

***Challenges of Antimicrobial Resistance – The next global crisis?***  
*Innovative financial and regulatory models to address AMR*

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## ***Agenda***

### **Societal problem and root causes**

- Innovative financial and regulatory approaches
- International experiences
- Conclusion

# ***Antibiotic resistance is a huge societal problem***

## ***Impact and extent of antibiotic resistance***

### **Estimates**

- ❑ 700'000 death per year<sup>1</sup>
- ❑ Economic burden of CHF 100'000'000'000'000 by 2050<sup>2</sup>

### **Regional variation of resistant bacteria<sup>3</sup>**

- ❑ Prevalence in developing countries ca. 40-60%, strongly increasing
- ❑ approx. 17% in OECD countries

### **Development of resistance**

⇒ Infections that can be treated today become life-threatening again



**No. 5** on  
WHO's top 10  
threats to  
global health  
in 2019

1) Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations The Review on Antimicrobial Resistance Chaired by Jim O'Neill, 2014

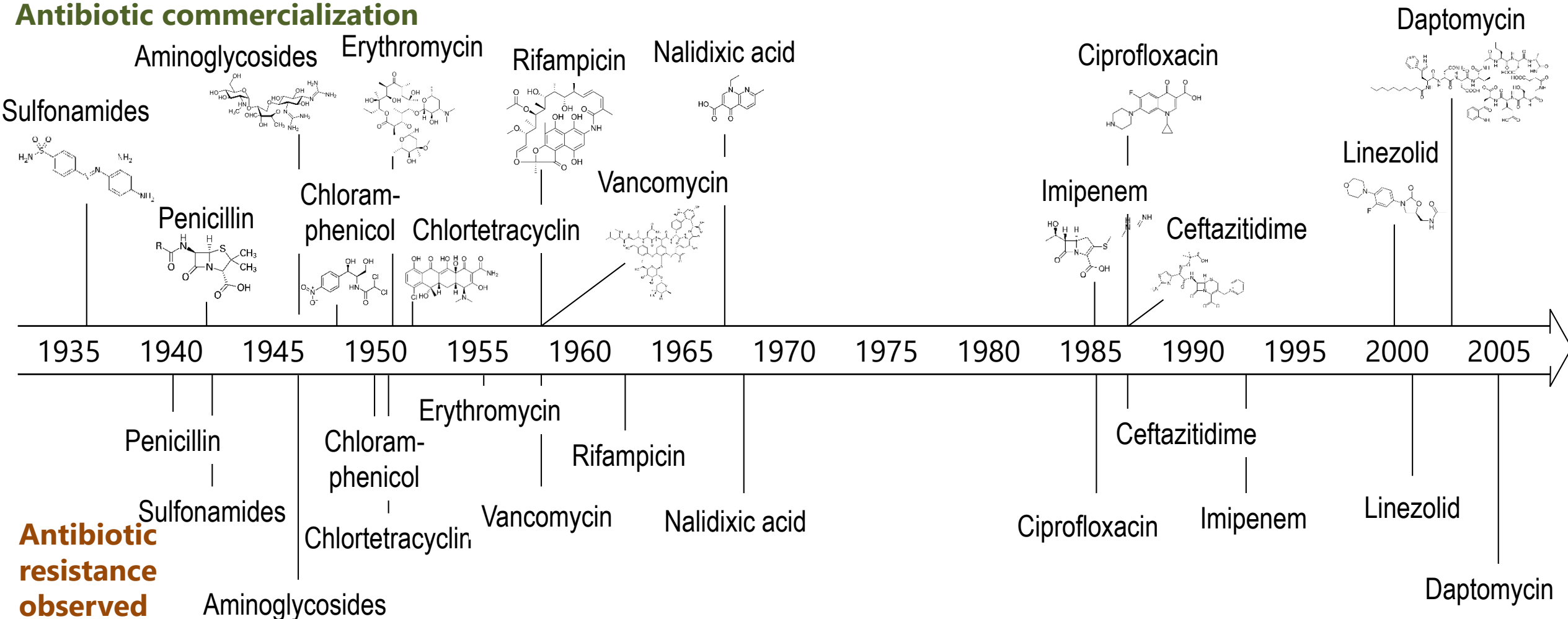
2) The World Bank. (2016). Drug-Resistant Infections: A Threat to Our Economic Future.

3) OECD (2018), Stemming the Superbug Tide: Just A Few Dollars More, OECD Publishing, Paris.

# New antibiotics on the market became rare and resistance to new antibiotics emerges soon after market entry of a new antibiotic class

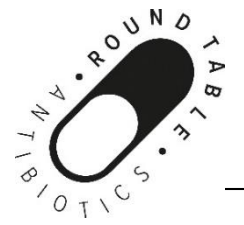
## Launch of new products and emergence of resistance

### Antibiotic commercialization

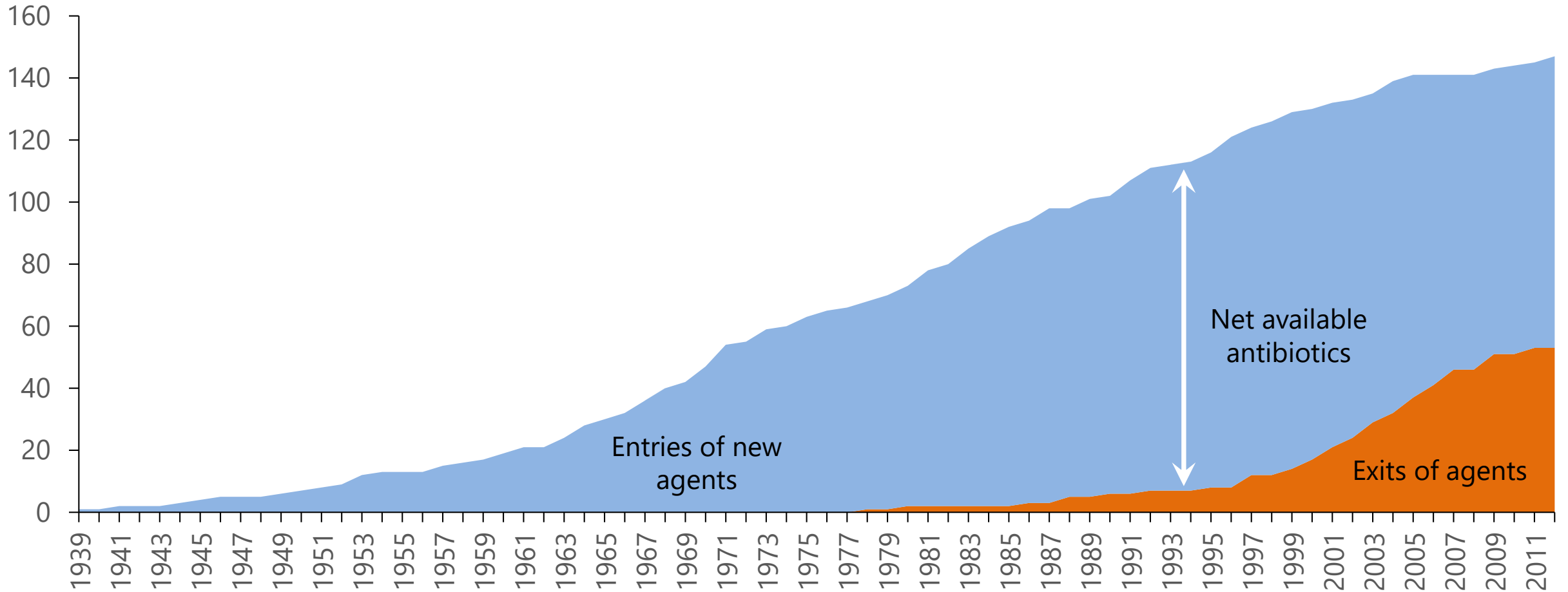


Source: Stephens, L. J., Werrett, M. V., Sedgwick, A. C., Bull, S. D., & Andrews, P. C. (2020). Antimicrobial innovation: a current update and perspective on the antibiotic drug development pipeline. *Future Medicinal Chemistry*, 12(22), 2035-2065. Structural chemical formulas: wikipedia.org

# The golden age of the antibiotics is over – the number of available antibiotics is decreasing



## Entry and exit of antibiotic agents



Source: Kinch, M. S., Patridge, E., Plummer, M., & Hoyer, D. (2014). An analysis of FDA-approved drugs for infectious disease: antibacterial agents. Drug discovery today, 19(9), 1283-1287.

## The current market incentives pose several issues:

- a) no incentives to develop new antibiotics
- b) no incentives to invest in a robust supply chain
- c) no incentives to sell/prescribe antibiotics responsibly



**Novartis zieht sich aus Forschung Antibiotika zurück**

12.7.2018, 18:07 Uhr

*(awp) / dba.* Novartis verabschiedet sich von der Erforschung von Infektionskrankheiten. Man habe sich für die Ressourcen in Bereichen einzusetzen, wo die Innovationschancen verspreche, erklärte der Konzernchef. Massnahme fallen rund 140 Stellen in der Region präsent.



**BRIEF**

**Achaogen files for bankruptcy protection seeks asset sale**

This white paper unpacks the systematic factors making antibiotic supply so fragile. For example, a global penicillin shortage now affects 39 countries. The paper links the causes of antibiotic shortages to recommendations for governments, regulators, the pharmaceutical industry and others.

Supply chain collapses lead to antibiotic shortages, which are linked to disease outbreaks and antimicrobial resistance. Commercial incentives underpinning the market are weak. Few pharmaceutical companies are willing or able to invest in rebuilding supply chains.



**Shortages, stockouts and scarcity**

The issues facing the security of antibiotic supply and the role for pharmaceutical companies

WHITE PAPER 31 MAY 2018

These of the main issues are: growth comes from the poor, there's low profitability and the supply chain has weak links.

**GLOBAL ANTIBIOTIC SUPPLY IS PATCHY, COMPLEX AND AT RISK OF COLLAPSING**

This white paper unpacks the systematic factors making antibiotic supply so fragile. For example, a global penicillin shortage now affects 39 countries. The paper links the causes of antibiotic shortages to recommendations for governments, regulators, the pharmaceutical industry and others.

To show where action is possible, the paper identifies three further areas where action is needed.

- 1 Pharmaceutical companies must bring a step change in their practices for antibiotic stock and inventory management, improve their agility, e.g., in response to supply chain issues and communicate information about their plans data earlier and in more detail to more partners
- 2 A unified approach – led by governments and supported by regulators and the industry – is needed to ensure multiple suppliers competing at critical links in the chain.
- 3 Success will depend on the development of strong incentives for pharmaceutical companies to enter and stay in the market.

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**Designing a Delinked Incentive for Critical Antibiotics: Lessons from Norway**

Christine Årdal, Jostein Johnsen, and Karianne Johansen

**Introduction**

Antibiotic resistance represents a serious threat to global public health.<sup>1</sup> As bacteria continue to evolve and are exposed to antibiotics, resistance develops,<sup>2</sup> yet antibacterial innovation has not held pace with the bacteria.<sup>3</sup> Almost all antibiotic classes on the market today were discovered prior to the 1980s,<sup>4</sup> and the current antibacterial pipeline offers only a few new ones.<sup>5</sup> Return on investment from developing a new antibiotic is significantly lower than other competing therapeutic areas. The reasons for this are multiple, including that resistance is still relatively uncommon and therefore many generic antibiotics are still highly effective; there is a desire to preserve the activity of new antibiotics and therefore uptake is slow; and demonstrating superiority through clinical trials is difficult for a number of reasons, including due to the paucity of patients.

This mismatch between innovation and public health need has led to calls for new economic incentives for developing new antibiotics, including by the United Nations, the G7 and G20 groups of countries, and the World Health Organization (WHO). A theoretical model – called “delinked” – has been

sales. In this way, the innovator is rewarded for the value of the innovation rather than unit sales. It also relieves any pressure on the innovator to maximize sales. There are two variations of delinkage. “Fully” delinked means that the innovator does not receive any revenues from volume sales, but rather simply a fixed annual payment. “Partially” delinked means that the innovator receives annual payments in addition to revenues from unit sales.

Several initiatives, including the United Kingdom’s AMR Review,<sup>7</sup> Duke Margolis Center for Health Policy,<sup>8</sup> and a report commissioned by the German government as leader of the G20 in 2017<sup>9</sup> have proposed delinked models but none have yet been tested. DRIVE-AB, a research project financed by the European Union’s Innovative Medicines Initiative, aimed to transform the way policymakers stimulate innovation, the sustainable use, and the equitable availability of novel antibiotics to meet unmet public health needs. We have explored delinked incentives and worked with the Norwegian government to explore how to operationalize such an incentive. This paper details the lessons learned from designing a Norwegian delinked incentive for antibiotics.

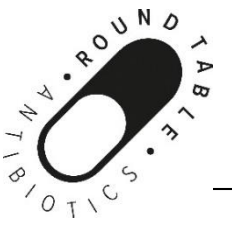
Sources:

NZZ (2018): Novartis zieht sich aus der Forschung zu Antibiotika zurück  
 Andrew Dunn (2019): Achaogen files for bankruptcy protection, seeks asset sale, <https://www.biopharmadive.com/news/achaogen-files-for-bankruptcy-protection-seeks-asset-sale/552737>  
 Access to Medicine Foundation (2018): Shortages, stockouts and scarcity  
 Årdal, C., Johnsen, J., & Johansen, K. (2018). Designing a Delinked Incentive for Critical Antibiotics: Lessons from Norway. *The Journal of Law, Medicine & Ethics*, 46(1\_suppl), 43-49.

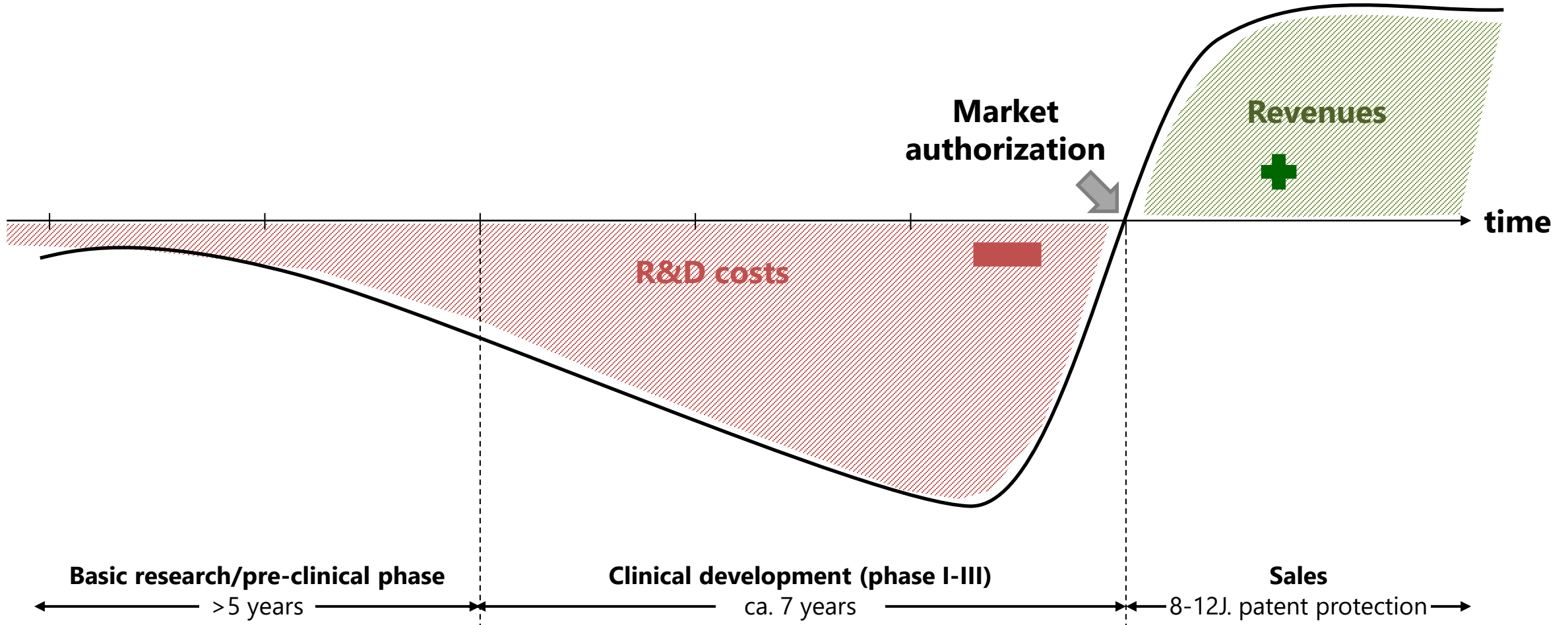
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# Expected future sales revenues are the main driver to invest into expensive pharmaceutical development

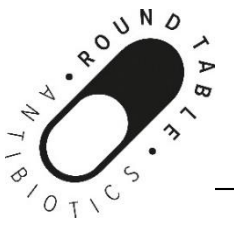


## Costs and sales revenues: usual drug market

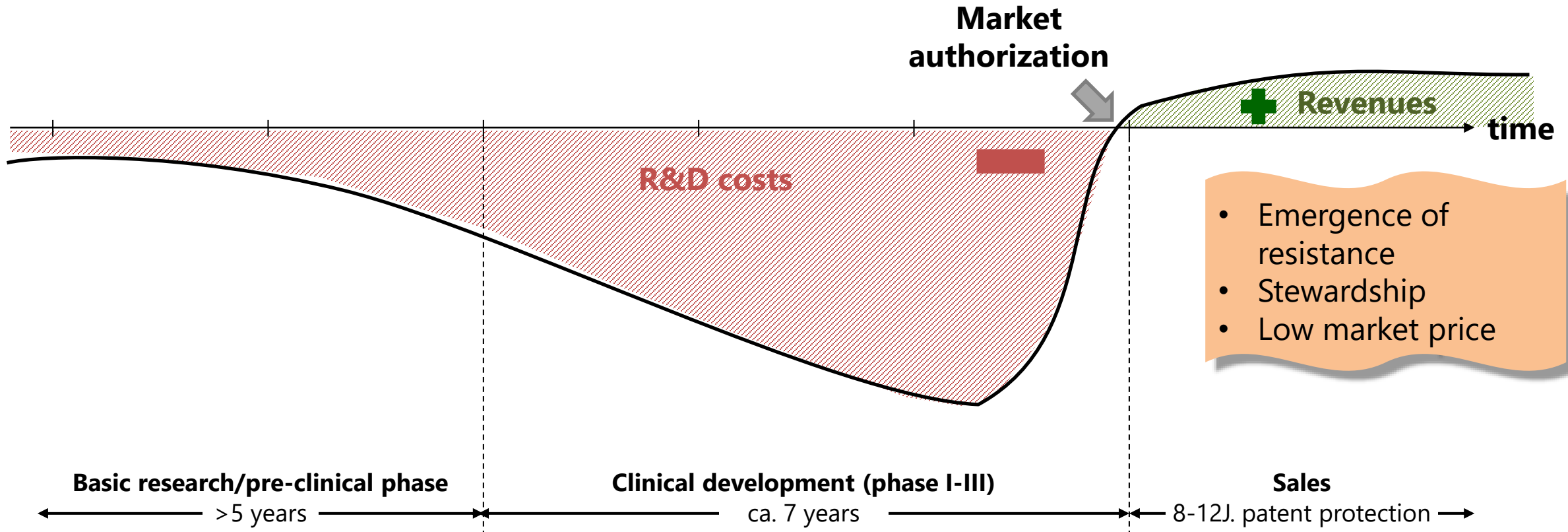




***Sales revenues and thus incentives to develop new antibiotics are substantially lower for antibiotics than for usual drugs.***



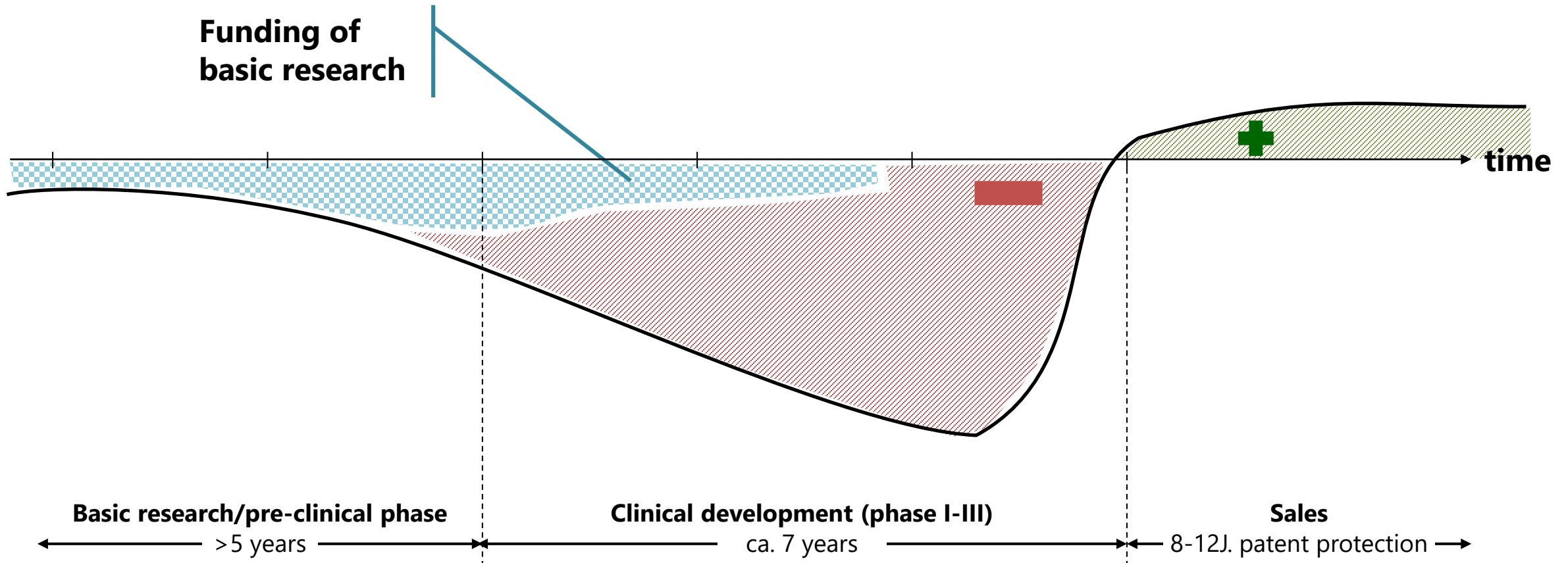
***Costs and sales revenues: antibiotic market***



**Basic research is promoted in particular at universities and university hospitals, e.g., NCCR Antiresist, SNF72 etc.**

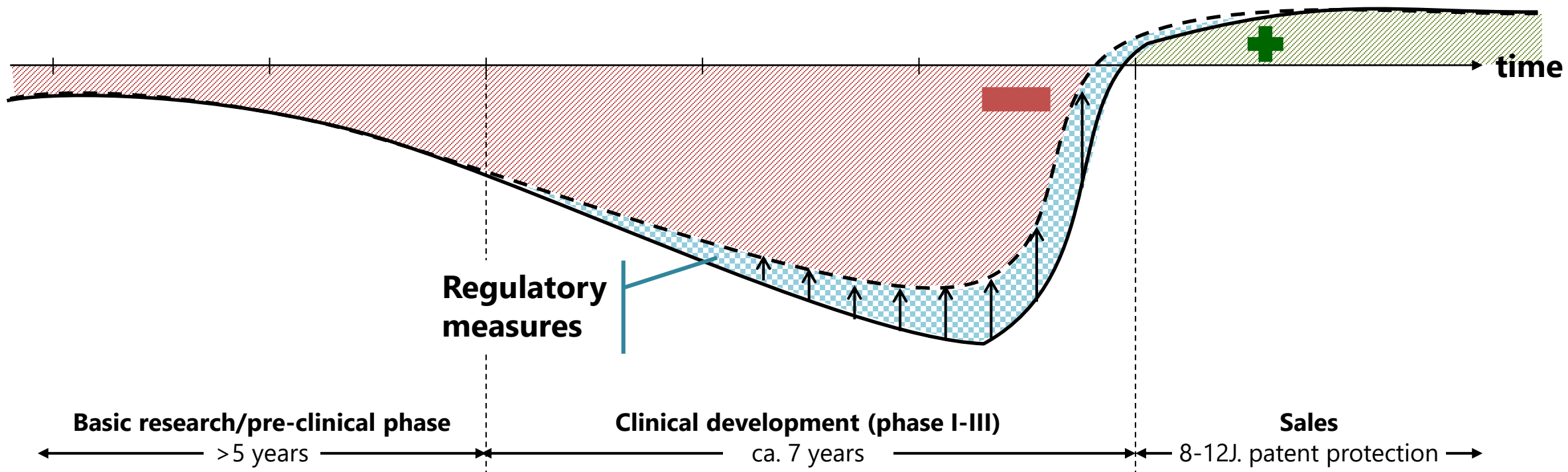


## **Funding for basic research**



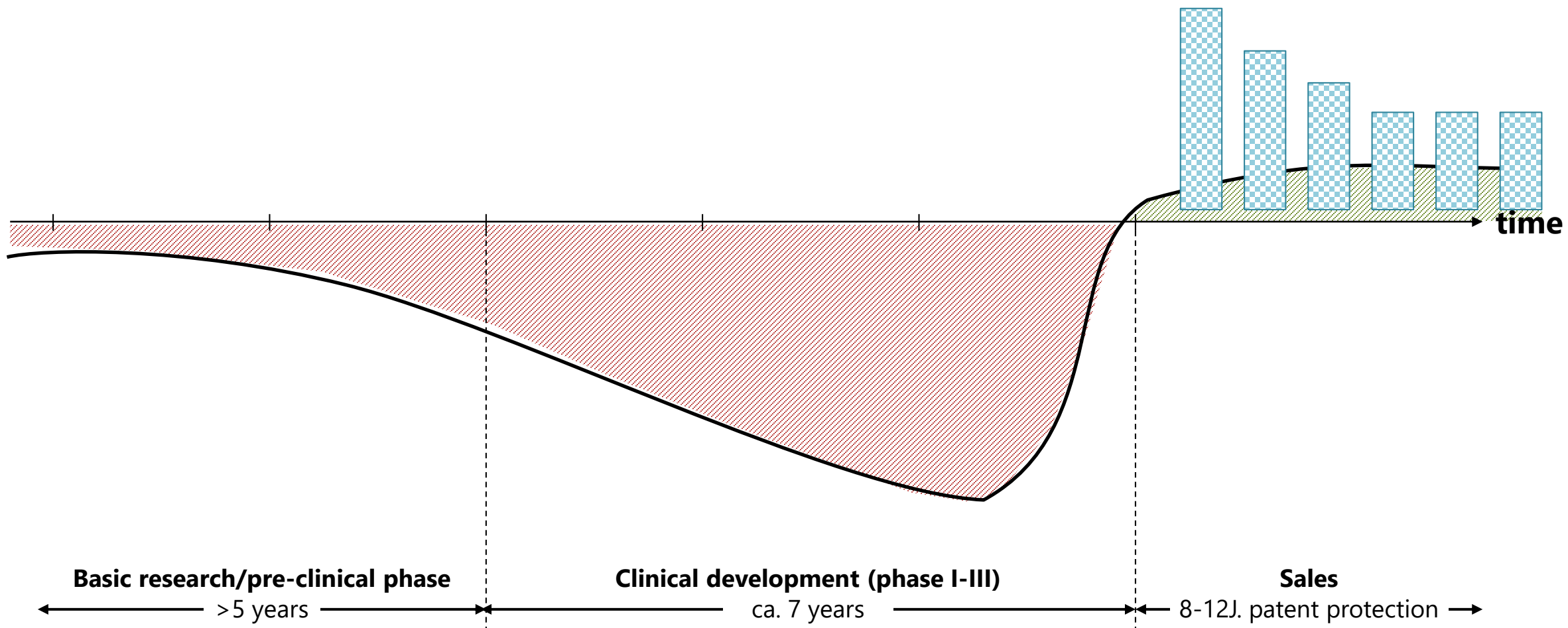
# Regulatory exemptions facilitate the market authorization process

## Regulatory measures



# Market entry premiums are a possibility to replace the market incentives

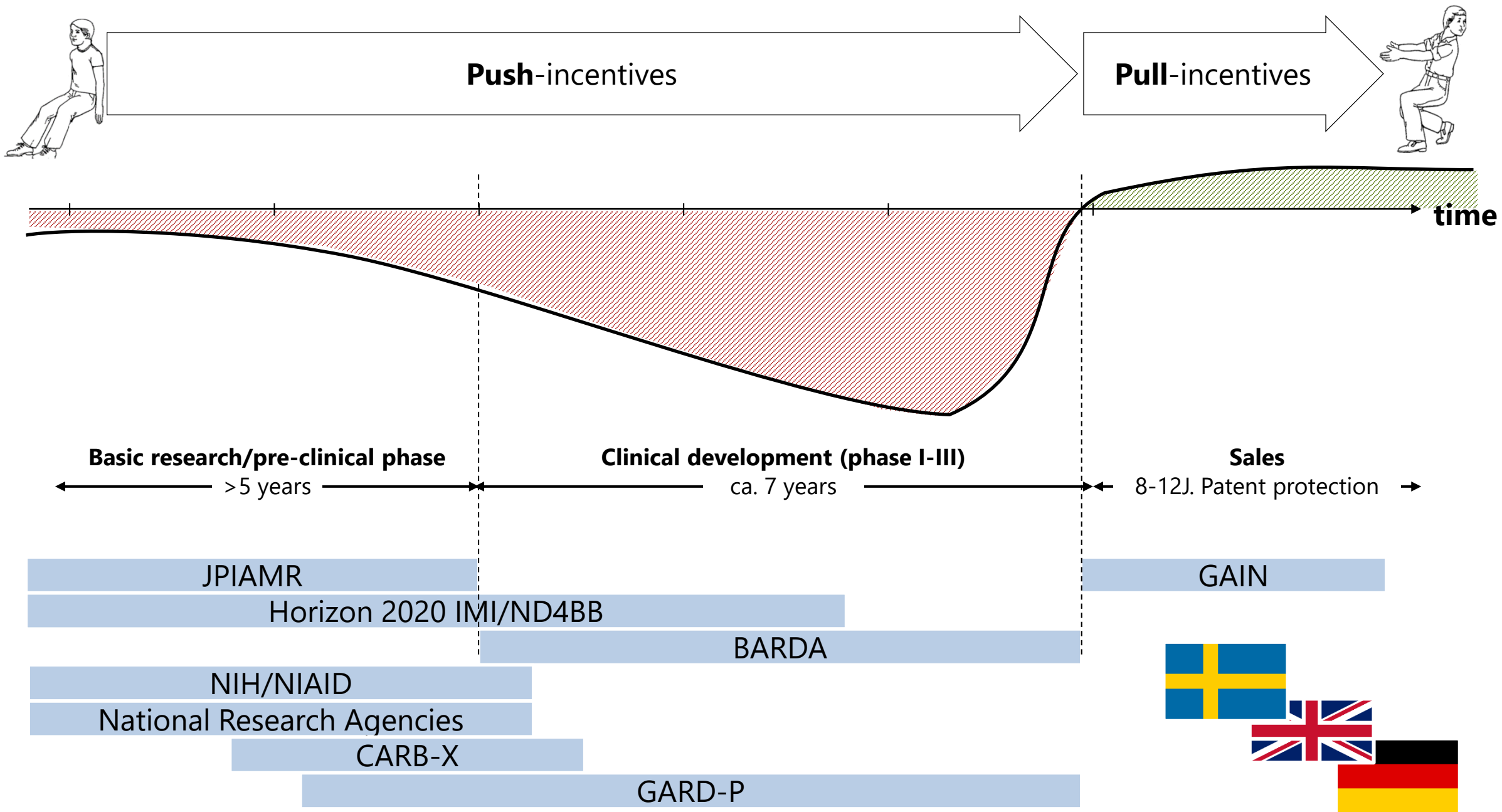
## Market entry premiums



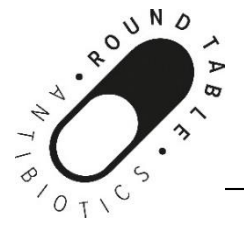
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## ***Agenda***

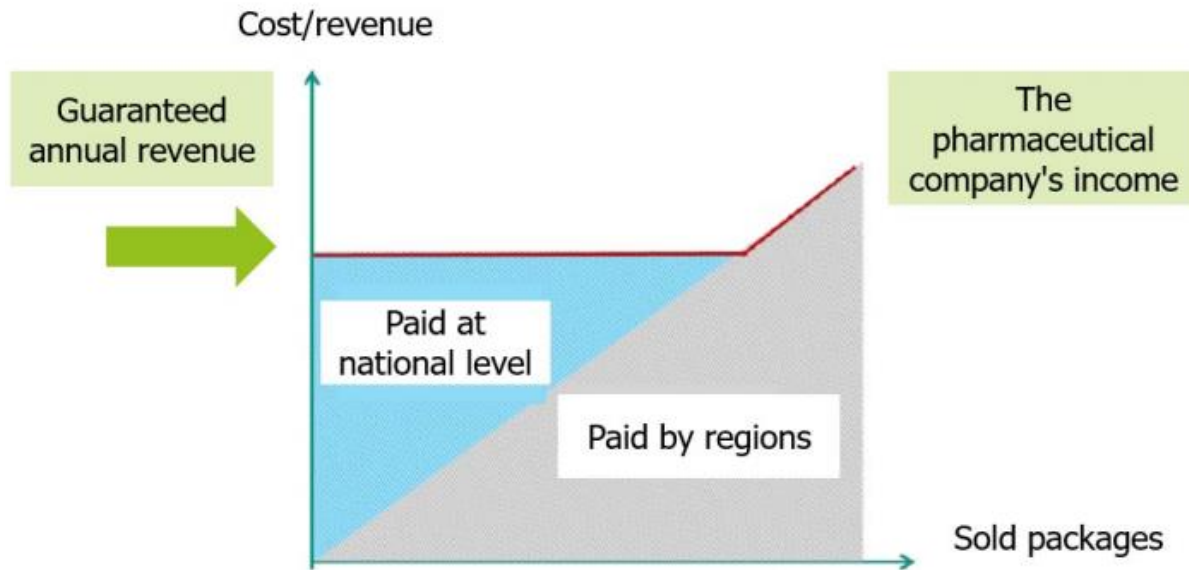
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# The de-linked Swedish model guarantees a minimum yearly income in exchange for rapid and timely supply of recently approved antibiotics



## Sweden – Exceptional Procurement Pilot (2018-2022)



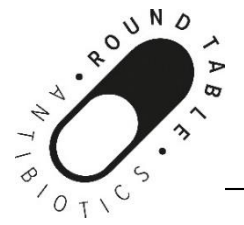
### Companies

- MSD, Shionogi, Pharmaprim, Unimedica Pharma

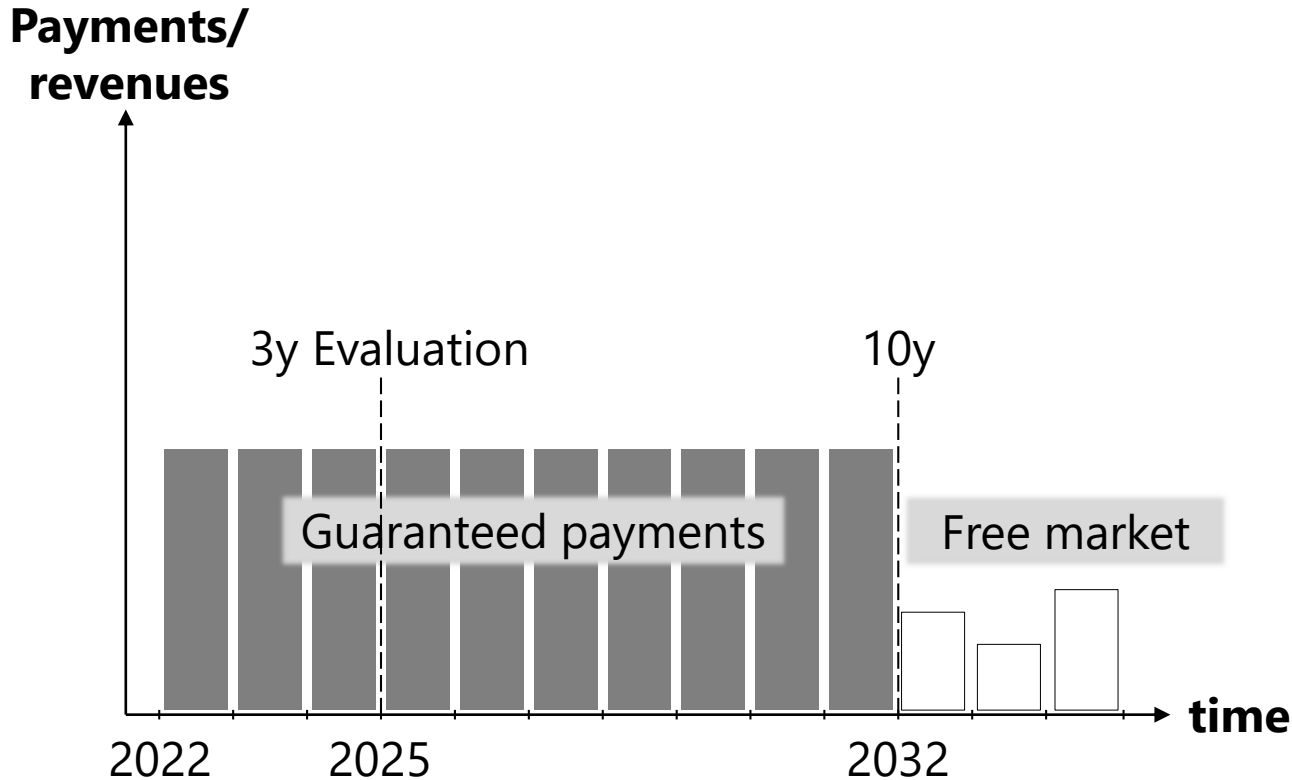
### Products

- Ceftolozane-tazobactam (Zerbaxa)
- Imipenem-cilastatin-relebactam (Recarbrio)
- Cefiderocol (Fetcroja)
- Meropenem-vaborbactam (Vaborem)
- Fosfomicin (Fosfomicin)

# The English model incentivizes companies to invest in research and development of new antibiotics – the new drug will be paid even if it's stored for reserves



## England: Value Based Subscription Model (2022-2031)



### Pilot program for two antibiotics

- Address WHO priority pathogens
- High unmet need in the UK
- Supply chain security
- One new, one existing drug

### Products

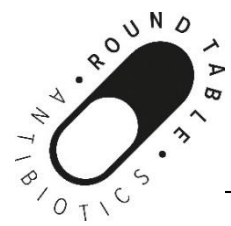
- Cefiderocol (Fetcroja)
- Ceftazidime-avibactam (Zavicefta)

### Structure

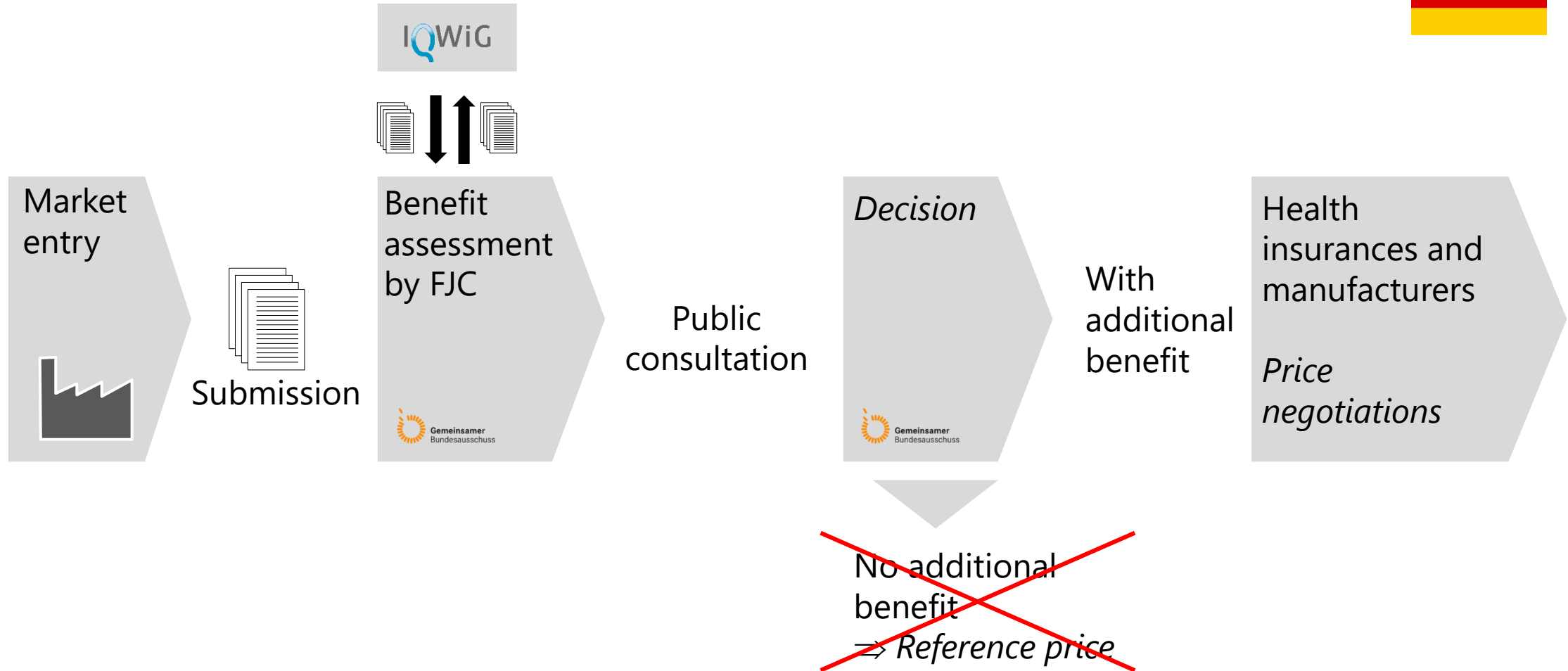
- Contract value is delinked from volumes
- Payment of a fixed annual fee (max £10m)
- Minimum period 3 years, max 10 years
- Selection of candidates end of 2020



# Regulatory exemptions in Germany ensure that manufacturers do not have to provide evidence for the additional benefit, leading to higher prices and lower market access barriers



## Germany (April 2020)



Source: Bundesgesundheitsministerium (2020): Gesetz für einen fairen Kassenwettbewerb in der gesetzlichen Krankenversicherung, <https://www.bundesgesundheitsministerium.de/fairer-kassenwettbewerb-gesetz.html> Arzneimittelmarktneuordnungsgesetz (AMNOG)

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## **Conclusion**

- ❑ Antimicrobial resistance is a silent pandemic and new antibiotics are urgently needed for the treatment of patients
- ❑ Existing measures are not sufficient to efficiently stimulate the development of new antibiotics
- ❑ Pull incentives are appropriate instruments to boost development, ensure supply and prevent inadequate prescribing.
- ❑ England, Sweden and Germany have taken the first step and launched distinct pilots.
- ❑ Switzerland should consider driving new antibiotics development by pull incentives to position the country as innovative, humanitarian, high-tech country.

**Thank you very much  
for your attention!**



Prof. Dr. Rudolf Blankart

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