Care for Rare Diseases & Orphan Drug Provision

Advanced Seminar Economics, Policy & Econometrics: Health Economics

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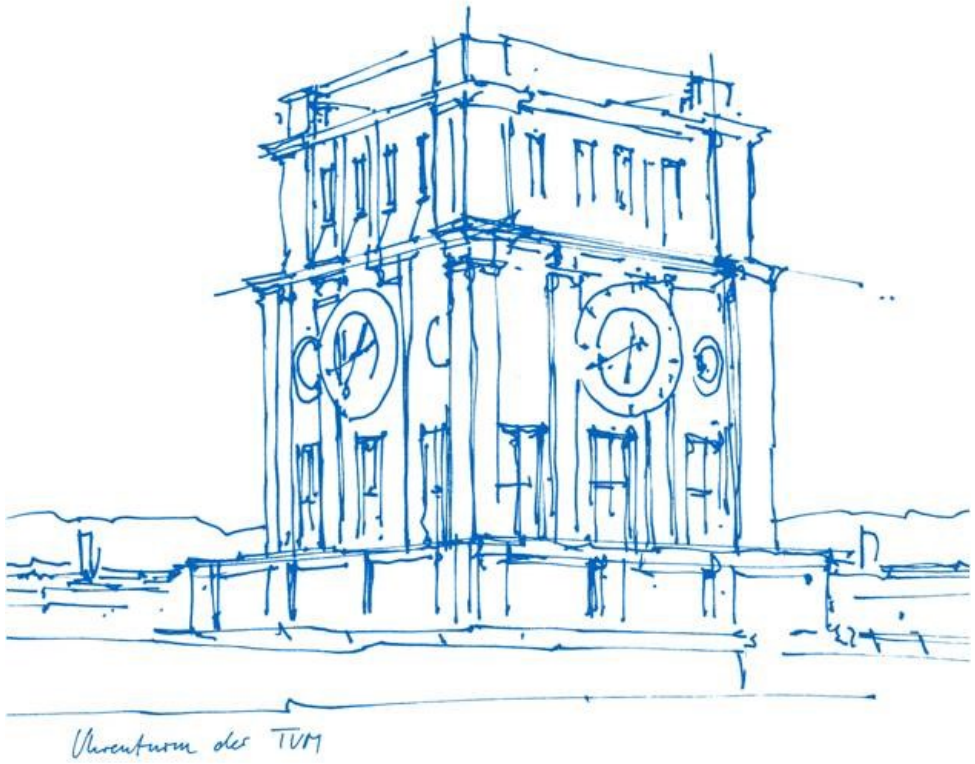
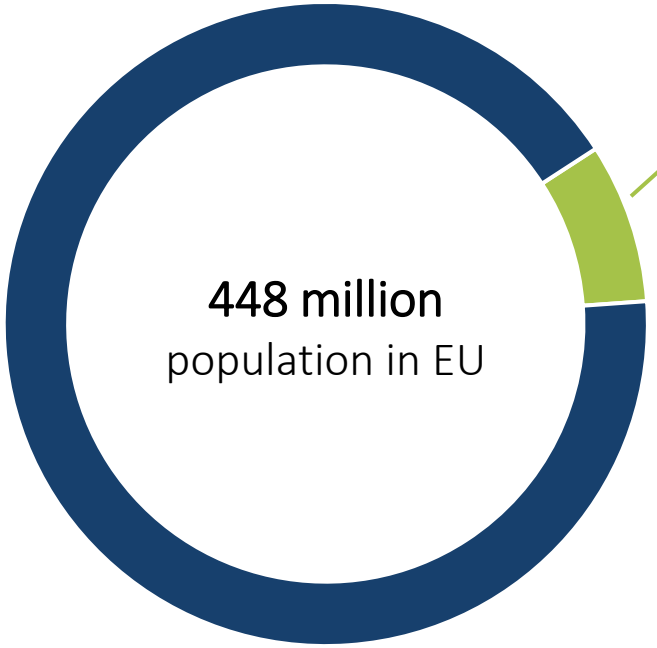


Agenda

What are Rare Diseases?

“Rare Diseases are diseases which are uncommon and afflict only about 0,05% of the population each.” ~ Definition of the German Federal Institute for Drugs and Medical Devices (BfArM)



36 million (1 in 12) directly affected

Over 6000
Rare diseases (EU)

80%
Have genetic cause

95%
Without approved treatment

4.8 years
Accurate diagnosis

70%
Affect children

30%
Die before age 5

What are the challenges about Orphan Drugs?

Lack information on disease natural history

Small target population & few patients eligible for trial

Severe adverse effects when administrating these drugs

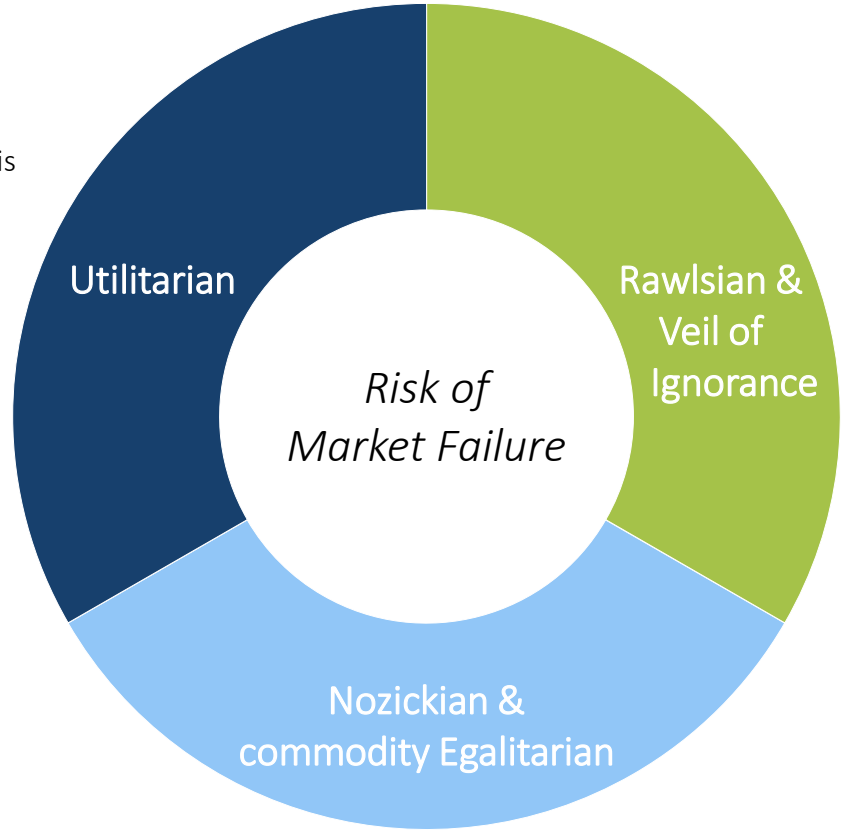
Limited upside given price caps

Due to less attractive risk-reward calculation, smaller availability of capital!

So does it make sense to support Orphan Drugs?

Utilitarian

- Maximize population welfare by resource (re)distribution efficiently
- The most cost-effective allocation of resources is not an equitable (re)distribution where a considerable population is left out
- A rift between the “normal, unincentivized” development and the societal optimum



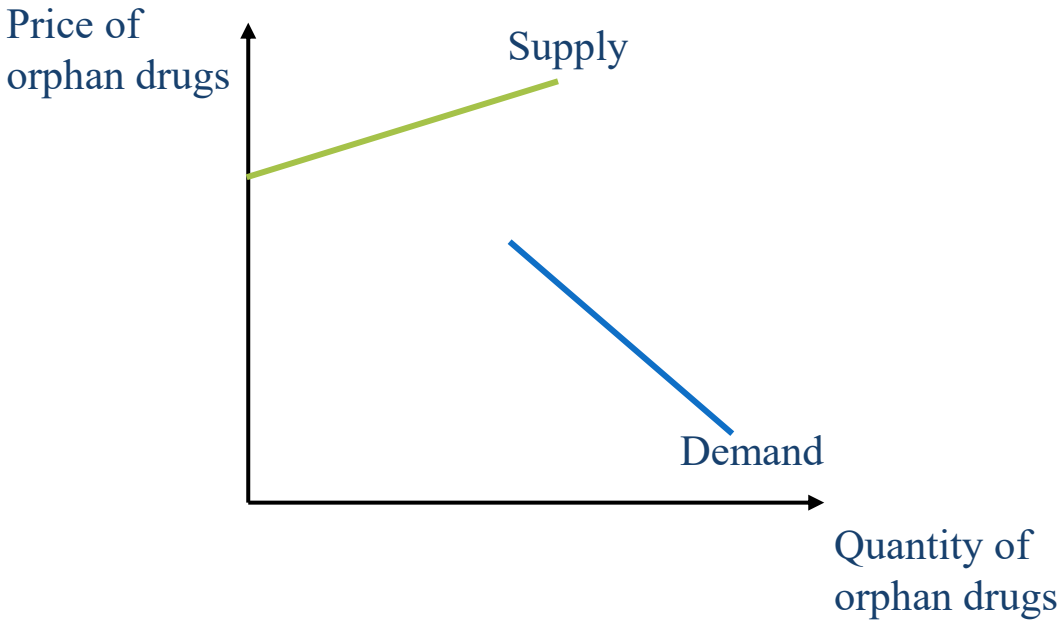
Rawlsian & Veil of Ignorance

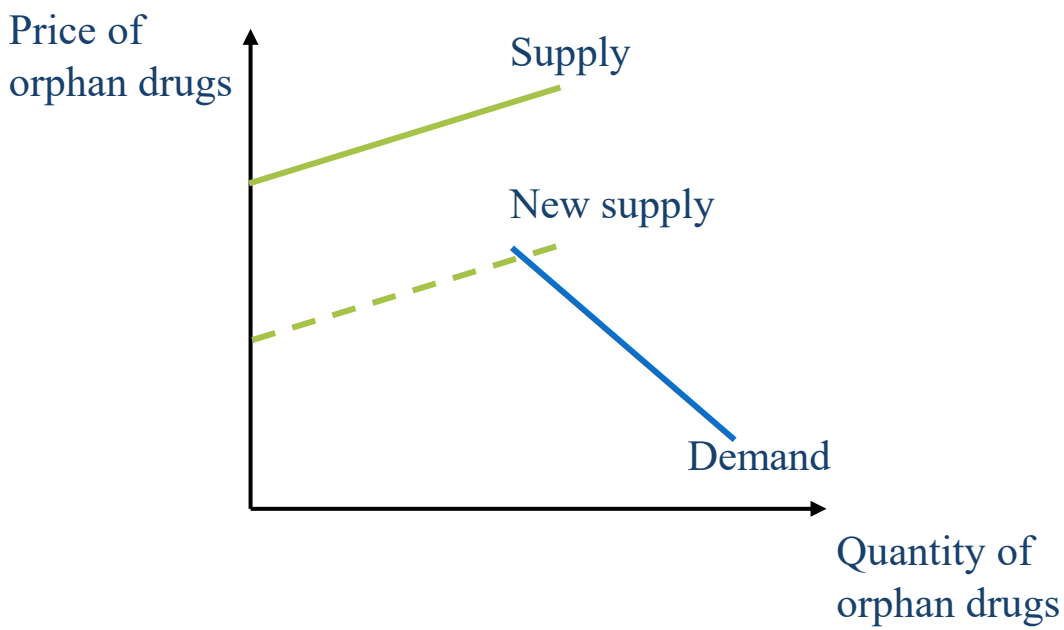
- Maximize welfare of the worst of member
- As a risk-averse individual, it is in your interest to fund treatment because there is a chance the often-lethal rare diseases might happen to you or your children

Nozickian & commodity Egalitarian

- Emphasize equal opportunity (to care), or
- Measure whether absolute resources owned satisfy bare minimum
- Both cases favor of helping patients with RDs

supply & demand curve

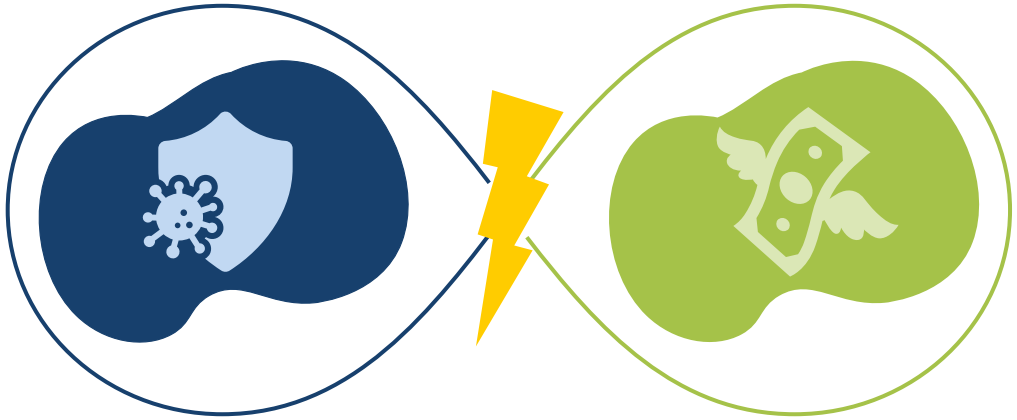




How can we resolve this funding gap?

Market Need

There are good reasons both economically and morally to support the development of Orphan Drugs as a society. Targeting rare diseases is absolutely necessary

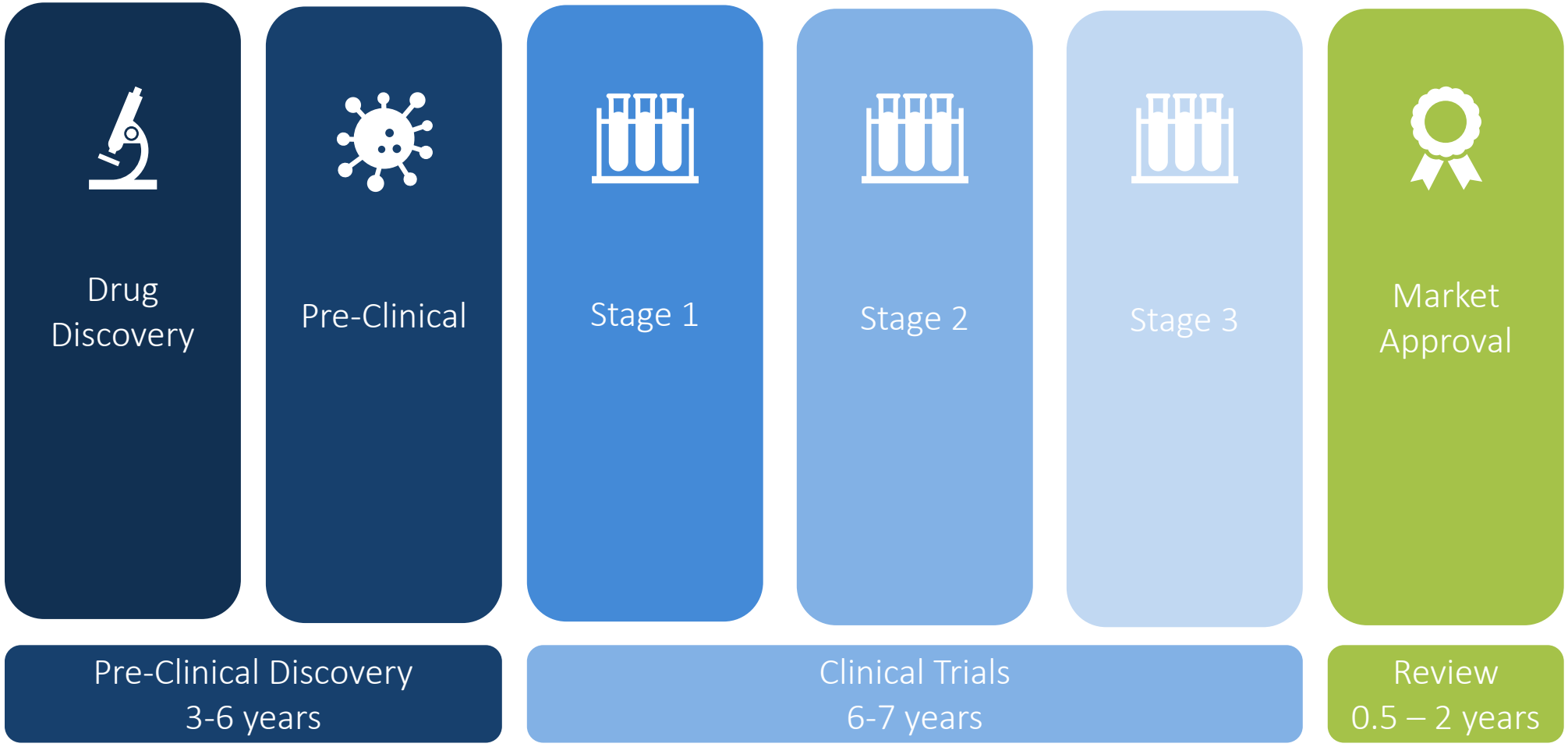


Market Incentives

The risk to reward ratio for Orphan Drug Development is much worse than developing “normal” drugs. Therefore, under normal consideration capital would not flow to the development of Orphan Drugs.

In order to mend the rift between how the market functions and what the market needs, Orphan Drug Development needs to be additionally incentivized!

From Ideation to Market Approval …



Drug discovery

What is happening during this stage of development? What is the goal?

- Drug Discovery has the primary focus on doing research on potential new pharmaceutical compounds or new ways of administrating a drug
- Often with the idea of targeting one specific disease a library of molecules is tested out – “see what sticks” approach
- At the end of the Drug Discovery out of thousands possible compounds, there should be a few hundred remaining, which shown some effect and are worth further pursuit

What are challenges specific to the Orphan Drug Development?

- Orphan Drugs get discovered the same way as normal drugs, with the key difference being that the decision to develop something for Rare Diseases is more unlikely due to the smaller commercial reward in case of success

What is being done to support Orphan Drug Development?

- Since there is not much special about discovering Orphan Drugs, there is also no special support
- Mostly supported through federal grants which target specific research objectives (e.g. rare diseases)

Deep Dive: Federal Grants

"A grant is a way the government funds your ideas and projects to provide public services and stimulate the economy." ~ U.S. Government (grants.gov)

Why is it an incentive for Orphan Drug Development?

In any drug development process, the first stage is the stage with the most risk associated. With high costs and no product even remotely in sight, federal grants can support the (fundamental) research on rare diseases which might turn into Orphan drugs at some point.

Why are potential shortcomings?

The federal grants most often target general research in medical areas of need and do not specifically target the development of Orphan Drugs (even though some do). Most research grants are also focused on Research and less on development.

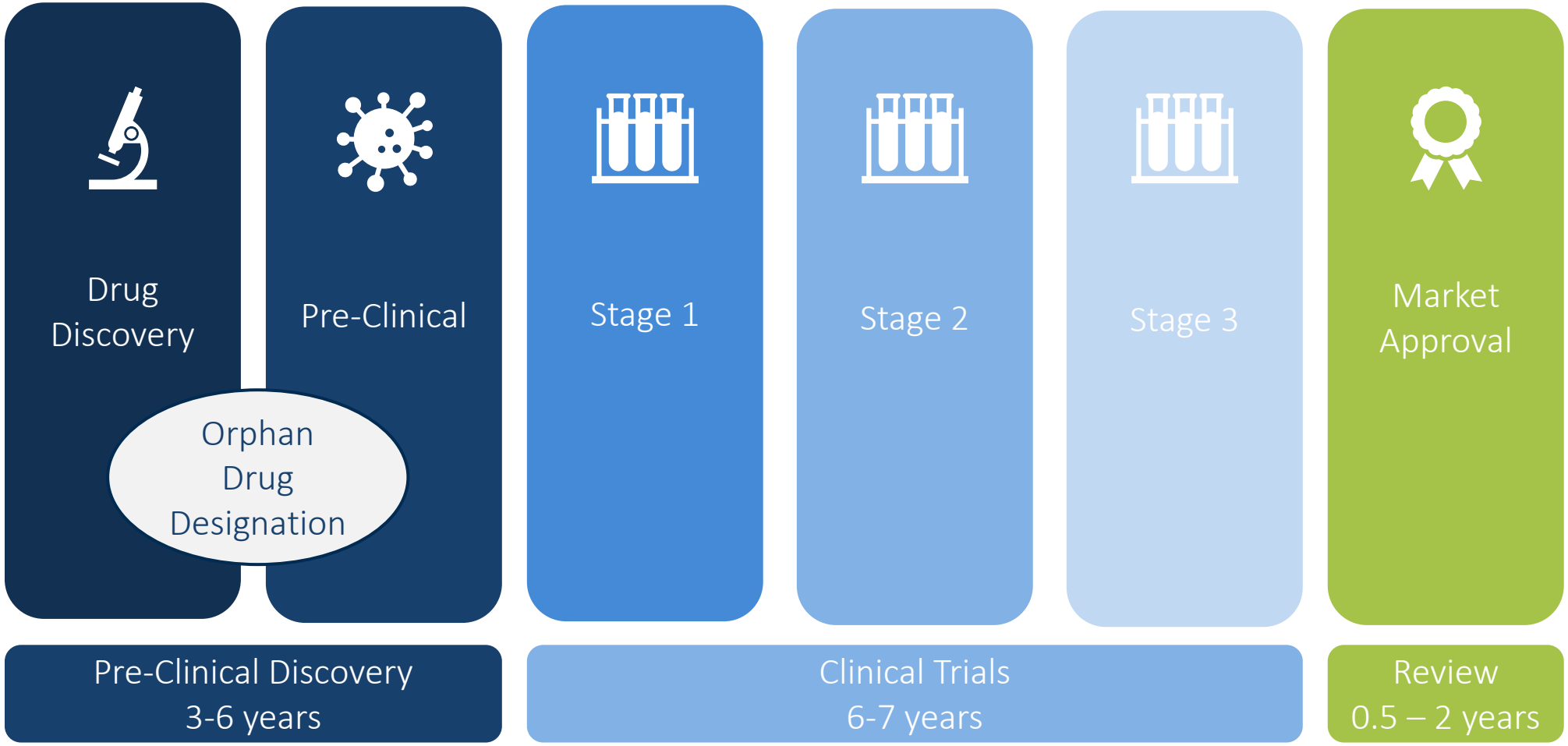
How is it implemented?

HORIZON EUROPE

FDA

In both regions, grants are available, but they are not exclusive a benefit of Rare Diseases.
In the EU, most grants are for later phases.

From Ideation to Market Approval …



Pre-Clinical

What is happening during this stage of development? What is the goal?

- Since moving a drug to clinical trials is associated with high costs, risks and administrative effort, preclinical trials are conducted.
- In these trials first indications regarding efficacy, toxicity and safety information can be gathered.
- The goal is to decide whether to continue with a drug candidate

What are challenges specific to the Orphan Drug Development?

- During preclinical trials drugs are mostly tested in vitro (test tubes) or in vivo (small animals) so the process is still similar to “normal” drug development.
- Continuing with the development beyond this point becomes a challenge without additional support.

What is being done to support Orphan Drug Development?

- Companies that are targeting a Rare Disease can file for Orphan Drug Designation (ODD) at this point of the development process.

Deep Dive: Orphan Drug Designation (ODD)

"A status given to certain drugs called orphan drugs, which show promise in the treatment, prevention, or diagnosis of orphan diseases." ~ U.S. Government (NIH)

What are the requirements for getting Orphan Drug Designation?

In both the EU and the U.S. some requirements have to be met to gain Orphan Drug Designation. Both regions require the disease to be very serious (either lethal or chronically debilitating) and rare (definitions differ). Additionally, in both regions the company that applies for ODD needs to present preclinical data to show the promise of the new drug (or its superiority).

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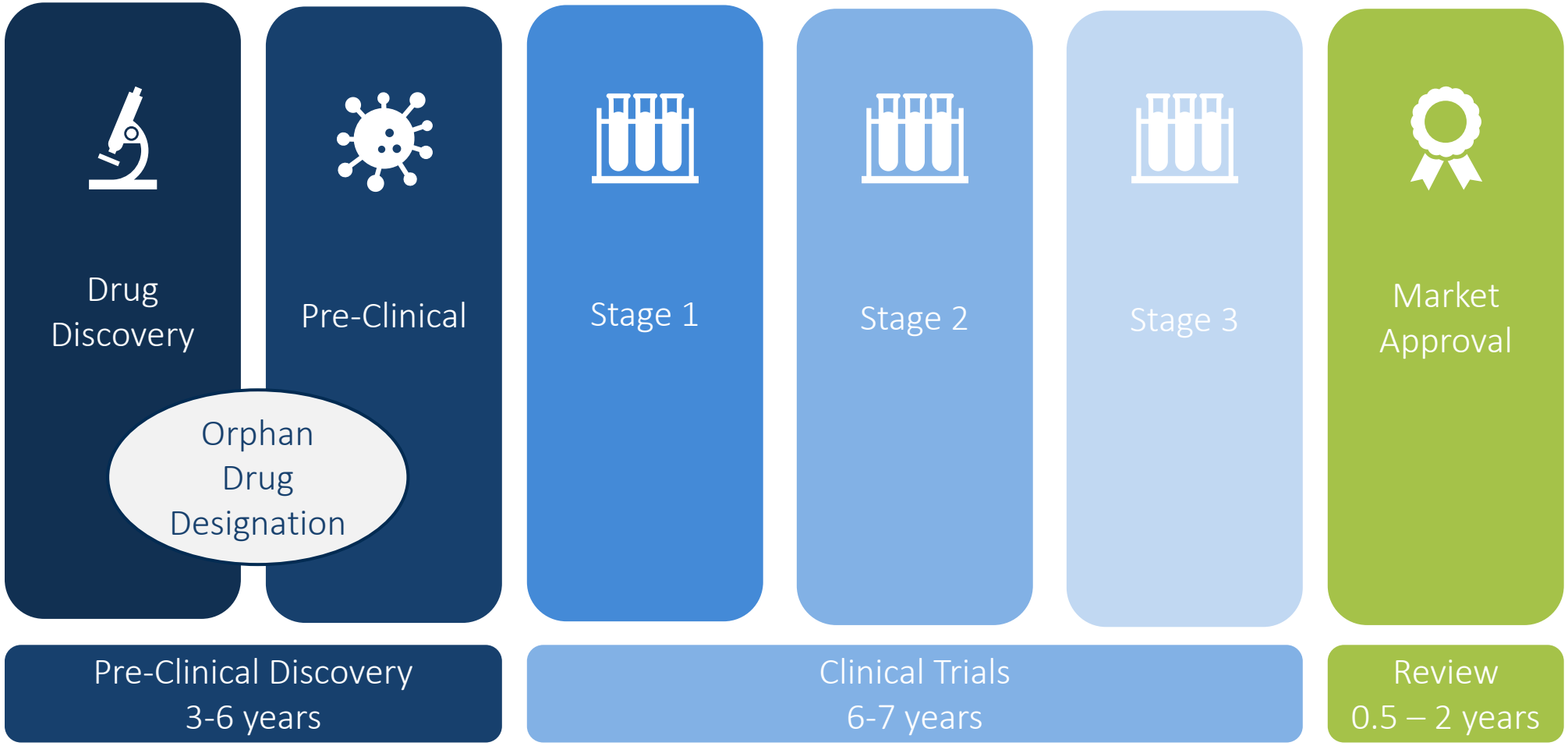
Deep Dive: Orphan Drug Designation

	EU	US
Coverage:	Prevention, diagnosis, or treatment of	
Seriousness:	Life threatening or chronically debilitating	
Rarity:	5 in 100,000 0.005%	< 200,000 affected 1984 - 2024 [0.060%, 0.086%]
Profitability:	Without incentives it is unlikely that the marketing of the product would generate sufficient return to justify the necessary investment	
Effectiveness:	Potential efficacy or clinical superiority	No existing satisfactory method or clinical superiority
Control:	Reassess during marketing authorization EMA central review of prevalence since 2018	Every drug for every indication must be proven anew, cannot cite previous

From Ideation to Market Approval …



Clinical Trial Set-Up

What is happening during this stage of development? What is the goal?

- Before a drug can be marketed the producing company needs to prove the efficacy and safety of a drug.
- Usually this process contains 3 stages.
- In Phase 1 healthy patients are administered the drug to test for potential side effects.
- In Phase 2 patients with the targeted diseases are treated to test whether the drug is effective.
- In Phase 3 the drug is tested on a much larger scale than in Phase 1 on healthy patients to test for less prevalent side effects.

What are challenges specific to the Orphan Drug Development?

- Usually in Phase 2 between 100-500 people with the disease are tested to gain insights for the efficacy. Since rare diseases are much less common, as the name suggest, it might be hard to find enough volunteers.
- The entire process to go through all 3 stages of clinical trails usually takes 6-7 years, which is often too long for life-threatening rare diseases.

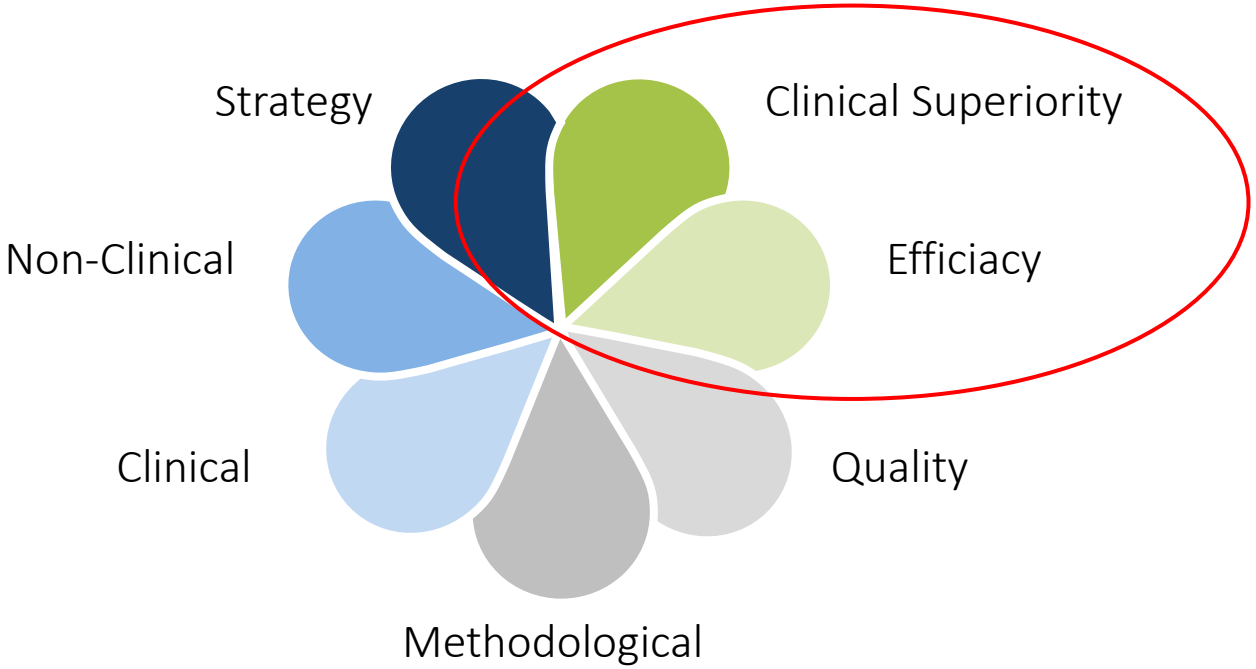
What is being done to support Orphan Drug Development?

- In order to support the setup for the clinical trials, companies can apply for Protocol assistance (~86% of companies receive protocol assistance)
- Additionally, often times the regulations allow for shorter, less rigorous trials, e.g. the number of patients to be tested is reduced or Phase 1 & 2 can be combined.
- In the U.S., companies can deduct up to 25% of their trial expenses from their taxes.

Deep Dive: Protocol Assistance

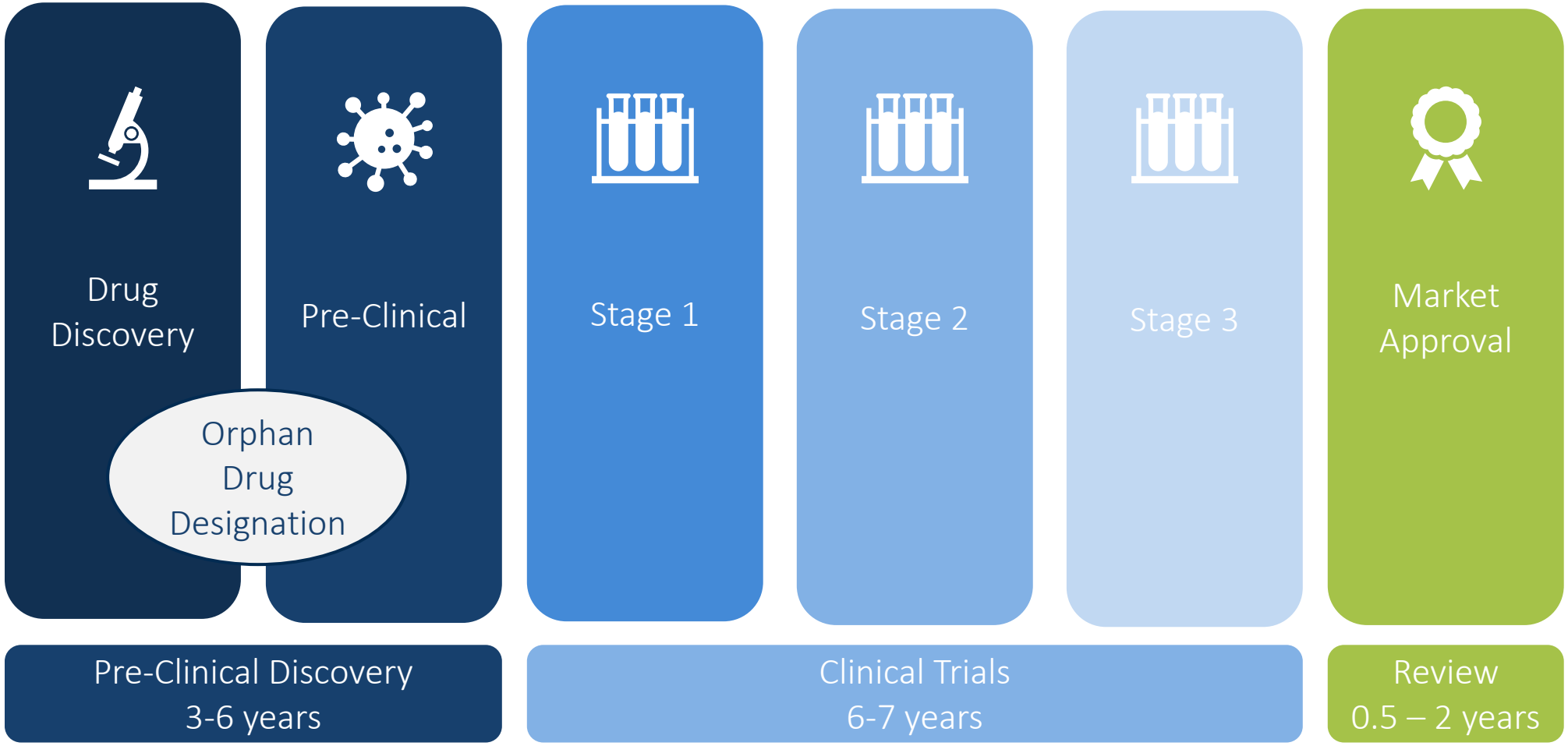
“We provide scientific advice by advising on the appropriate tests and studies required in the development or quality of a medicine.” ~ European Medicines Agency(EMA)

All companies can apply for scientific assistance in their drug development process



Protocol assistance is exclusive to the development of Orphan Drugs

From Ideation to Market Approval …



Getting Approval

What is happening during this stage of development? What is the goal?

- After successfully demonstrating the use for the drug the last step to enter the market is getting approval from the relevant authorities.

What are challenges specific to the Orphan Drug Development?

- Marketing an Orphan Drug and recouping the development costs is especially hard for Orphan Drugs due to the limited patient pool.
- A lengthy approval process might make the difference between life and death even more so than for “normal” drugs.

What is being done to support Orphan Drug Development?

- Producers or Orphan Drugs are granted a longer period of Market Exclusivity
- There used to be a program in the U.S. that upon receiving market approval, companies additionally received a (tradeable) Priority Review Voucher.
- For Orphan Drugs most fees are drastically reduced or void.
- There are options to gain faster and special sorts or approval.

Deep Dive: Fee Reductions

	Fee type	Amount	Reduction
EU	Scientific Advice & Protocol Assistance	€53,600 – €107,300	75% for non-academia 100% for academia / SME / pediatric
	Application for market approval	€357,600+	10% for non-SME 90% for SME
	Annual fees after approval	€128,100	90% for SME
US	Application for market approval	$3,242,026 – 4,048,695	100%
	Annual program fees after approval	$393,933 – 416,734	100% if annual global revenue < $50m

Deep Dive: Non-Standard Approvals

	Conditional Approval	Approval under Exceptional Circumstances
Criteria:	Positive risk-reward balance	Lack of alternatives
	Clinical superiority (on surrogate points)	Unable to provide full info regarding efficacy & safety due to rarity / not possible / unethical
	Likelihood to provide comprehensive clinical data post approval	
Validity period:	Limited	Limited
Post-market constraint:	Submit confirmatory studies to convert to indefinite approval	Submit confirmatory studies to convert to indefinite approval
		Annual re-assessment until indefinite approval 100% under additional monitoring

Deep Dive: Market Exclusivity

Patent

A patent is a protection on a technical invention which satisfies

- *Novelty*
- *Inventive step*
- *Industrial applicability*

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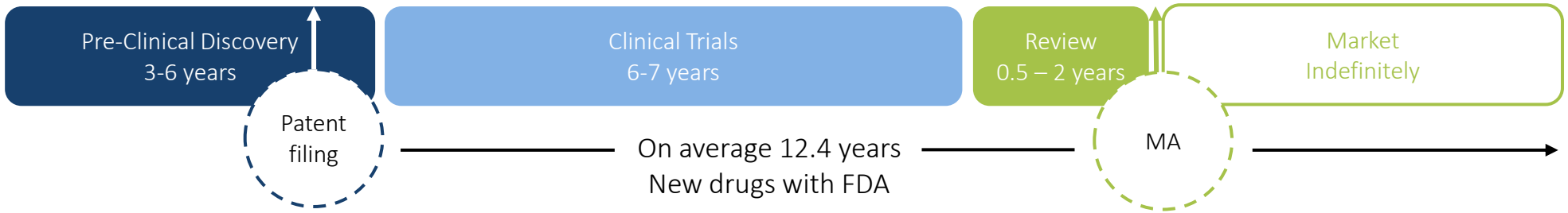
Market Exclusivity

Market Exclusivity (ME) means that for the duration of the ME no other application for market approval or extending an existing one will be approved

Deep Dive: Market Exclusivity

	Patent	EU	US
Application	National or European Patent office	EMA	FDA
Protection duration	[Filling date, ~20 years]	[Market approval, 10 years] +2 years if pediatric plan submitted May be reduced to 6 years if evidence shows profitable enough	[Market approval, 7 years] +6 months if pediatric study conducted & submitted



Maintenance	Patent office at national level where registered	EMA	FDA
Enforcement	Respective judicial authority	Same, but much simpler proving infringement	
Transfer	Y	Y by transfer of designation	N

Deep Dive: Market Exclusivity / Pricing

Due to increased utilization of external reference pricing (ERP) in the EU, (list) prices in the EU are significantly lower than in the US. Drugs in the U.S. cost on average more:

- *1.64x*
- *1.49x*
- *1.46x*
- *2.11x*
- *1.86x*
- *1.57x*
- *1.81x*

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Recap

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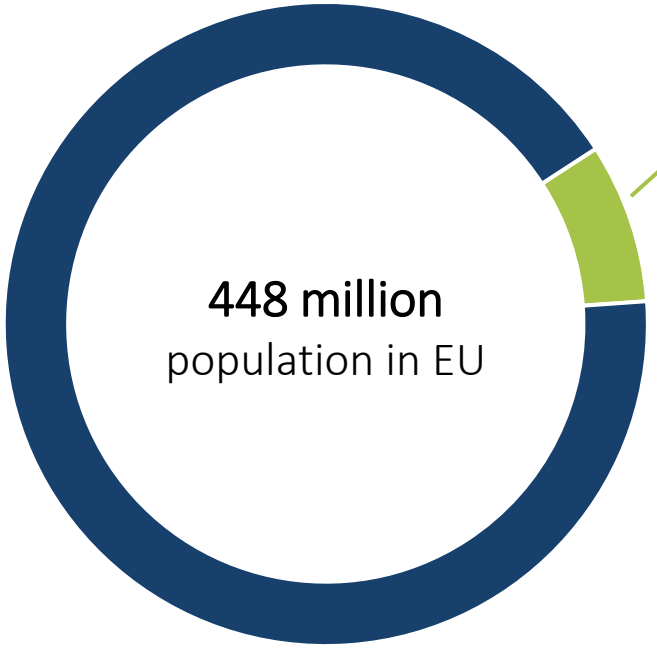

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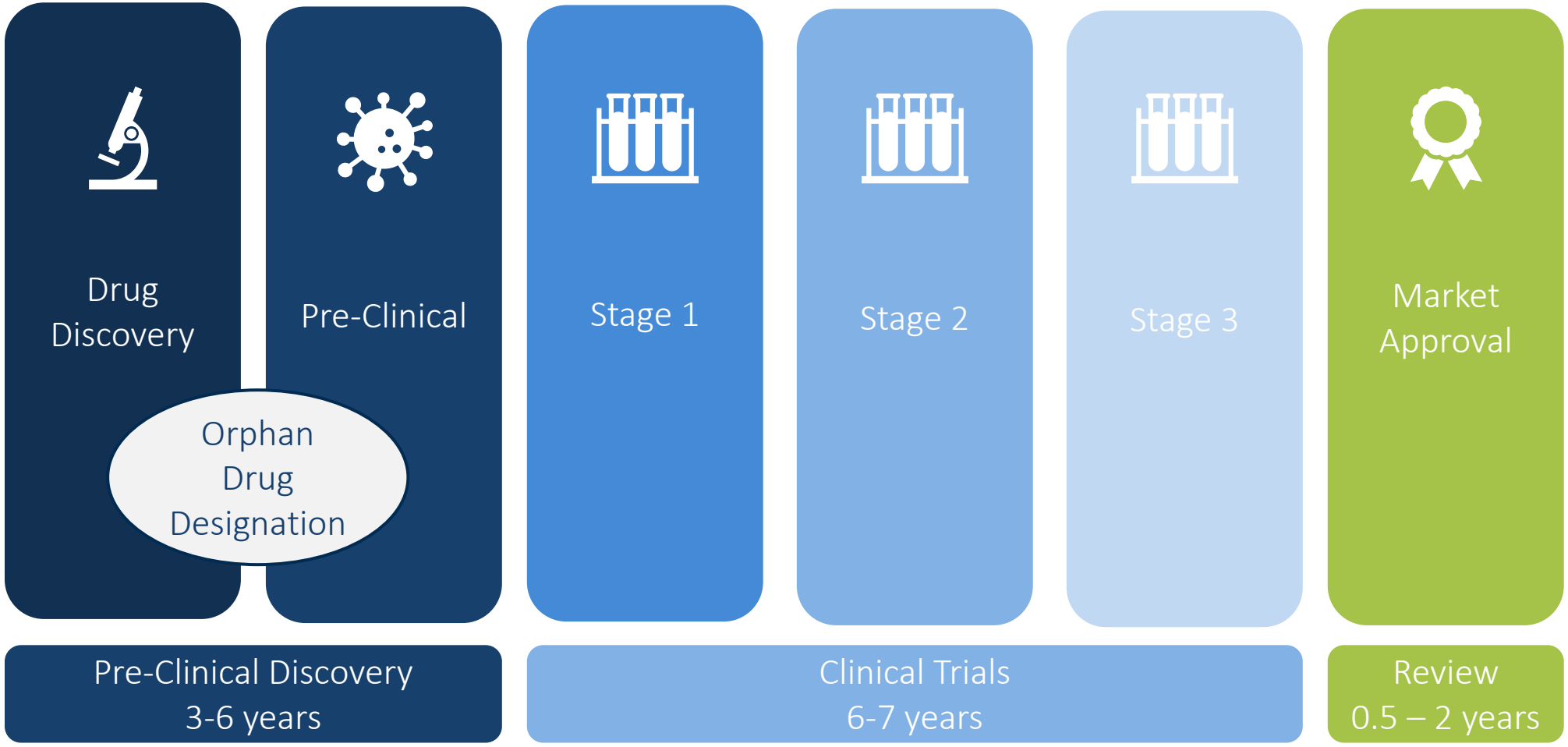
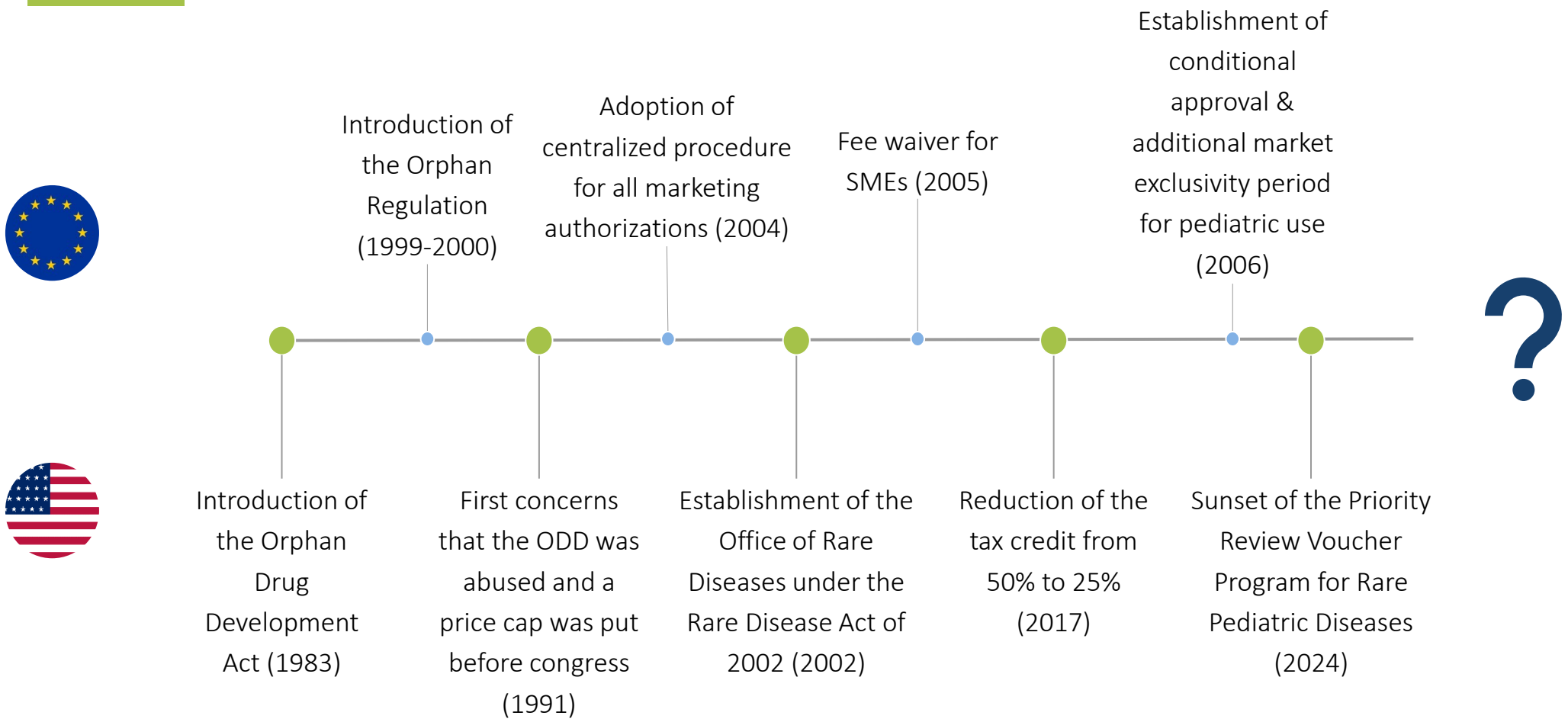
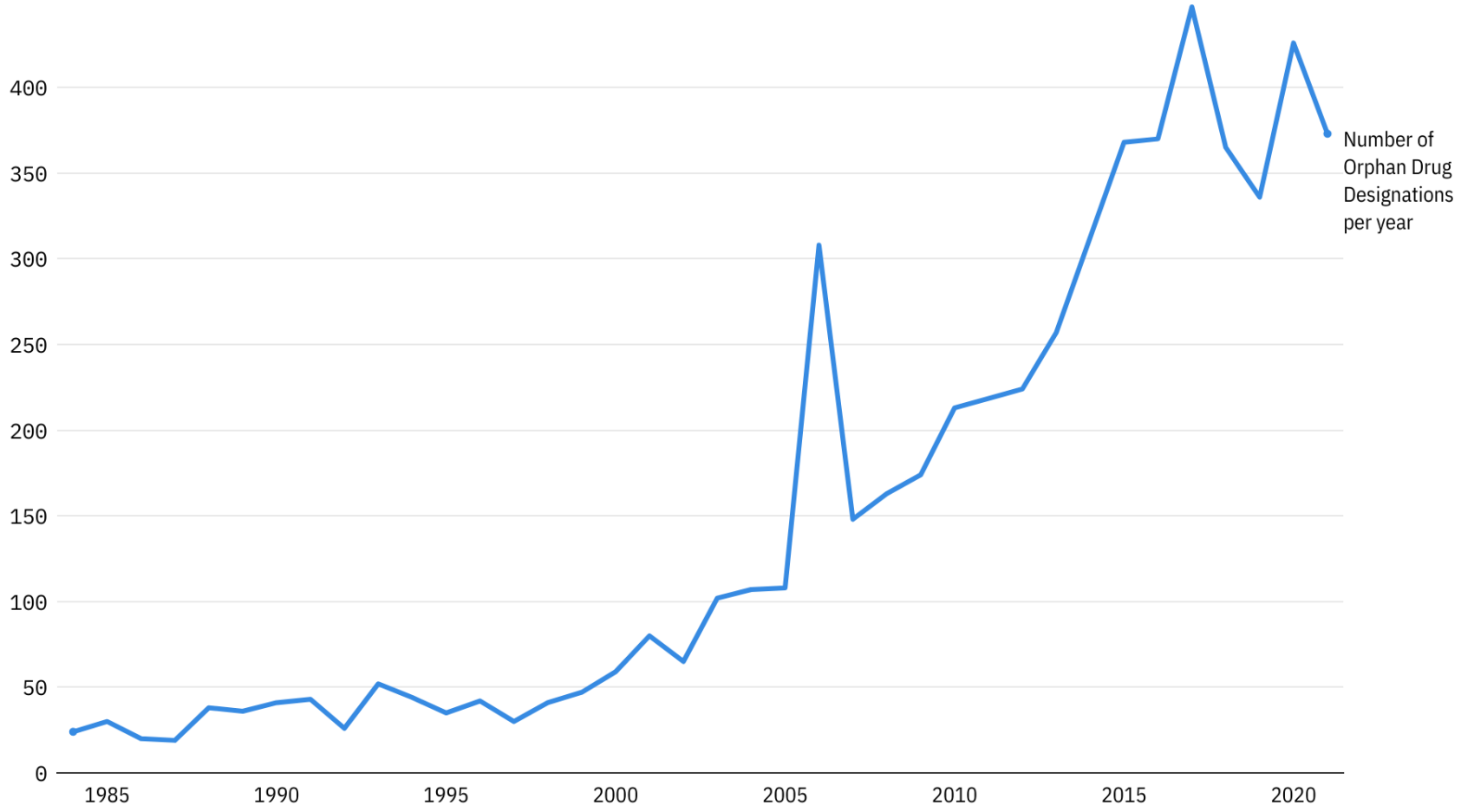


A short trip back in time …



So were all the measures effective?



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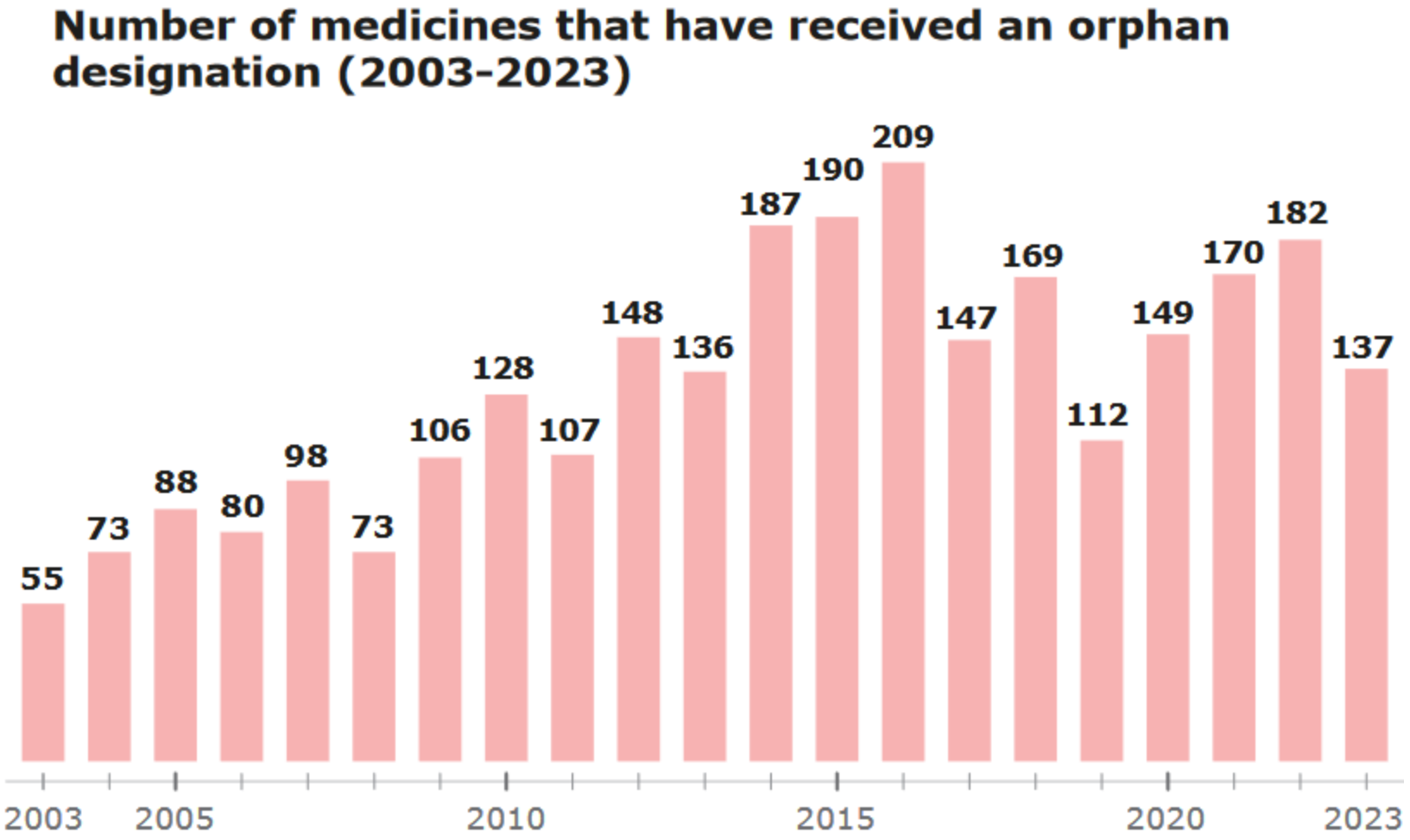

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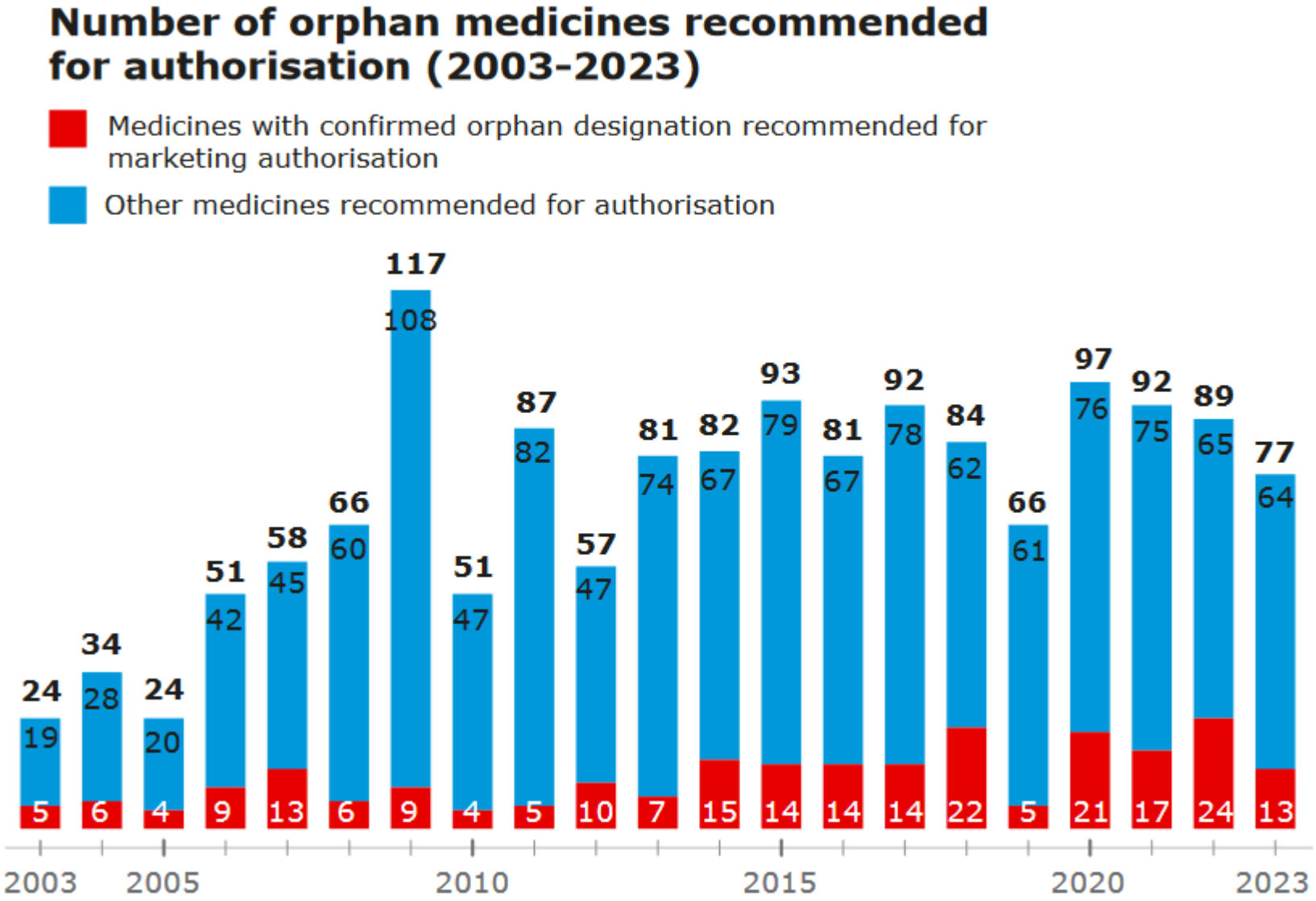

Some points for discussion …

Are there too many incentives for Orphan Drug Development by now?

Can the same principles be applied to Neglected Diseases?

When medicine becomes more personalized, is every drug an “Orphan Drug”?