The complexity of developing innovative medicines for rare diseases
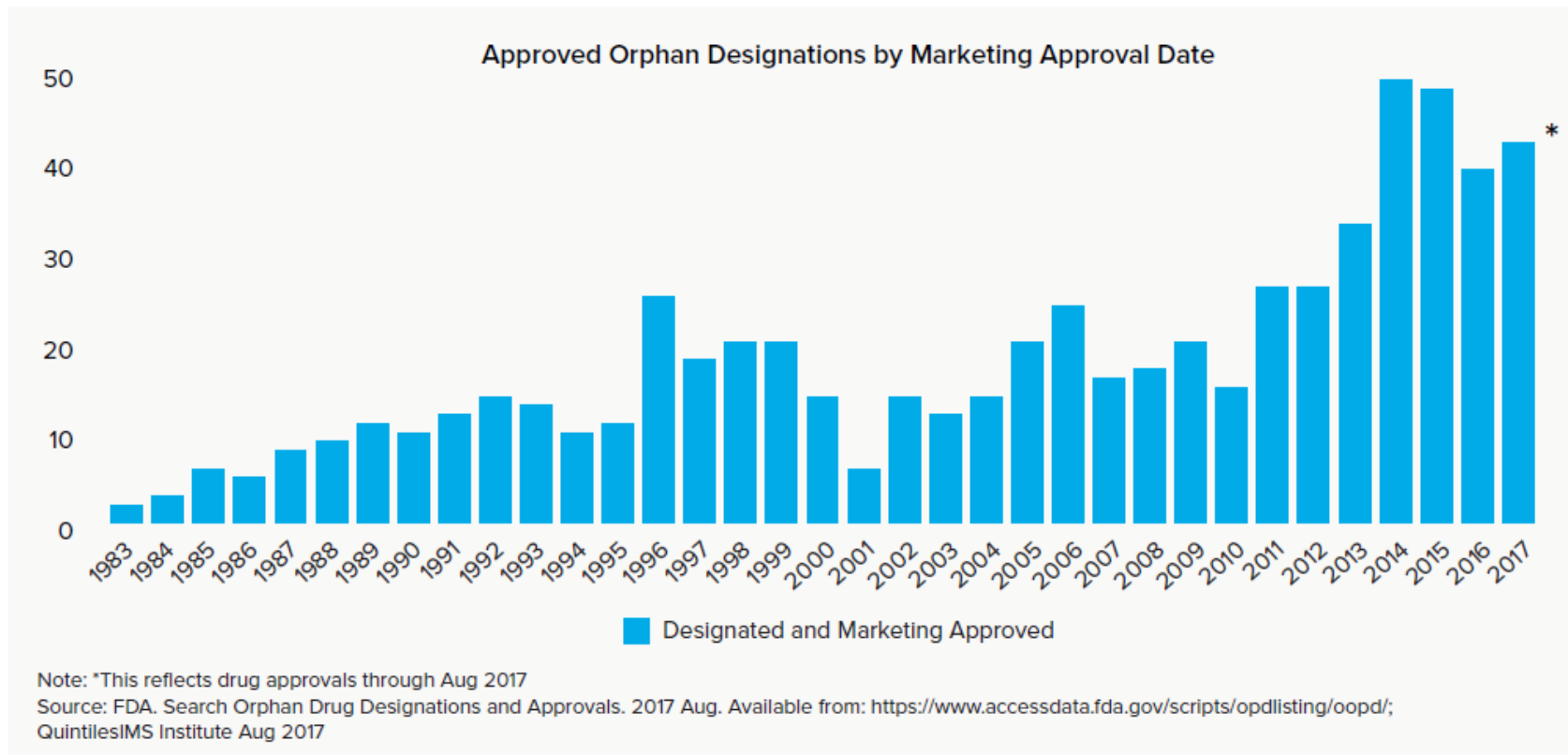
Diego Ardigó, MD PhD

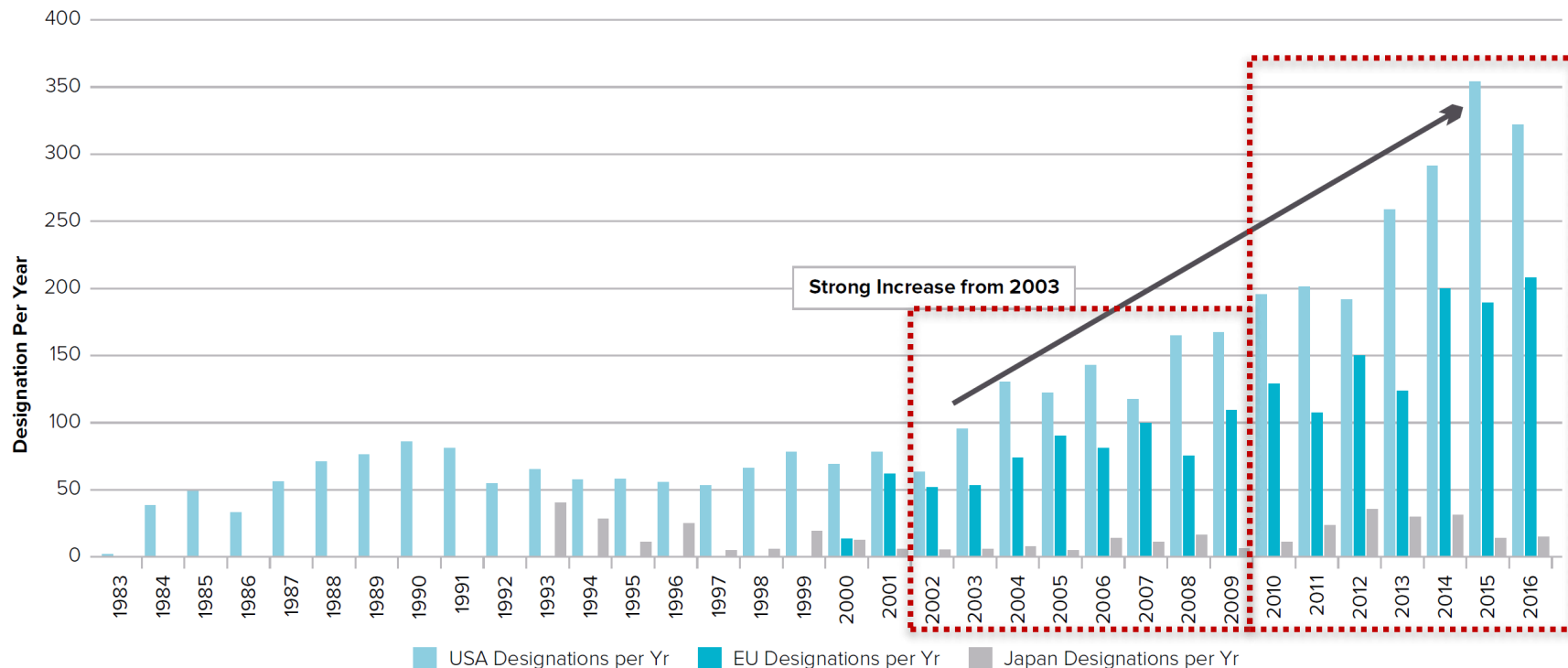*R&D Rare Disease Unit Head*
Corporate Research & Development
Chiesi Farmaceutici S.p.A.

Chairman Therapies Scientific Committee
International Rare Disease Research Consortium (IRDiRC)

Rare disease drugs approved in US with orphan designation

Approved Orphan Designations by Marketing Approval Date

Note: *This reflects drug approvals through Aug 2017
Source: FDA. Search Orphan Drug Designations and Approvals. 2017 Aug. Available from: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/;
QuintilesIMS Institute Aug 2017

Historical trend of OD designations in EU, US, & Japan

Strong Increase from 2003

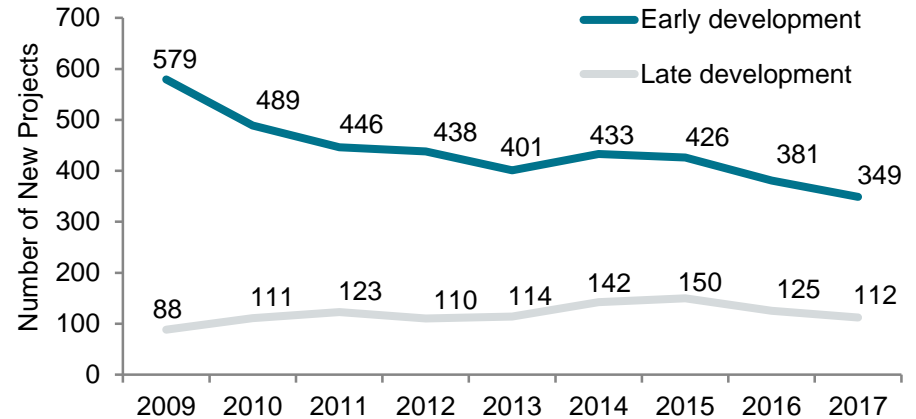USA Designations per Yr   EU Designations per Yr   Japan Designations per Yr

Source: EvaluatePharma® February 2017

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Rare disease development trends

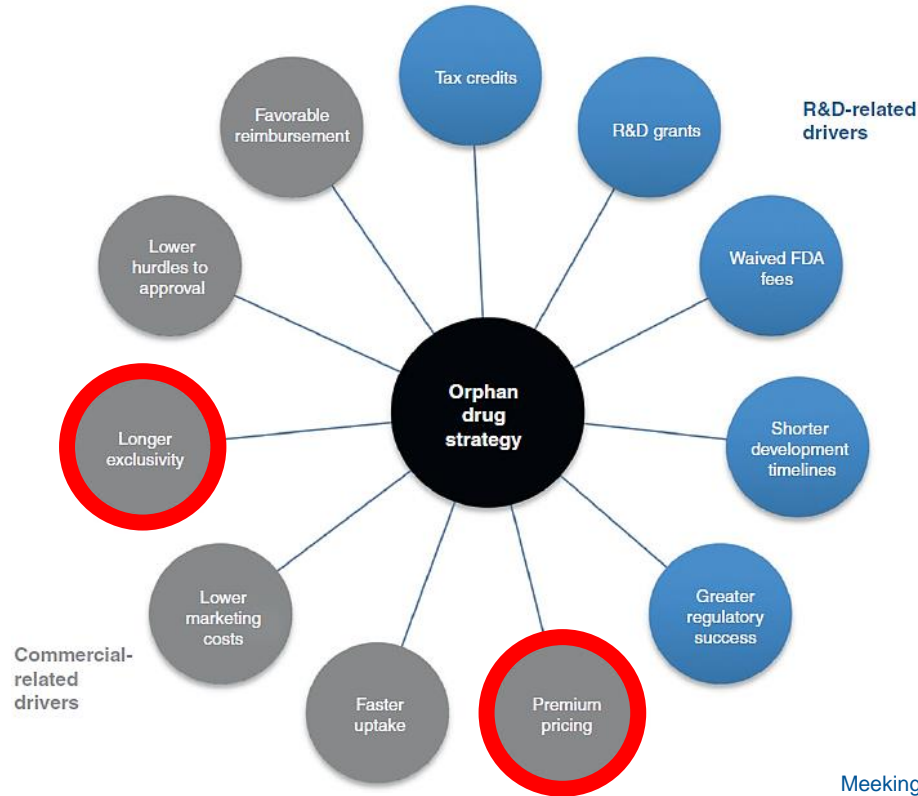One third of new projects entering the industry's pipelines is on a rare disease indication …
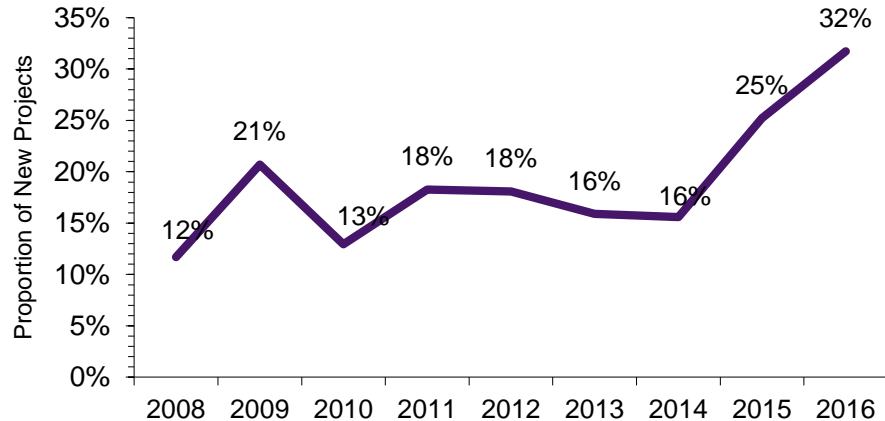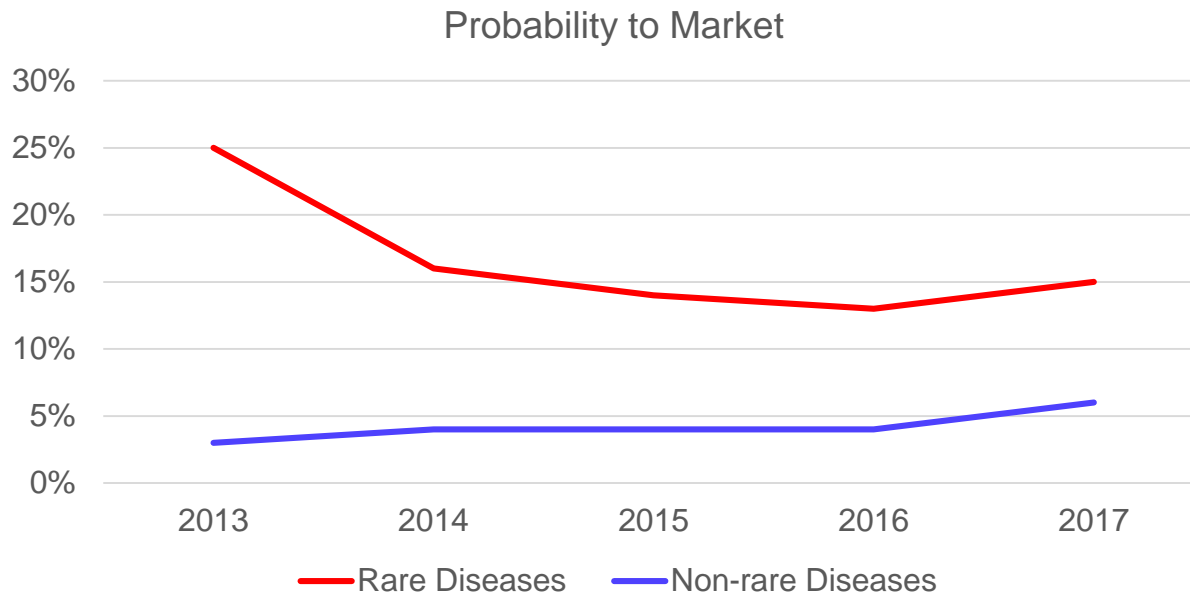

… but the number of new projects is decreasing

Source: CMR database (2018)

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Key incentives for Orphan Drug development

Meekings KN, Drug Discovery Today 2012;17(13/14):660-4

Success Rates For Rare Vs. Non-rare Over Time

Probability to Market

Success rates from preclinical phase to market resulting in the different years for active substances entering the phase 3 years before (i.e. resulting in 2017, for active substances entering the phase in 2008 -2014) – CMR Methodology (WHOLE INDUSTRY, line ext. excluded)

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Competition in orphan indications: the case of Lysosomal Storage Disorders
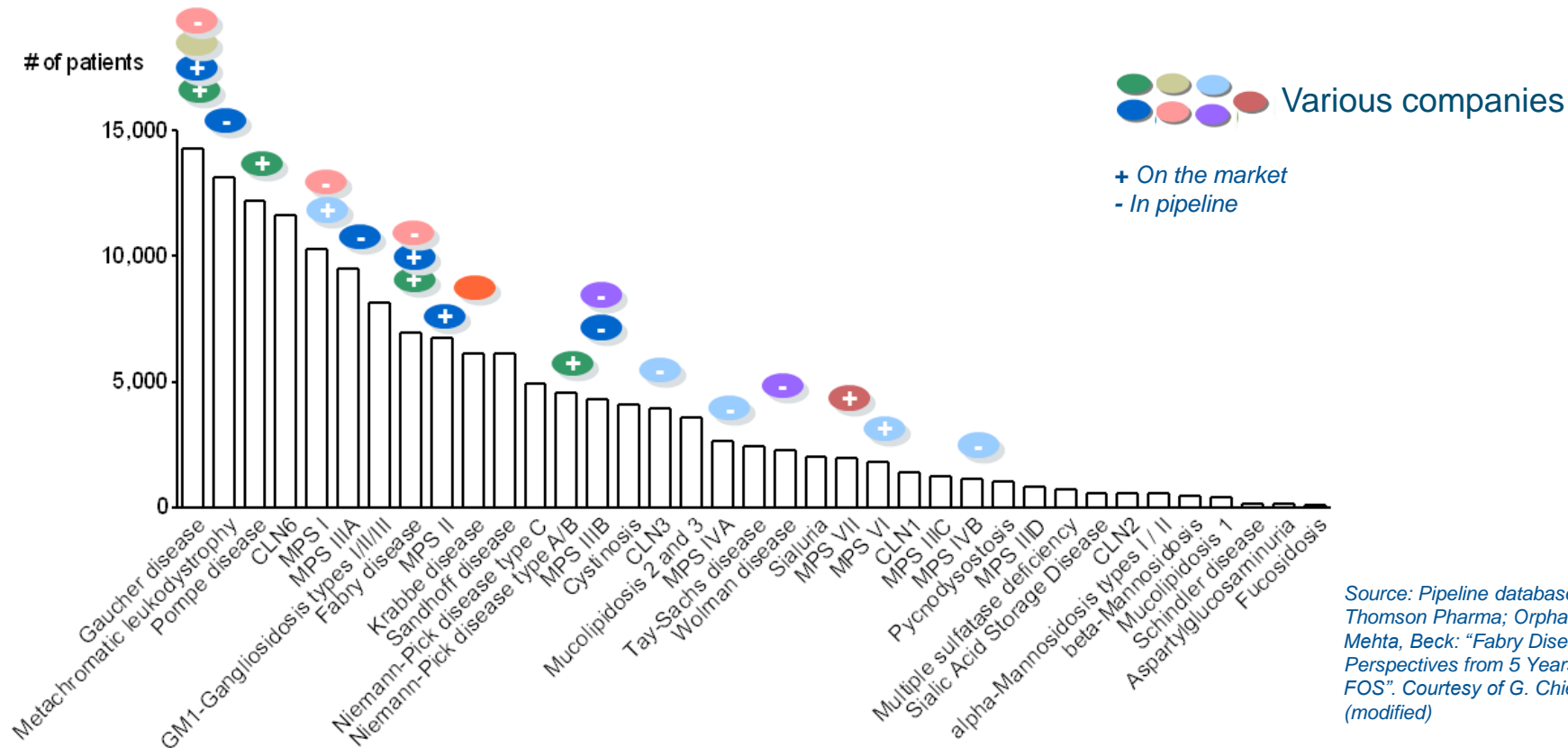
Source: Pipeline database, Thomson Pharma; Orphanet; Mehta, Beck: "Fabry Disease, Perspectives from 5 Years of FOS". Courtesy of G. Chiesi (modified)

Average price of orphan drugs in US 2013-2017

| Complexity of RD drug development | D. Ardigó | 27 Oct 2018 | XI FORESIGHT TRAINING COURSE |

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Data source: Evaluate Pharma May 2018; personal elaboration

Is this sustainable?

TECHNICAL SUSTAINABILITY

ECONOMIC SUSTAINABILITY

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Development of a drug (small molecule, large indications)

| Pre-clinical package *to support FIH* | ◆ | Phase I | Phase II | ◆ | Phase III | ◆ **MA** | Post-approval |

Pre-clinical package
to support FIH

- Proof-of-Concept
- PK/ ADME
- Genotoxicity
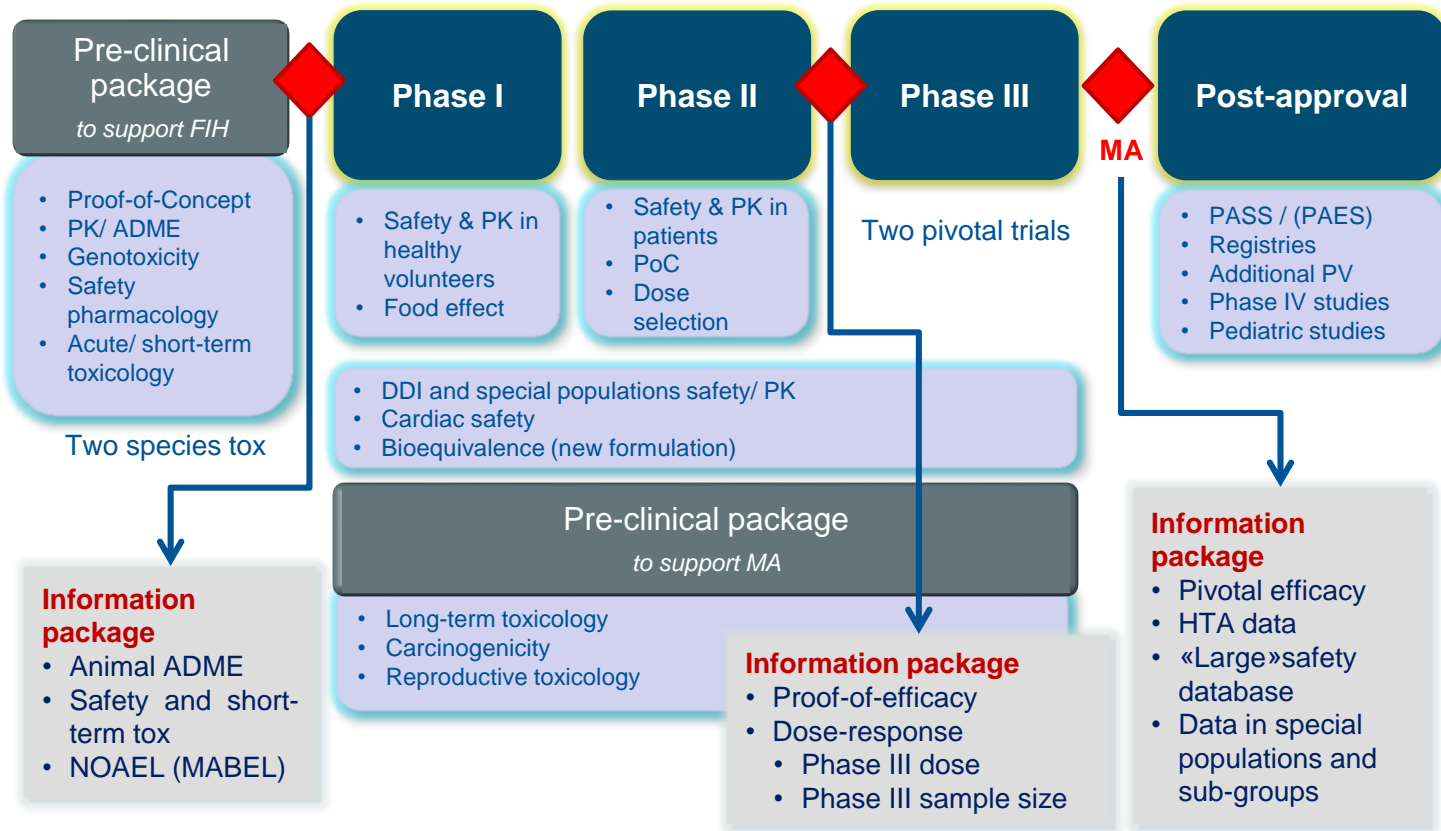- Safety pharmacology
- Acute/ short-term toxicology

Two species tox

Phase I
- Safety & PK in healthy volunteers
- Food effect

Phase II
- Safety & PK in patients
- PoC
- Dose selection

- DDI and special populations safety/ PK
- Cardiac safety
- Bioequivalence (new formulation)

Phase III

Two pivotal trials

Post-approval
- PASS / (PAES)
- Registries
- Additional PV
- Phase IV studies
- Pediatric studies

Information package
- Animal ADME
- Safety and short-term tox
- NOAEL (MABEL)

Pre-clinical package
to support MA

- Long-term toxicology
- Carcinogenicity
- Reproductive toxicology

Information package
- Proof-of-efficacy
- Dose-response
  - Phase III dose
  - Phase III sample size

Information package
- Pivotal efficacy
- HTA data
- «Large»safety database
- Data in special populations and sub-groups

- Consolidated
- Based on risk management and gate reviews
- Almost linear progressive increase in costs
- Long-term predictability

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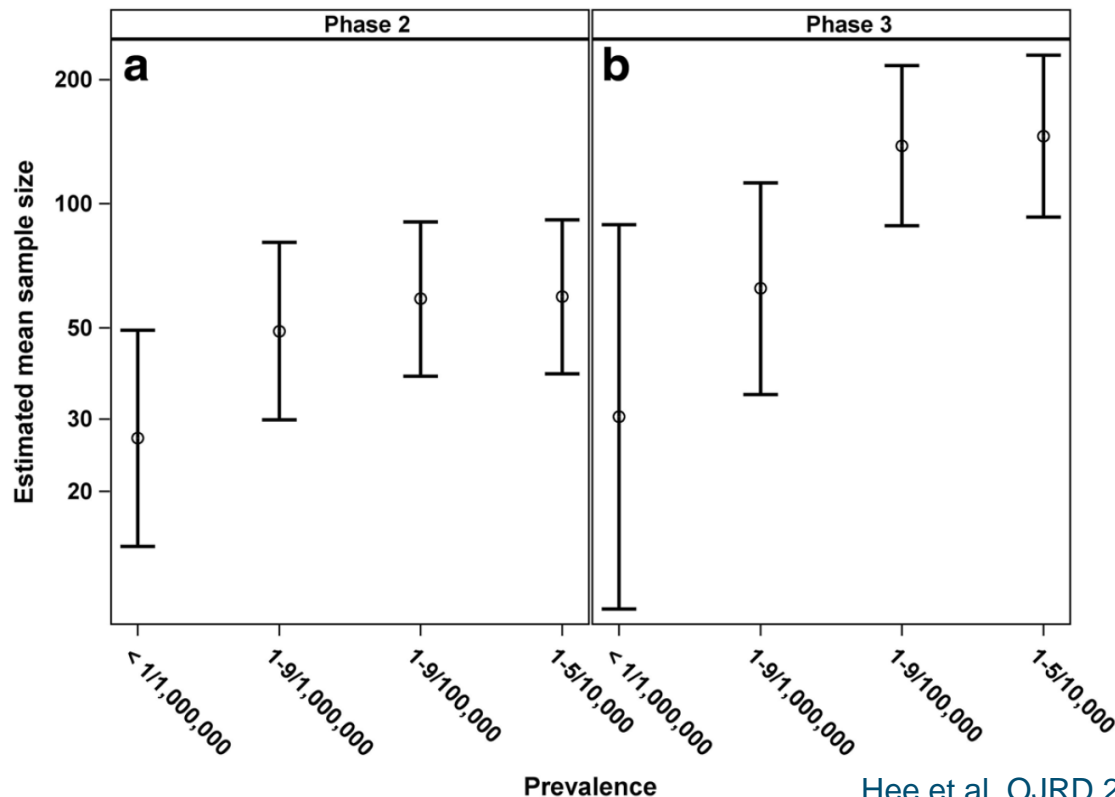# Differences in development of an orphan drug (small molecule)

Pre-clinical package
to support FIH

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- PK/ ADME
- Genotoxicity
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- Acute/ short-term toxicology

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- ~~Consolidated~~
- ~~Based on risk management and gate reviews~~
- ~~Almost linear progressive increase in costs~~
- ~~Long-term predictability~~

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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

Hee et al. OJRD 2017

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Where this complexity comes from?

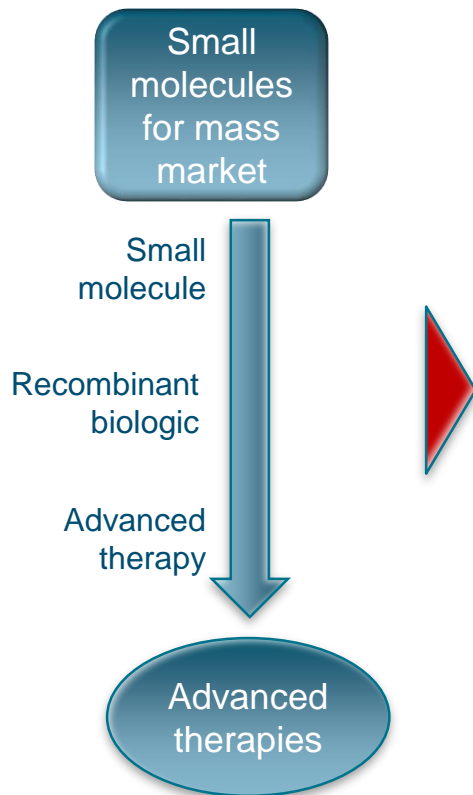Small molecules for mass market → Frequent / Rare → Orphan indications
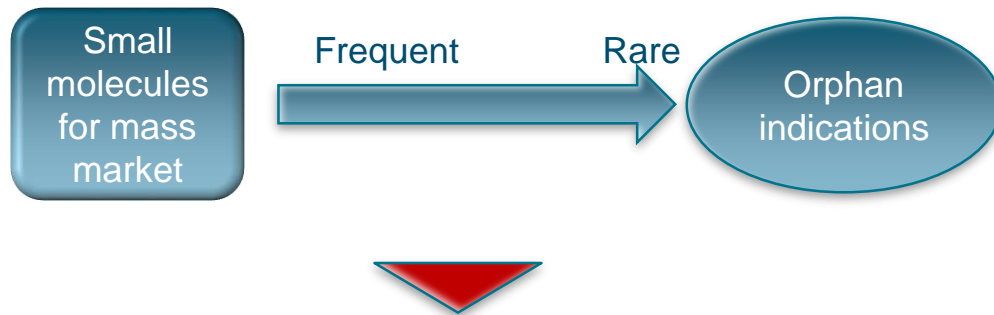
Significant impact on clinical development:

- Knowledge of the disease
- Proof-of-concept
- Dose-finding
- Proper phase III planning/ de-risking
- Understanding and management of clinical risks

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Where this complexity comes from?

Small molecules for mass market

Small molecule

Recombinant biologic

Advanced therapy

Advanced therapies

Significant impact on product quality:

- Process control
- Robustness/ reproducibility
- Safety risks

Significant impact on pre-clinical development:

- Proof-of-concept
- PK and tox

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Where this complexity comes from?
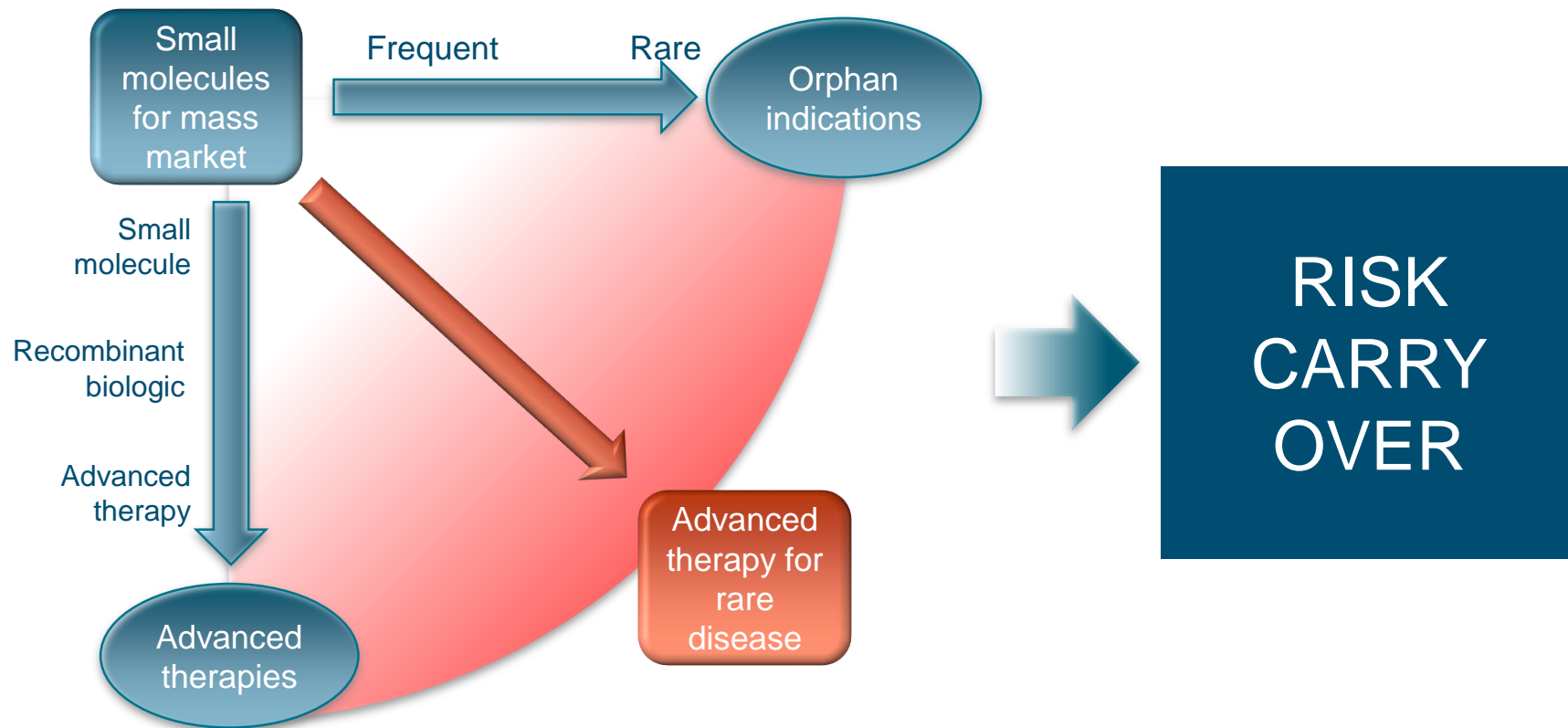
Consequences of risk carry-over

Additional risk-minimization measures

Post-approval commitments

Value for payers

Price definition

Level of evidence

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The several billion dollars question …

Is it worth **paying for** an orphan or ultra-orphan drug?

- Total health gain maximization
- Vertical equity
- Value assessment

???

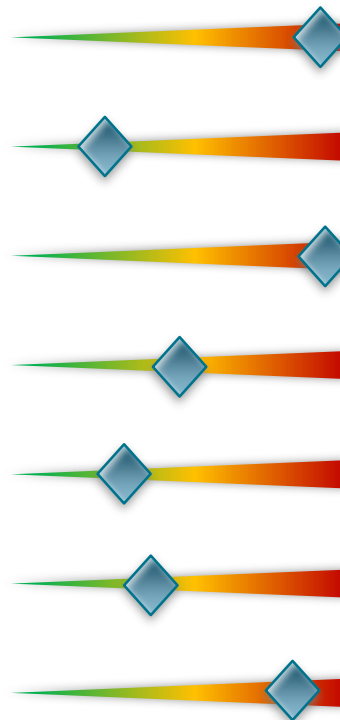Is it worth **investing in** an orphan or ultra-orphan drug?

- Return on investment
- Level of uncertainty

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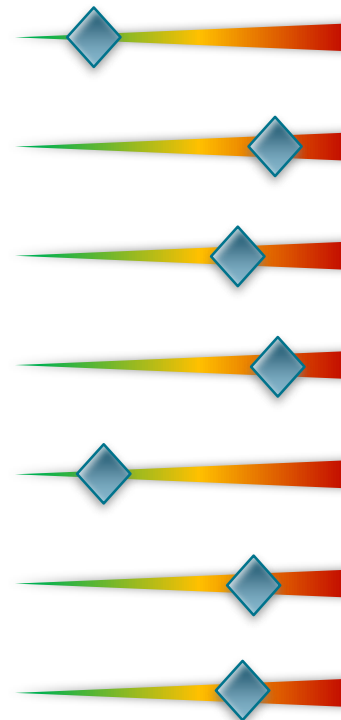
Determinants of the return on investment

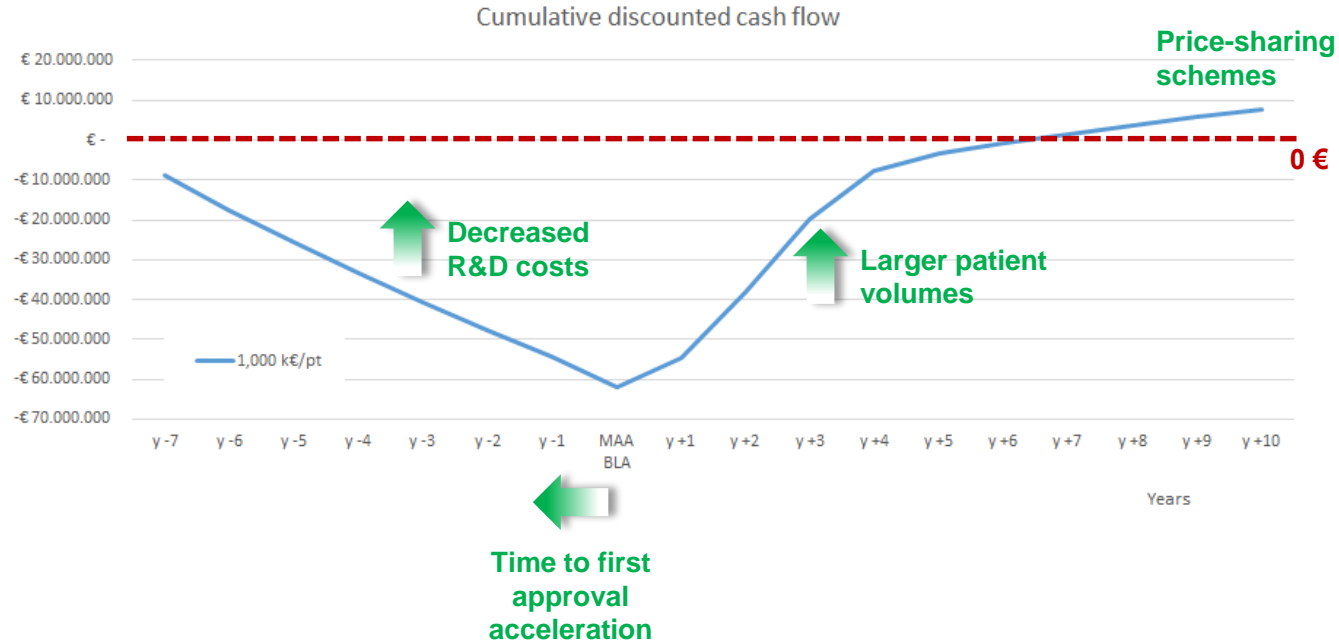| Return-on-investment	Large indication	Orphan
Patients treated (volumes)		
Price per-patient		
Development costs		
Technical risks/ uncertainty		
Regulatory risk		
Reimbursement risk		
Time to market/ break-even		

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Potential solutions to the price conundrum

- Getting out from bargaining on a single dimension (i.e. price)
- Considering stakeholder needs and interests

Cumulative discounted cash flow

Price-sharing schemes

Decreased R&D costs

Larger patient volumes

0 €

1,000 k€/pt

Time to first approval acceleration

Years

… before it is too late.