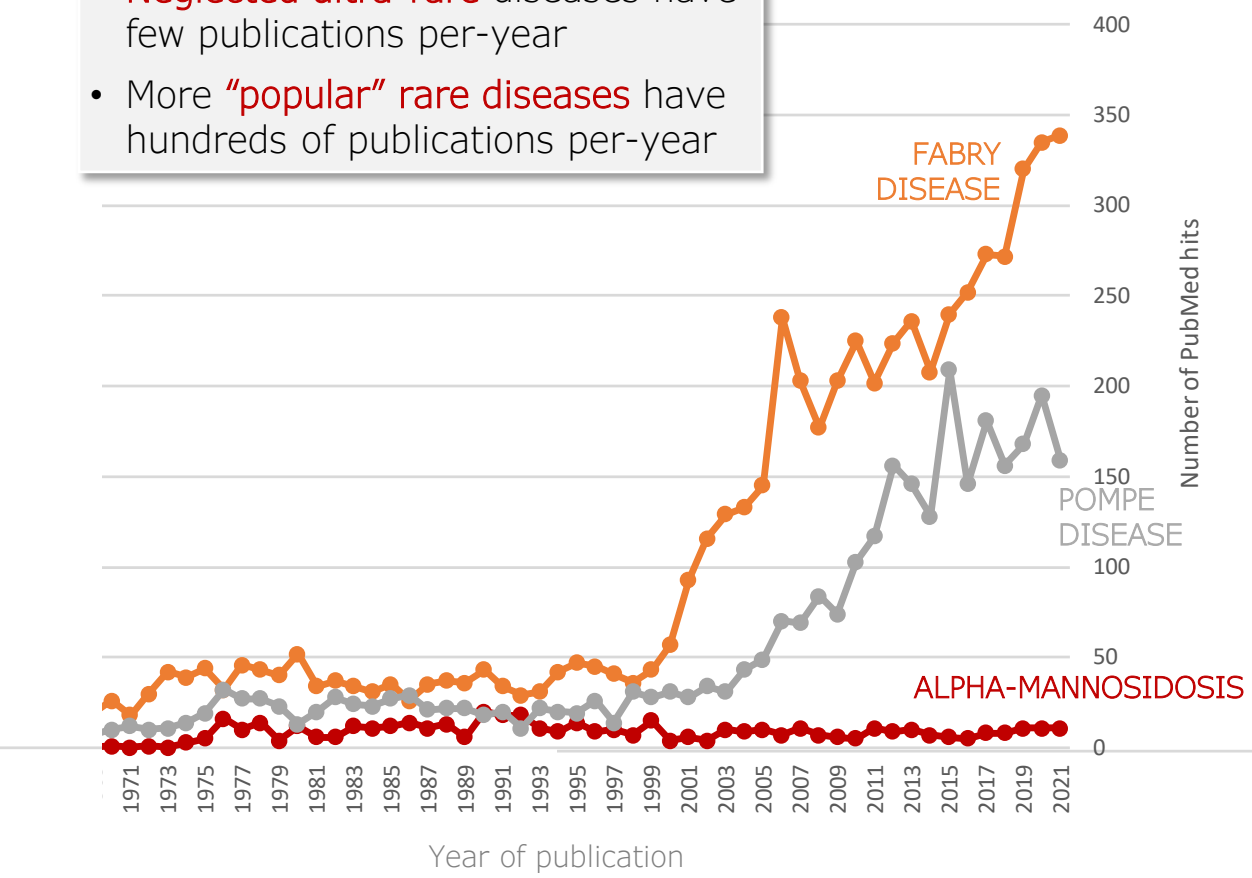
Effects of prevalence and phase of study adjusted by for prevalence, phase, gender, age, presence of a DMC, whether FDA regulated, intervention model, trial regions, number of countries, year of start, and number of arms



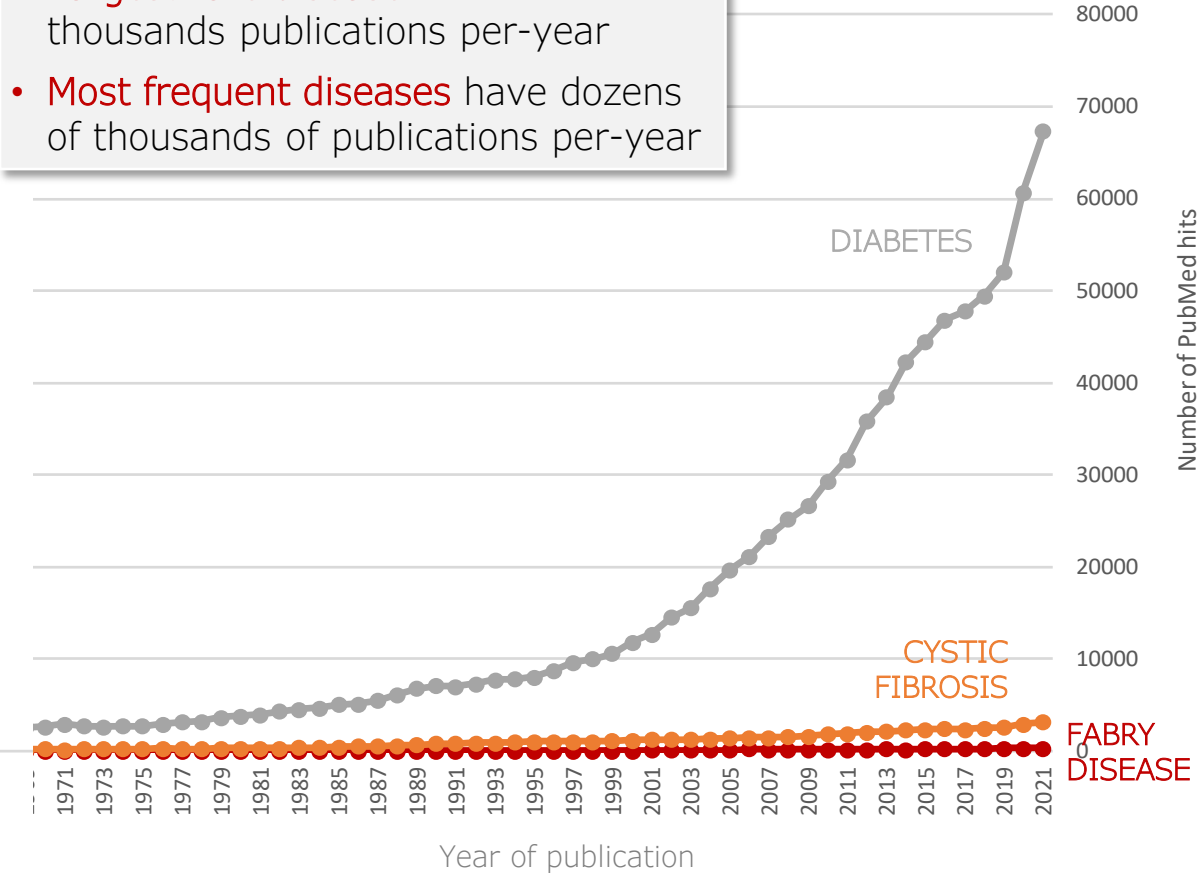
Source: Hee et al. OJRD 2017

Body of literature available in rare and non-rare diseases

- Neglected ultra-rare diseases have few publications per-year
- More "popular" rare diseases have hundreds of publications per-year



- Largest rare disease has few thousands publications per-year
- Most frequent diseases have dozens of thousands of publications per-year



Source: PubMed Medline

Types of marketing authorizations in US and EU

FDA

(Standard / Full) Marketing Authorization

Accelerated Approval pathway

- Applied to promising therapies treating serious/ life-threatening conditions
- Based on a “surrogate endpoint” that is reasonably likely to predict clinical benefit
- Requires a confirmatory study to confirm the MA

EMA

(Standard / Full) Marketing Authorization

Conditional Marketing Authorization

- Granted on less comprehensive clinical data than normally required
- Benefit of immediate availability outweighs risks; positive benefit-risk balance
- Comprehensive data post-authorization likely provided
- Subject to specific post-approval obbligations

Under exceptional circumstances

Granted to medicines where the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the condition to be treated is rare or because collection of full information is not possible or is unethical.

Main sources of regulatory flexibility in US and EU

Confirmatory study definition and design	• Clear identification of confirmatory trial(s) • Full application of the «adequate and well controlled» pivotal trial(s) statutory requirement • Flexibility in data interpretation and power requirements	• Highly dependent on the type of MA pursued • Flexibility in definition of the pivotal evidences (including open-label and integrated analyses) • Flexibility in data interpretation and power requirements
Choice of primary endpoint	• Highly dependent on the type of MA pursued • List of biomarkers «clinically relevant» / «reasonably likely to predict» (or to the requirements to be included)	• Highly dependent on the type of MA pursued • Flexibility in the choice of clinical or surrogate endpoint, although clinical data always needed
«Totality of evidence» VS primary endpoint	• Strong emphasis on definition of a primary endpoint, although secondary variables fully reviewed and considered.	• Emphasys on primary endpoint, but totality of evidence fully considered • If necessary, use of agreed post-hoc analysis
Role of alterantive data sources (long-term open label, external cohorts)	• Potential use of exploratory evidence and open-label trials to replace the second pivotal trial («supportive evidence») • Potential use of external control groups (e.g. NHS as alternative to placebo)	• Large flexibility in the definition of the set of confirmatory and supportive evidence – use of ISEs, OLEs, etc. • Interest for long-term data (beyond disease variability)

Our case

FDA

- Well-conducted pivotal placebo-controlled RCT with overall positive corroboration from clinical and biochemical markers of disease was basis of approval.
- Open-label extension study data with lack of control was perceived by Agency to be prone to bias and not formally accepted for use as confirmatory evidence.
- Value of multi-component / multi-responder analysis was perceived lower than single, continuous endpoints.

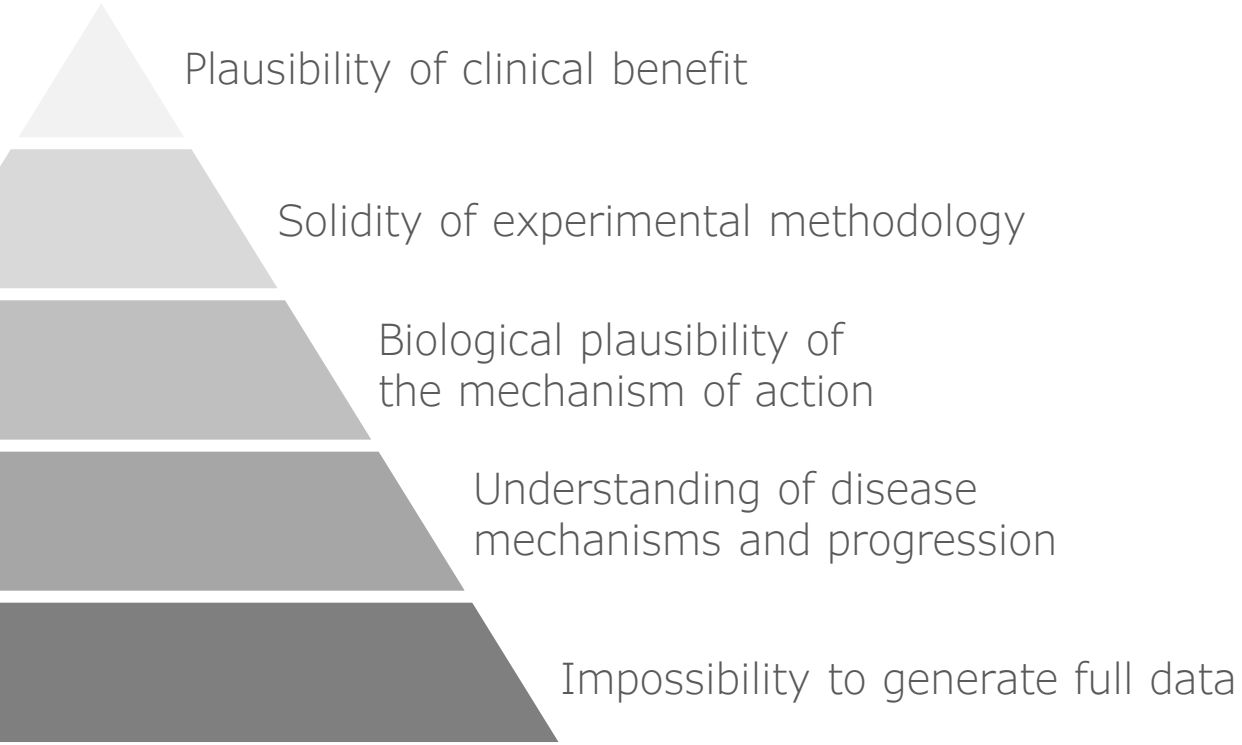
EMA

- Long-term integrated efficacy analysis from early development trials, treated RCT and OLEs used as part of the confirmatory evidence
- More willing to use integrated analysis with OLE data
- Agreement and use of post-hoc multi-domain responder analysis

For natural history data to be considered as suitable comparator, the population studied needs to closely match that included in the pivotal / registrational trials

The conceptual framework of regulatory flexibility

The basis for the application of flexibility



One paradigmatic case

FDA guidance on

Slowly Progressive, Low-Prevalence Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects

- Focus on building evidence of efficacy across the chain of pathophysicological events
- Strong emphasys on tissue/ organ damage
- Possibility to integrate clinical and animal data

Reflections based on the paper "FDA's flexibility in subpart H analysis by Sasinowski & Varond 2016 and personal experience

Additional considerations

	ISSUE		FLEXIBILITY shown by Agencies
CMC and technical development / Module 3	Accelerated Approval submission	Technical development at stress	• Capacity and flexibility to deal with complex dossier through Q&A • Intelligent use of PMCs/PMRs
	Small manufacturing scale / limited number of batches	Sub-optimal process and characterization at submission	