The 7th NCGM International Infectious Diseases Forum
(October 8, 2019)

Antimicrobial Drug Development and its Foresight

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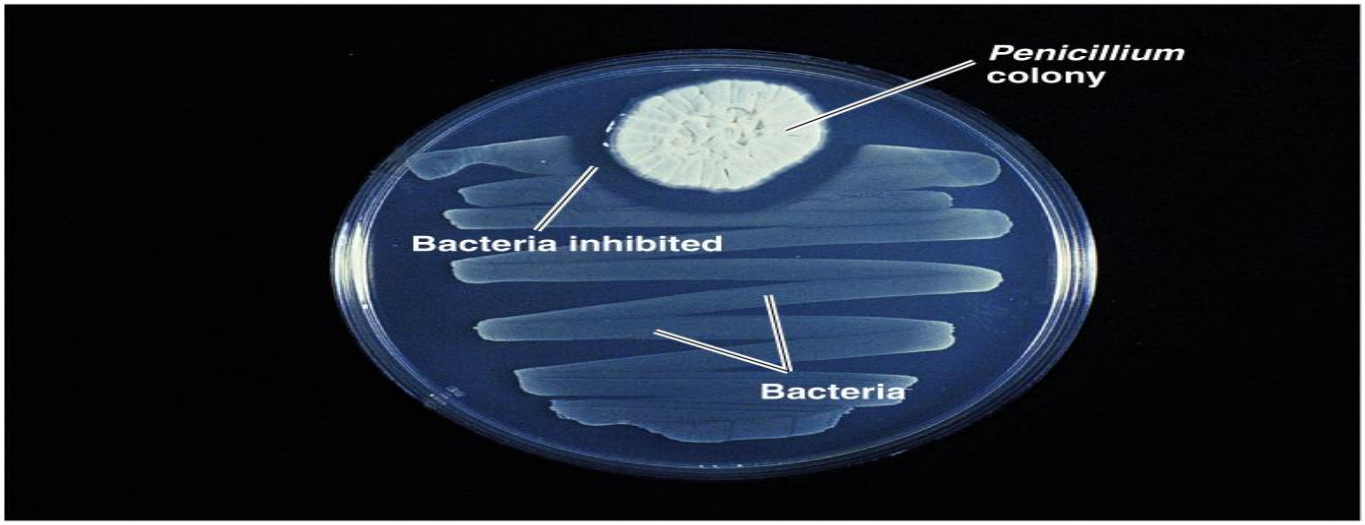
Kyorin Pharmaceutical Co. Ltd.,

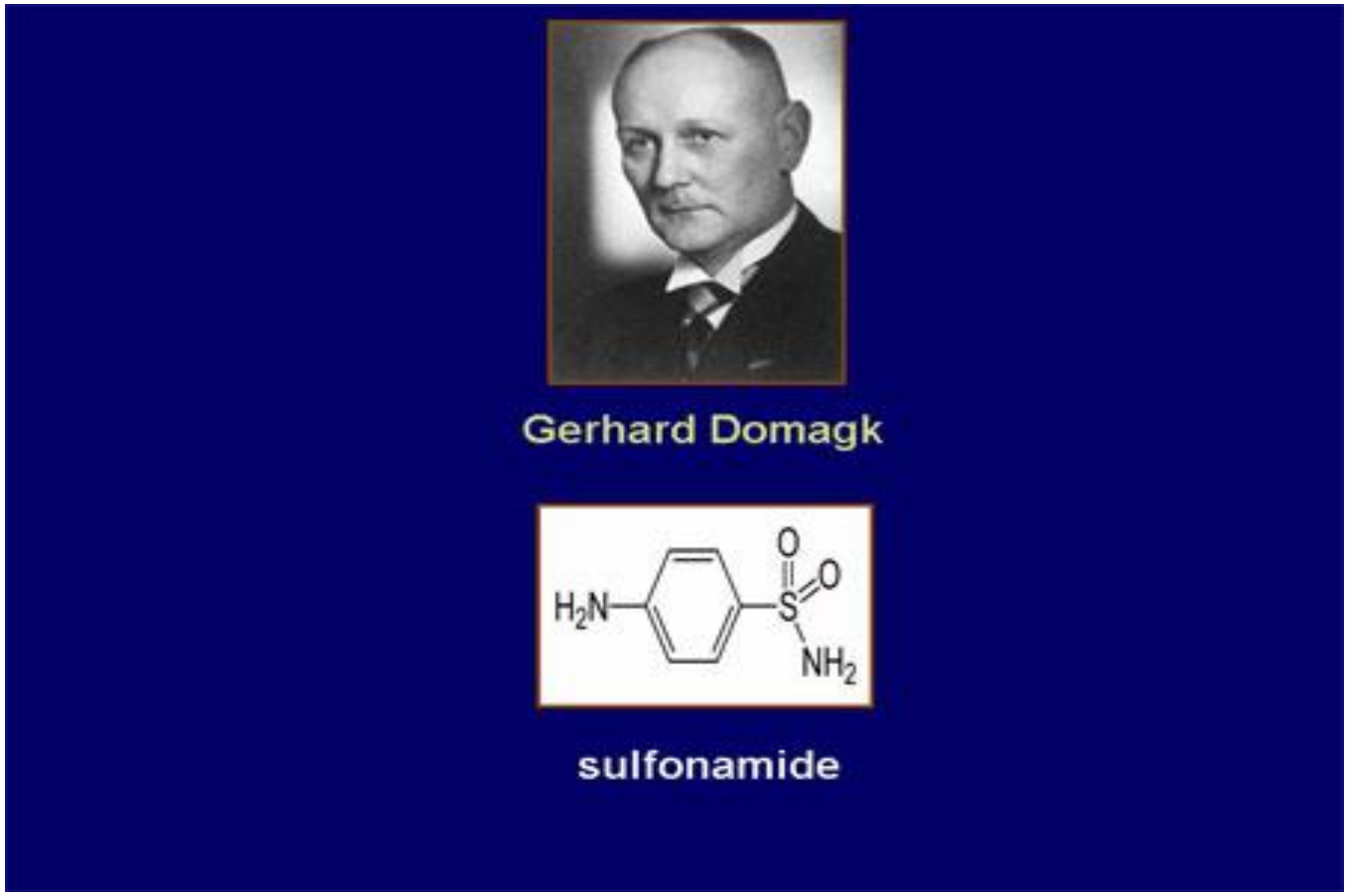
Today's Topics

1. History of Antimicrobials
2. Emergence and Spread of Drug-resistance (AMR)
3. Challenges to New Antimicrobials R&D
4. Incentives to Promote the Antimicrobials R&D
5. Current Antimicrobials Pipeline and Future Directions for New Antimicrobials R&D

Discovery of Penicillin by Fleming (1928)

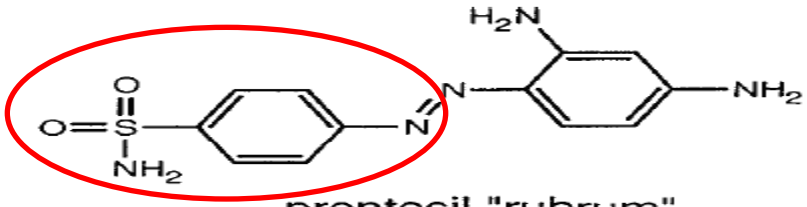


Discovery of Sulfonamide by Domagk (1935)



Gerhard Domagk

sulfonamide

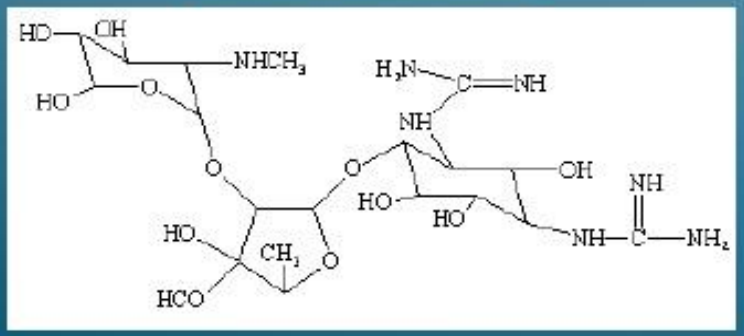


prontosil "rubrum"

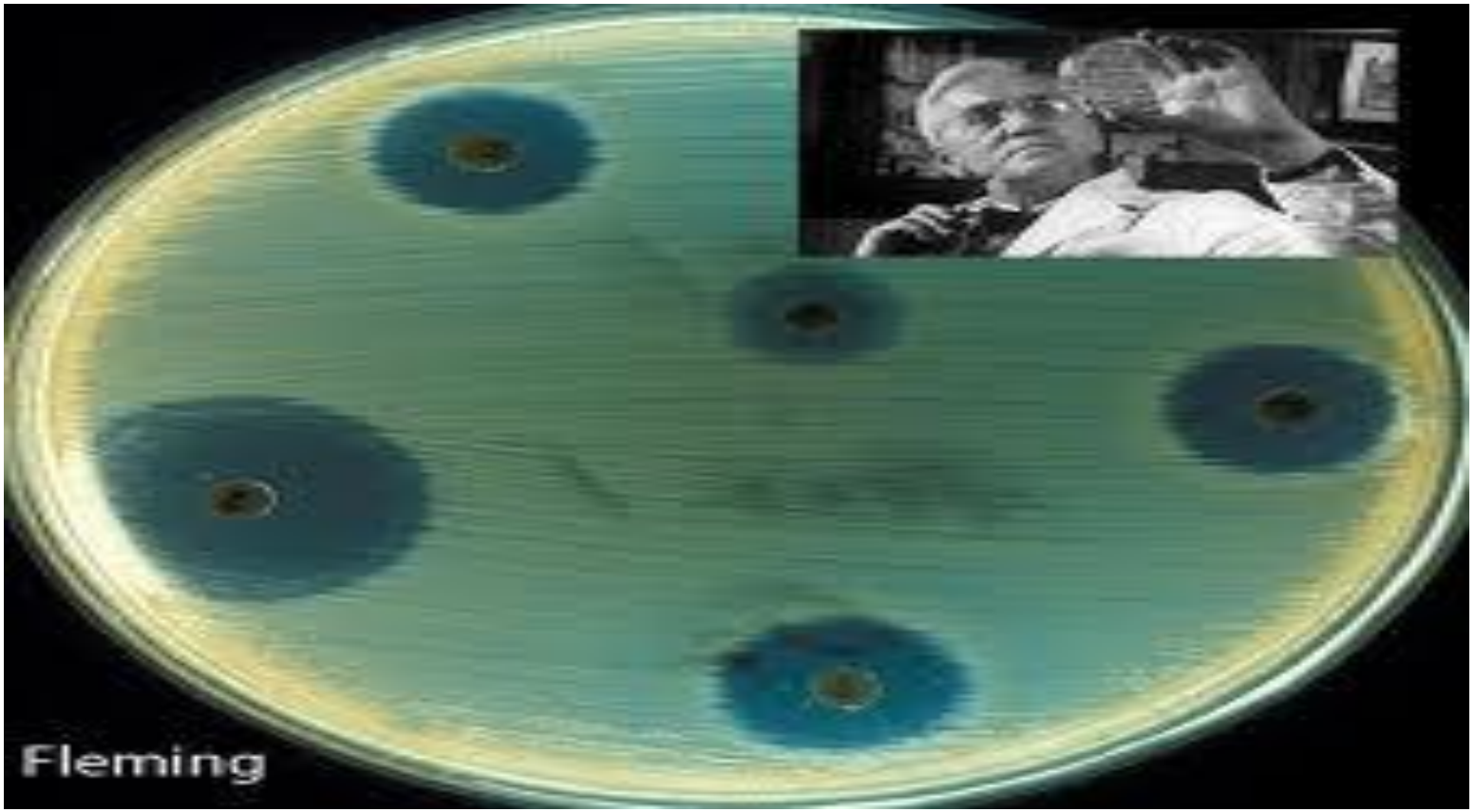
[Pro-drug]

Discovery of Streptomycin by Waksman(1943)

Selman Waksman

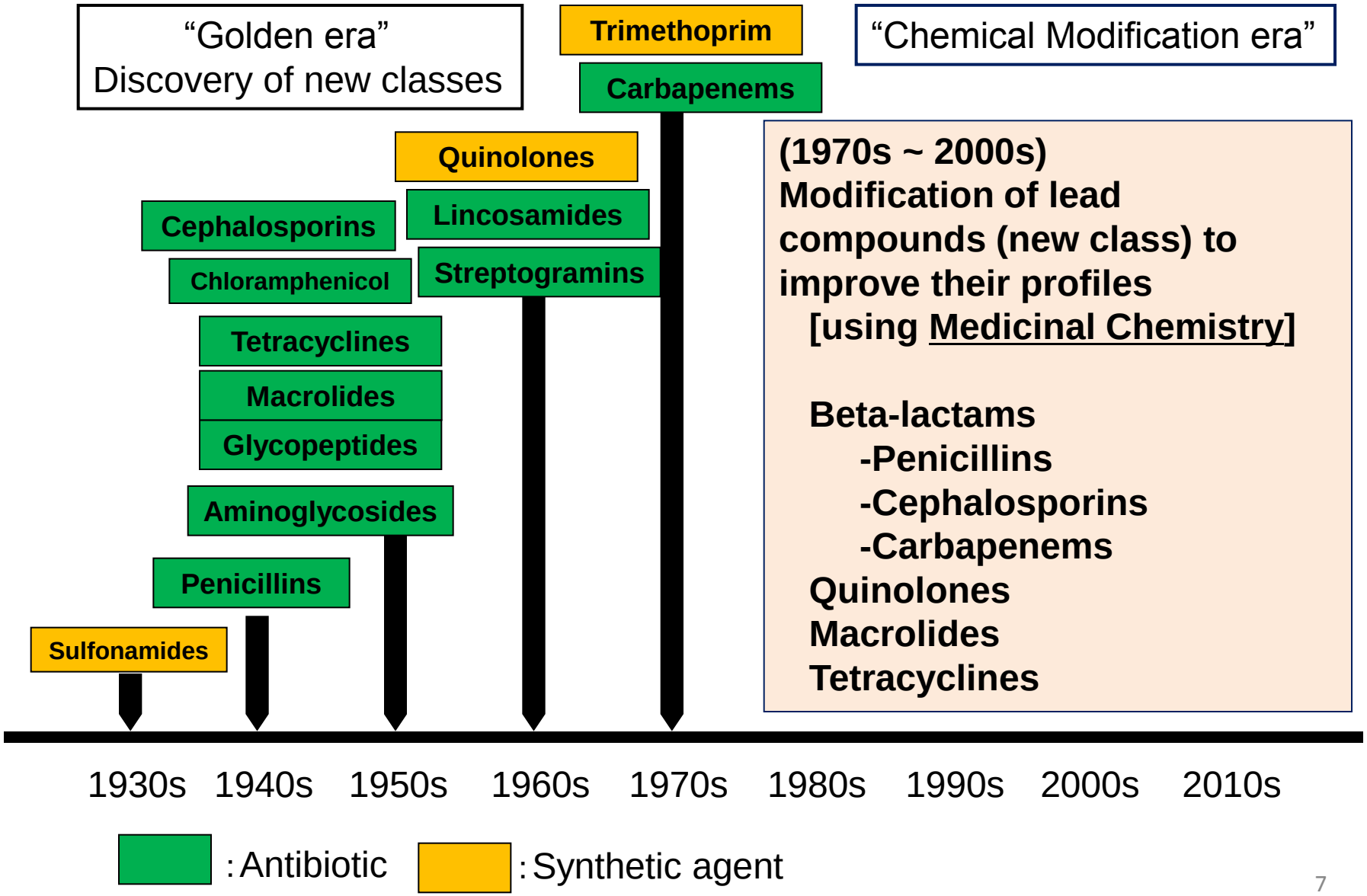


The Waksman's screening method is similar to the serendipitous discovery of penicillin by Fleming



Waksman's method, "screening for antimicrobial activity against test bacteria by detecting zone of growth inhibition ", was widely adopted by pharmaceutical industry and produced the major classes of antibiotics over next 20 years.

Golden era of antibacterial agents discovery



Development of Antibacterial Agents (Chemical Modification era 1970s~2000s)

Chemical Modification Approach
[Structure-Activity Relationships study]

β-lactams
- **-Penicillins**
- **-Cephalosporins**
- **-Carbapenems**

Quinolones
Macrolides
Tetracyclines
(Oxazolidinone)

Improve:
- **-Activity (potency)**
- **-Spectrum**
- **-PK profile**
- **-Safety(side-effects)**
- **-Physicochemical profile (stability, water solubility)**

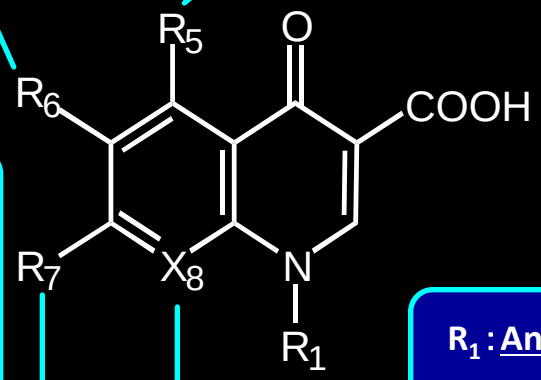
Structure-Activity Relationship of Quinolones

R_6: Effect on the antibacterial activity (DNAgyrase)

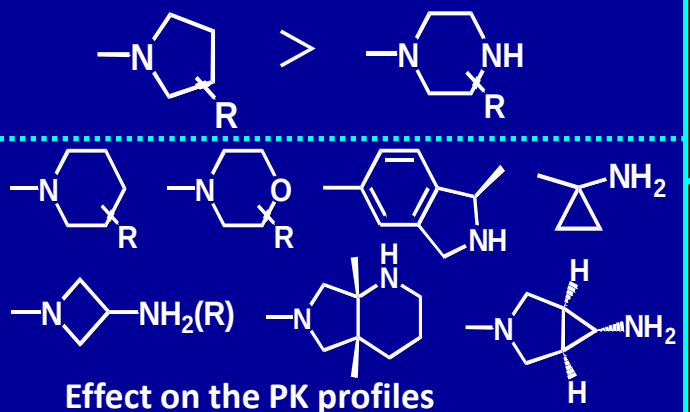
F > Cl > Br > H

R_5: Control of activity against Gram-positive bacteria (*S. aureus*)

NH_2 ～ CH_3 > H



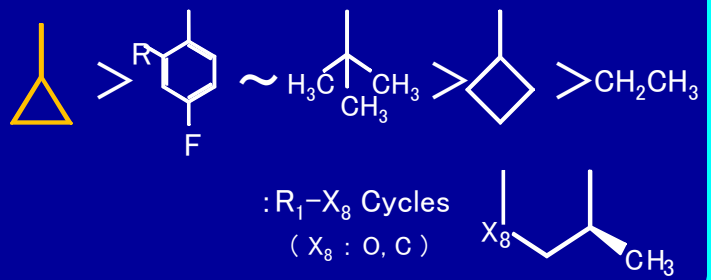
R_7: Control of antibacterial potency and spectrum



Effect on the PK profiles

- Oral absorption
- Metabolic stability
- Tissue distribution

R_1: Antibacterial potency



X_8: Effect on the activity against Gram-positive and anaerobic bacteria
Effect on the activity against quinolone-resistant strains

(・Inhibitory activity against DNA gyrase and Topoisomerase Ⅳ) → CCl, CF ≧ $COCH_3$, CCH_3 > CH

Effect on PK profile (BA) → CF ～ CCl ～ $COCH_3$ > N > CH

Successive generations of antibiotic classes

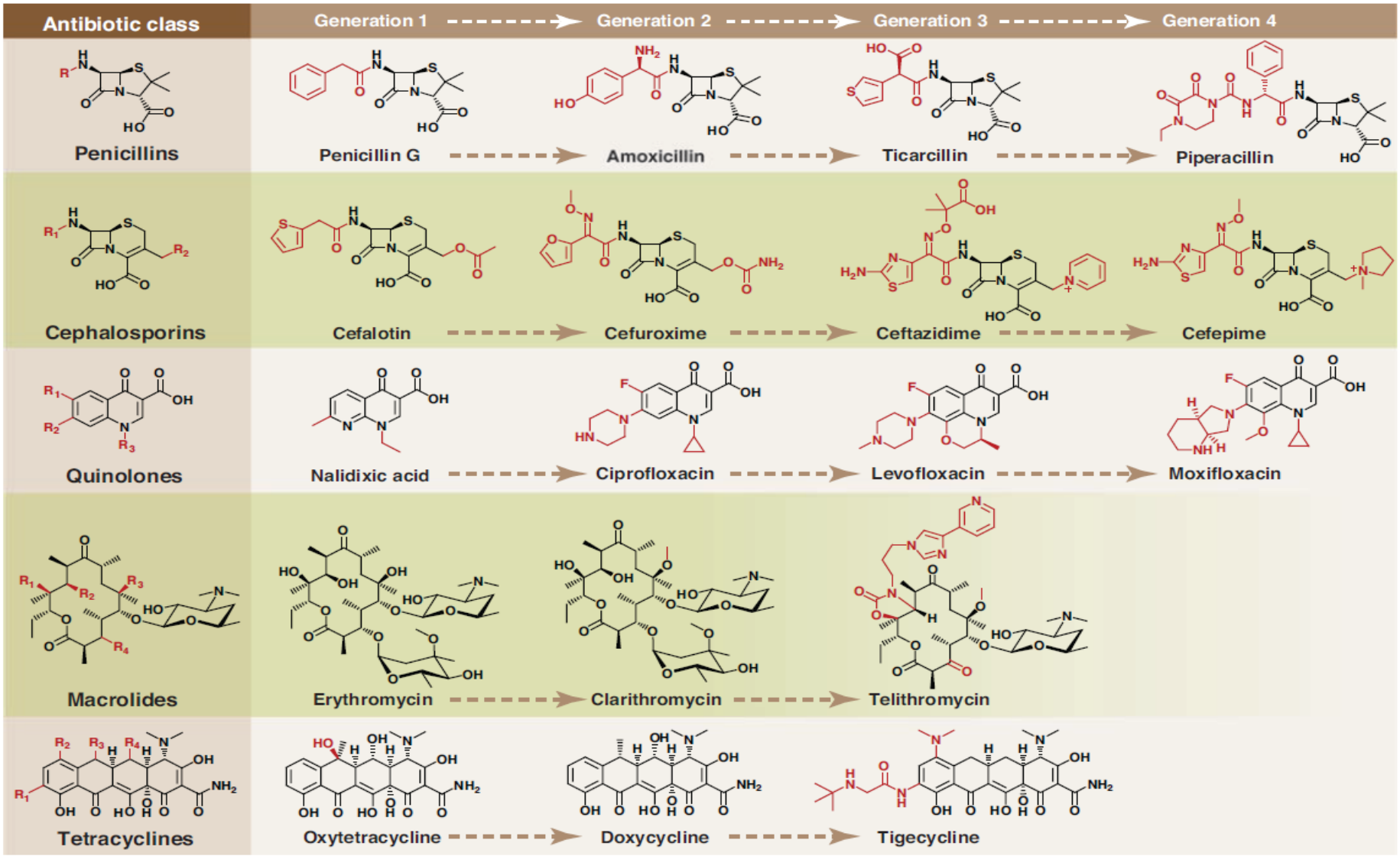


Fig. 2. Synthetic tailoring is widely used to create successive generations of antibiotic classes. Scaffolds are colored black; peripheral chemical modifications are colored red. The quinolone scaffold is synthetic, whereas the other scaffolds are natural products.

M.A.Fischbach and C.T.Walsh Science 325,1089, 2009

Emergence and Spread of Drug-resistance bacteria

The ability of bacteria to evolve in response to pressure from antibiotics has been recognized since the discovery of penicillin. In less than a century, a complex array of factors has let to the emergence of bacteria that no longer respond to any approved antibiotics. **NIAID, (2014)**

We enter the twenty-first century, alarm bells are ringing owing to the widespread emergence of bacterial resistance to the drug developed in the twentieth century. **I.Chopra (2012)**

World Health Day 2011

World Health Organization

COMBAT ANTIMICROBIAL RESISTANCE

WHY IS AMR A GLOBAL CONCERN?

> **AMR kills** – Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness and greater risk of death.

> **AMR challenges control of infectious diseases** – AMR reduces the effectiveness of treatment because patients remain infectious for longer, thus potentially spreading resistant microorganisms to others.

> **AMR threatens a return to the pre-antibiotic era** – Many infectious diseases risk becoming uncontrollable and could derail the progress made towards reaching the targets of the health-related United Nations Millennium Development Goals set for 2015.

> **AMR increases the costs of health care** – When infections become resistant to first-line medicines, more expensive therapies must be used. The longer duration of illness and treatment, often in hospitals, increases health-care costs and the financial burden to families and societies.

> **AMR jeopardizes health-care gains to society** – The achievements of modern medicine are put at risk by AMR. Without effective antimicrobials for care and prevention of infections, the success of treatments such as organ transplantation, cancer chemotherapy and major surgery would be compromised.

> **AMR compromises health security, and damages trade and economies** – The growth of global trade and travel allows resistant microorganisms to be spread rapidly to distant countries and continents.

COMBAT DRUG RESISTANCE
No action today, no cure tomorrow

Antibiotic Resistance Threats (CDC, 2013)

Kyorin

ANTIBIOTIC RESISTANCE: THE GLOBAL THREAT

Severe antibiotic resistance – when bacteria change and cause antibiotics to fail – is happening RIGHT NOW, across the world

The full impact is unknown. There is no system in place to track antibiotic resistance globally

Without urgent action, modern medicine will be obsolete and minor injuries will once again be deadly

SUPER RESISTANT BACTERIA: PROBLEM TODAY, CRISIS TOMORROW

In **INDIA**, over **58,000** babies died in one year as a result of infection with super-resistant bacteria usually passed on from their mothers[1]

In the **EUROPEAN UNION**, antibiotic resistance causes **25,000** deaths per year and 2.5m extra hospital days[2]

IN THAILAND, antibiotic resistance causes **38,000+** deaths per year and 3.2m hospital days[2]

In the **UNITED STATES**, antibiotic resistance causes **23,000+** deaths per year and >2.0m illnesses[2]

Serious Pathogens List (WHO, CDC, ESKAPE)

Bacteria (WHO category)	WHO (2017)	CDC (2013)	ESKAPE (2008-9)
Acinetobacter baumannii, carbapenem-R	Critical	Serious (MDR)	Yes
Pseudomonas aeruginosa, carbapenem-R	Critical	Serious (MDR)	Yes
Enterobacteriaceae, carbapenem-R, 3rd-gen ceph-R (ESBL+)	Critical	Urgent (carbapenem-R) Serious (ESBL+)	Yes
Enterococcus faecium, vancomycin-R	High	Serious (VRE)	Yes
Staphylococcus aureus, methicillin-R, vancomycin-I/R	High	Serious (MRSA) Concerning (VRSA)	Yes
Helicobacter pylori, clarithromycin-R	High		
Campylobacter spp., fluoroquinolone-R	High	Serious (drug-R)	
Salmonellae spp., fluoroquinolone-R	High	Serious (drug-R)	
Neisseria gonorrhoeae, 3rd-gen ceph-R, fluoroquinolone-R	High	Urgent (drug-R)	
Streptococcus pneumoniae, penicillin-NS	Medium	Serious (drug-R)	
Haemophilus influenzae, ampicillin-R	Medium		
Shigella spp., fluoroquinolone-R	Medium	Serious	
Clostridium difficile		Urgent	
Candida spp. fluconazole-R		Serious (Flu-R)	
M. tuberculosis		Serious (drug-R)	
Group A *Streptococcus*		Concerning (erythro-R)	
Group B *Streptococcus*		Concerning (clinda-R)	

World Health Day 2011

World Health Organization

DIRECTOR-GENERAL STATEMENT

WHO is issuing a policy package to get everyone, especially governments and their drug regulatory systems, on the right track, with the right measures, quickly. Governments can make progress, working with health workers, pharmacists, civil society, patients, and industry. We all can and coordinate our response.

[Issues of Action plans]

We can expand surveillance efforts.
We can improve drug regulatory and supply systems.
We can foster improved use of medicines for human and animal health.
We can actively prevent and control infections in health services and beyond.
We must stimulate a robust pipeline for new antimicrobials, diagnostics and Vaccines.

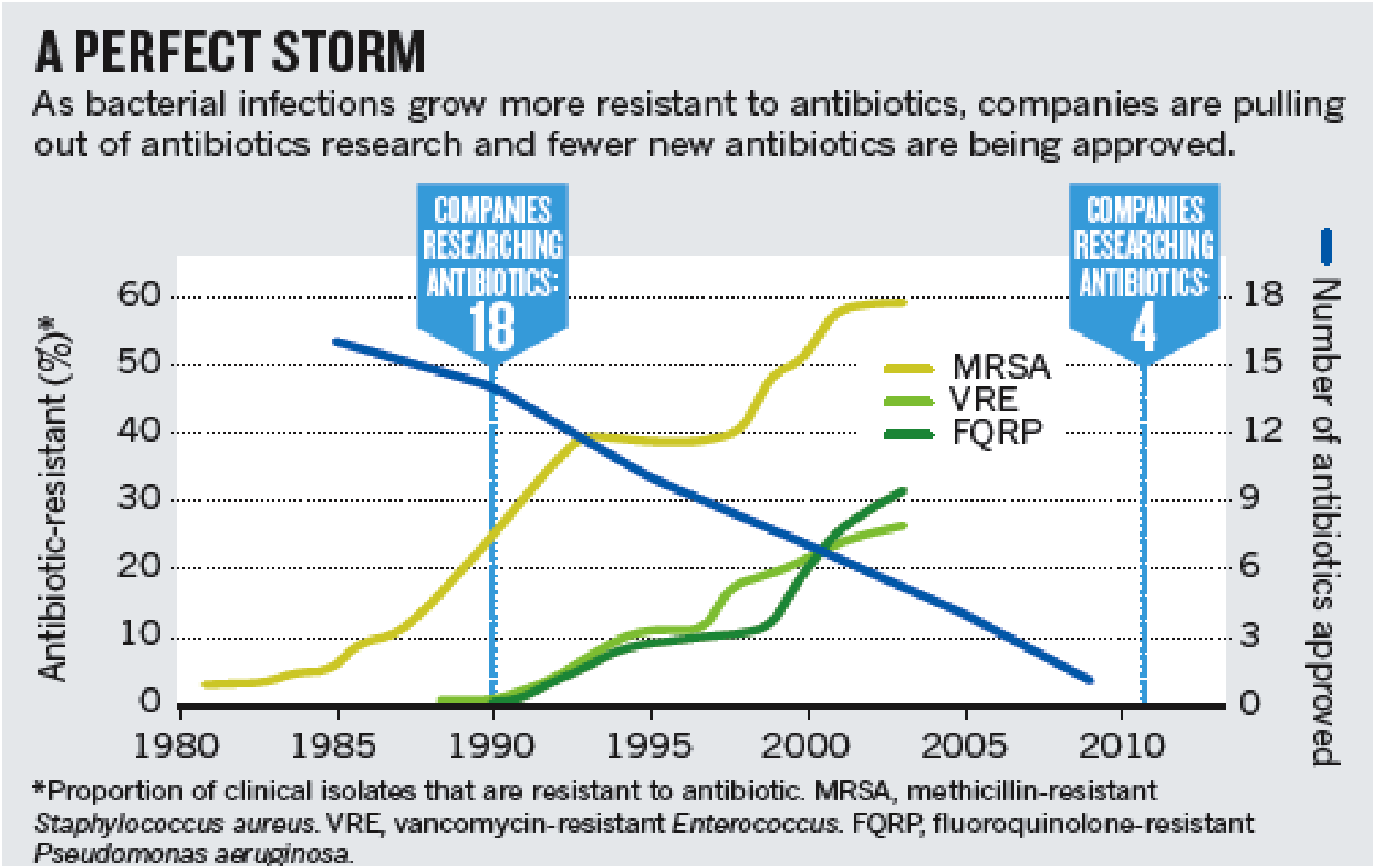
COMBAT DRUG RESISTANCE
No action today, no cure tomorrow

The crisis of no new antibiotics

New antibiotics to tackle drug resistant bacteria are much needed.

But, the antibiotic pipeline is dry

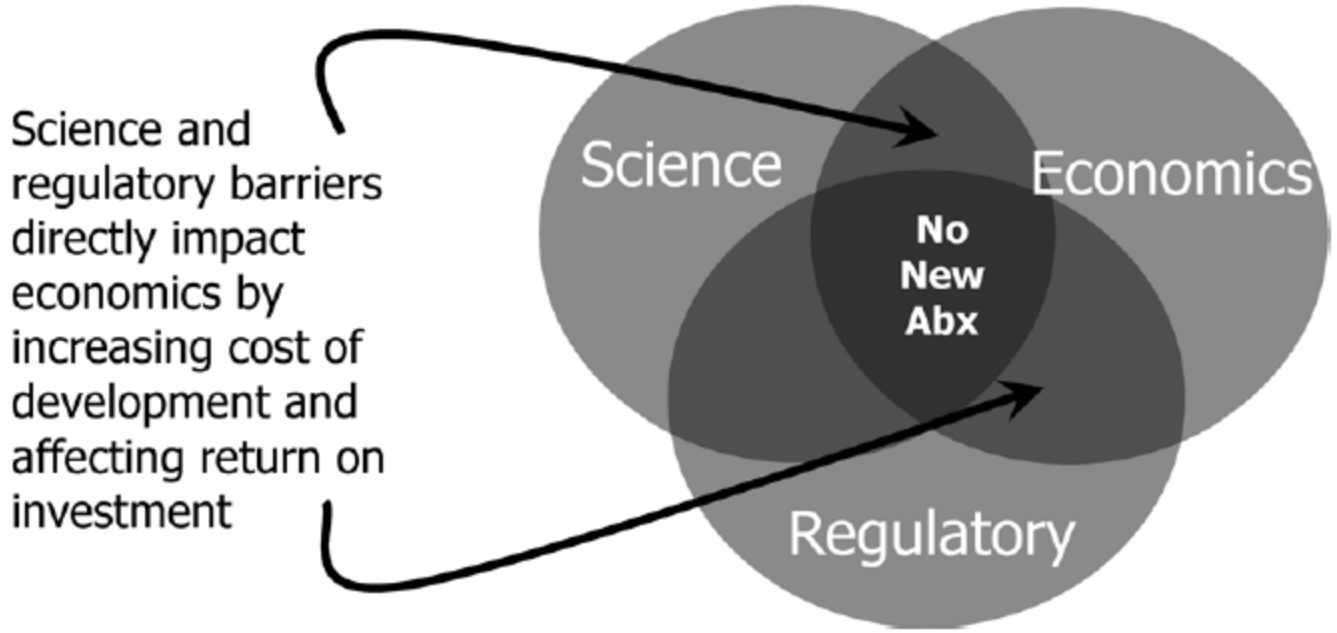
Approval of New Antibiotics and Emerging of Resistant Bacteria



M.A.Cooper & D. Shlaes, Nature 472: 32 (2011)

Challenges to Development of New Antimicrobials

1. Science: low hanging fruit plucked
2. Economics: not a good investment
3. Regulatory: R&D too risky/expensive



Spellberg B. Crit Care 2014; 18:228

Why the antibiotic pipeline is dry?

Three big challenges to development of new antibiotics

-Hard to discovery

-Hard to development/Regulatory

-Low return on investment

Low hanging fruit plucked

Hard to develop new antibacterial agents with chemical modification

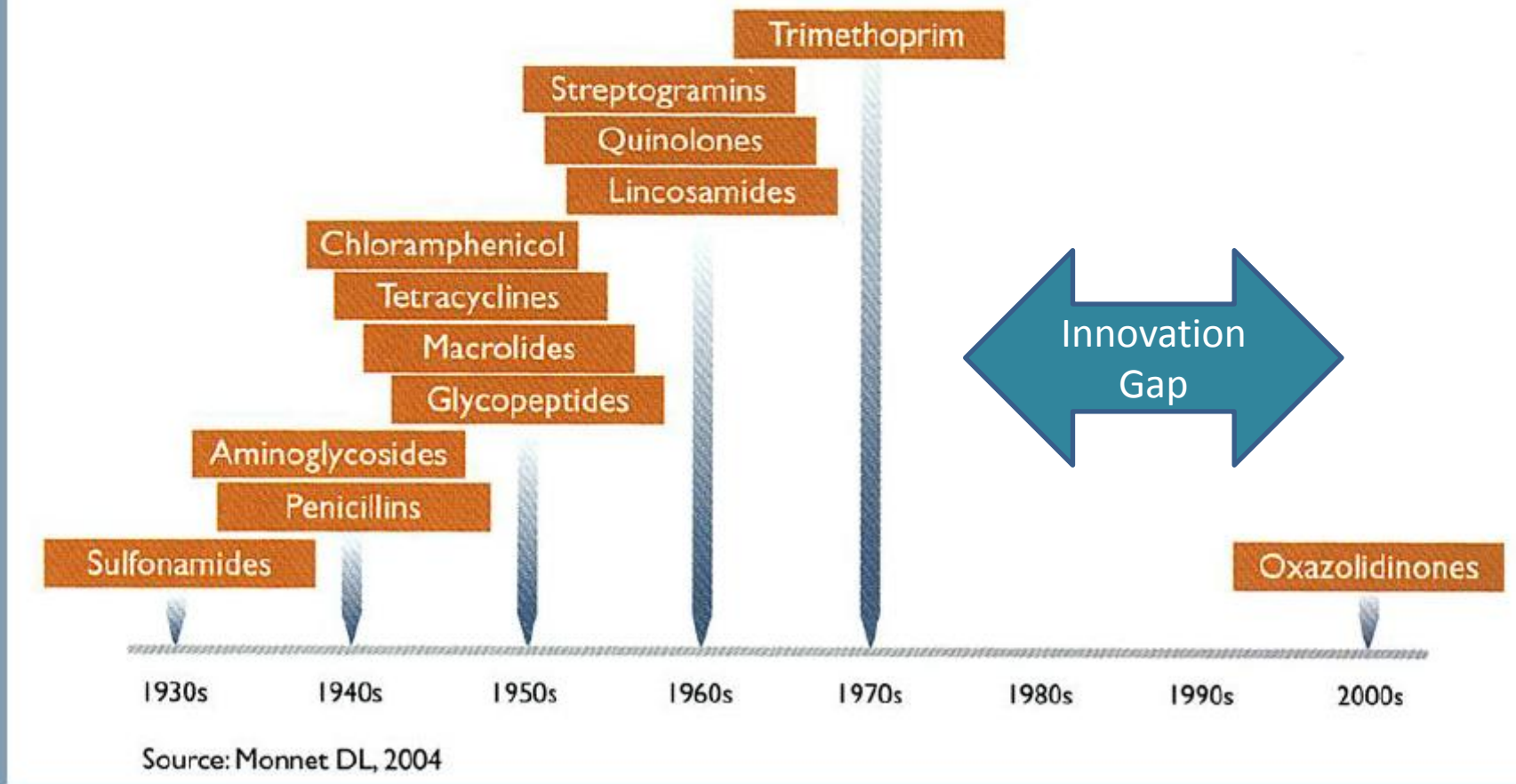
Current issue:

Limitation of generation of modified molecules to improve

Bulk cost
IP Issues
Cross-resistance
Safety

⇒New major class of Scaffolds is needed

New Antibacterial Classes???



Senate IDSA Presentation (2011)

Hard to Discovery of Novel Class (new leads) of Antibacterial Agents

GSK study : Genomics-derived and Target-based approach to screening for new classes drugs with new MOA

Evaluation more than 300 genes
70 HTS(High-throughput screening) campaigns
67 target enzymes , 3 whole-cells
Chemical libraries :260,000 ~ 530,000 compounds
Period : 1995~2001 (7 years)
Cost : around $1M/HTS campaign

Result : only 5 leads.
[PDF, FabI, FabH, MetRS, PheRS]

- **Problems of nature of the chemical libraries**
  Molecular weight, Polarity (Issues on Lipinski's rule of Five)
- **Problems to pass bacterial outer membrane in GNB**

Payne D.J. et al, Nature Rev. Drug Discovery: 6 (2007)

Challenges on the antibiotic development value chain

Challenges					
	Discovery Void Lack of new class leads Underlying scientific challenges, especially **penetration of Gram (-) bacteria**	**"Valley of Death"** Many potential leads not taken up in development due to **lack of interest and funding** – resulting in a brain drain	**Difficult patient recruitment and high cost**	**Insufficient alignment between leading agencies worldwide**	**Low market attractiveness**

Chorzelski,S. et al., Breaking through the wall: Global Union for Antibiotic Research & Development Initiative (2015)

Why the antibiotic pipeline is dry?

Three big challenges to development of new antibiotics

-Hard to discovery

-Hard to development/Regulatory

-Low return on investment

Challenges on the antibiotic development value chain

Challenges	Discovery Void	"Valley of Death"	Difficult patient recruitment and high cost	Insufficient alignment between leading agencies worldwide	Low market attractiveness
			Recruiting patients with required pathogens and indications difficult and **costs for trials are high**	**Differing standards between regulator agencies** lead to additional costs and effort	

Chorzelski,S. et al., Breaking through the wall: Global Union for Antibiotic Research & Development Initiative (2015)

Solutions to the lack of new antimicrobials

Regulatory/Development challenge:

-Difficult patient recruitment and high cost for clinical trials for AMR-

- **New pathways to facilitate approval : Clear and feasible regulatory guideline on clinical trial designs for AMR**
- **Global alignment of regulatory approval process**

Issues:

-Reducing number of patients: PK/PD study, Safety

-Rapid diagnostics for pathogen and AMR

-Orphan-drug route

Why the antibiotic pipeline is dry?

Three big challenges to development of new antibiotics

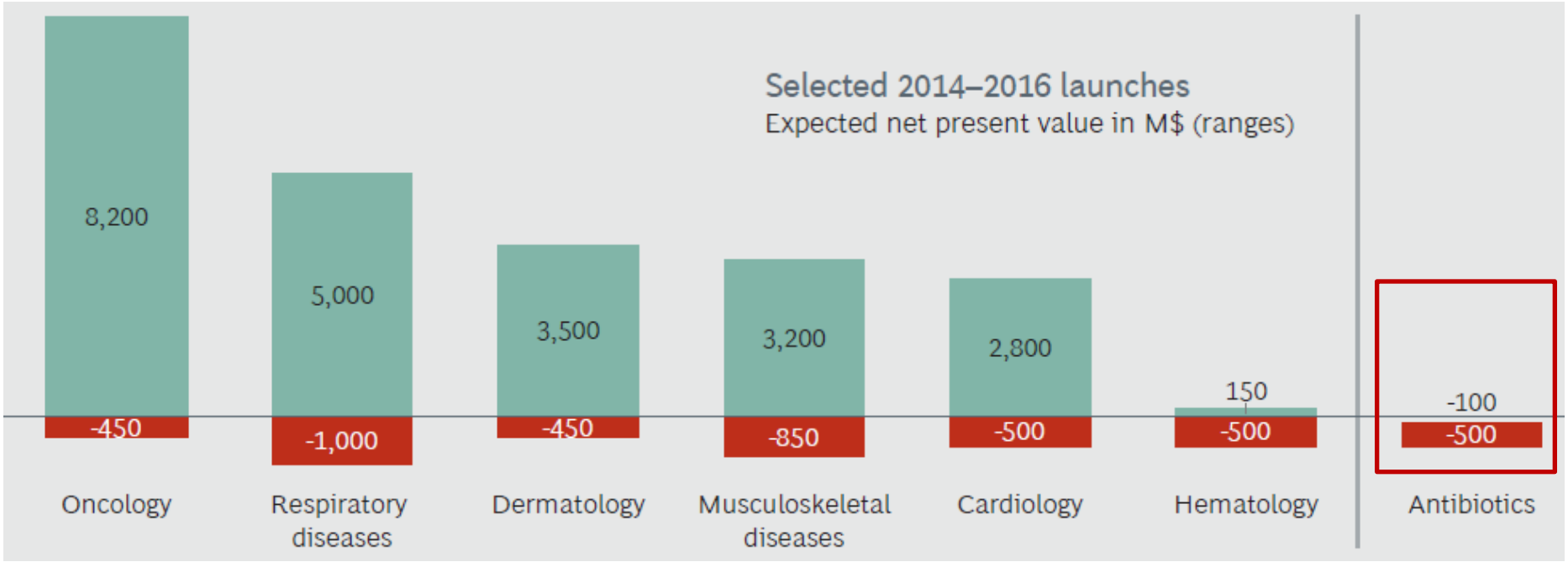
-Hard to discovery

-Hard to development/Regulatory

-Low return on investment

Relative Value of Antimicrobials vs Other Classes Pharmaceutical Development

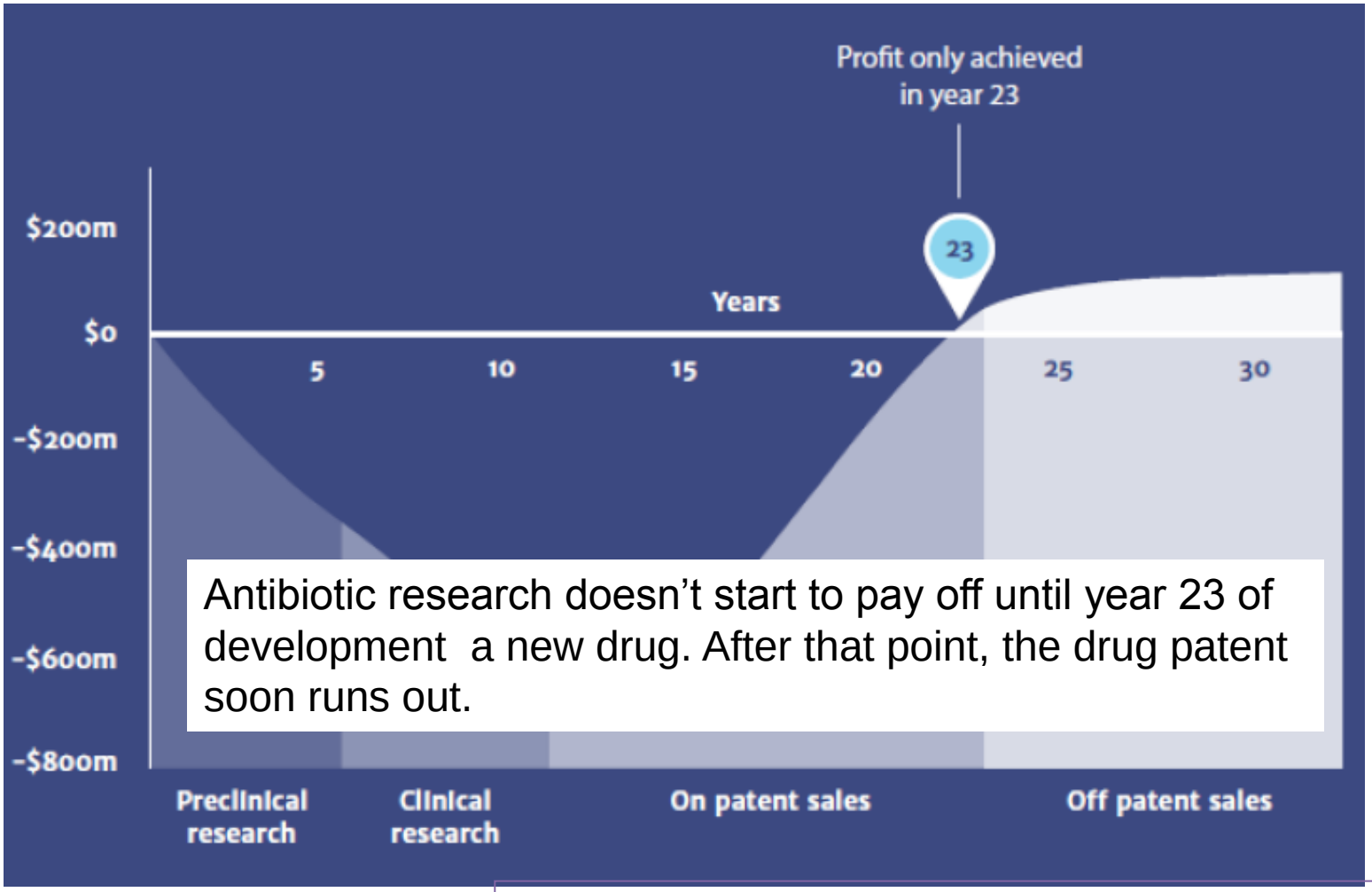
Expected Net Present Value of Antimicrobials : Negative



Note: Assumptions: Varying development costs per TA ($600M–1,400M). Development costs include costs of failure. Duration of development between 6–8 years (varies across therapeutic areas).
10-year revenue projections for all NMEs, COGS, and SGA based on EvaluatePharma data. Discount rate of 9%.
Source: BCG analysis; EvaluatePharma

Follow up report for the German GUARD Initiative by BCG, Feb., 2017

Current Economic Model of Antimicrobial Development



Antibiotic research doesn't start to pay off until year 23 of development a new drug. After that point, the drug patent soon runs out.

J O'Neill, Tackling drug-resistant infections globally : The Review on Antimicrobial Resistance (2017)

Solutions to the lack of new antimicrobials

Economics : improve return on investment(ROI)

-Maintaining the appropriate incentives

"Push" incentive:

Grants, Funding , Tax incentive for R&D

"Pull" incentive :

Pricing , Reimbursement,

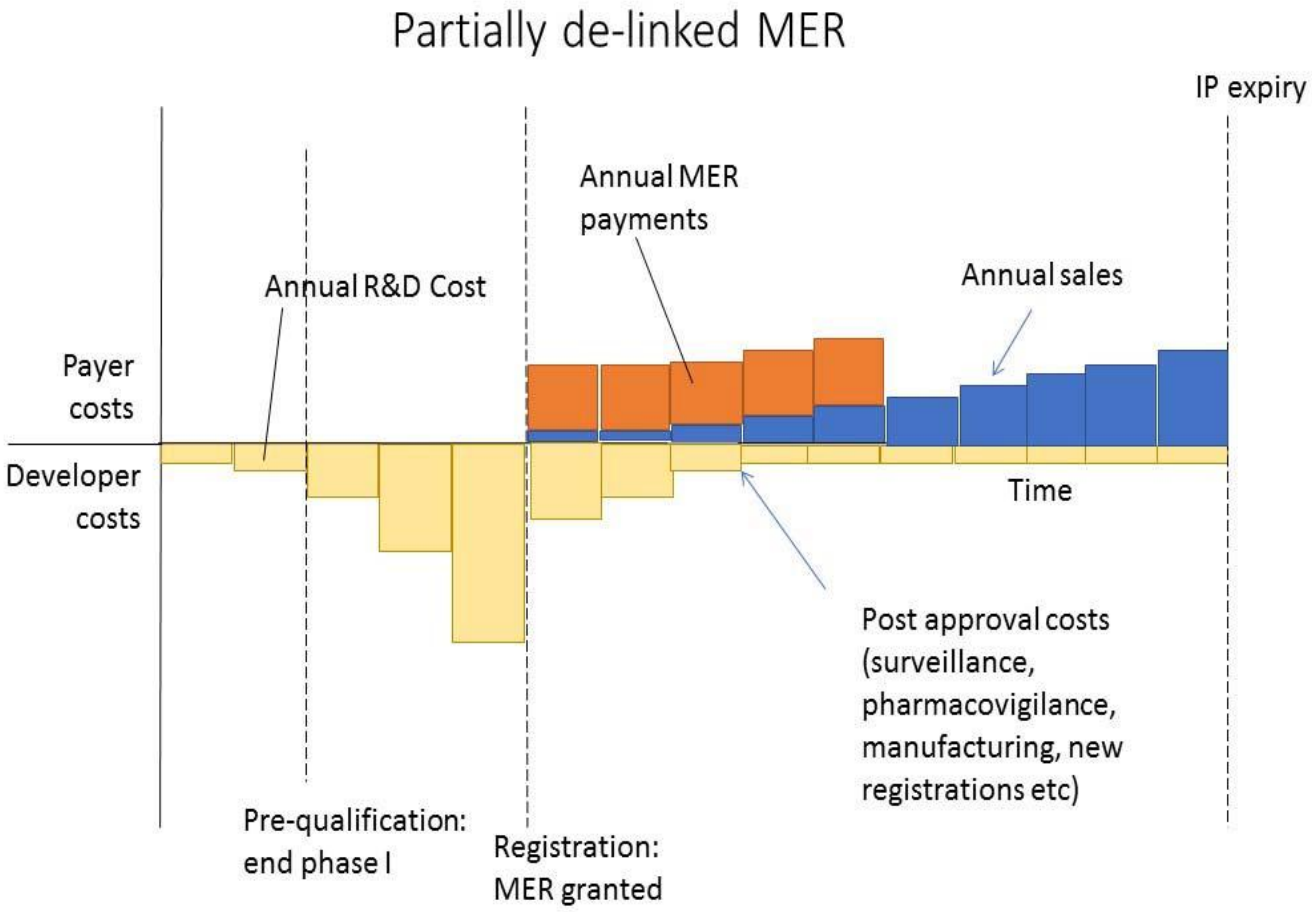
IP extension, Market exclusivity

Advance purchase

Market entry rewards

Transferable Exclusivity Extensions

Market entry rewards : The idea



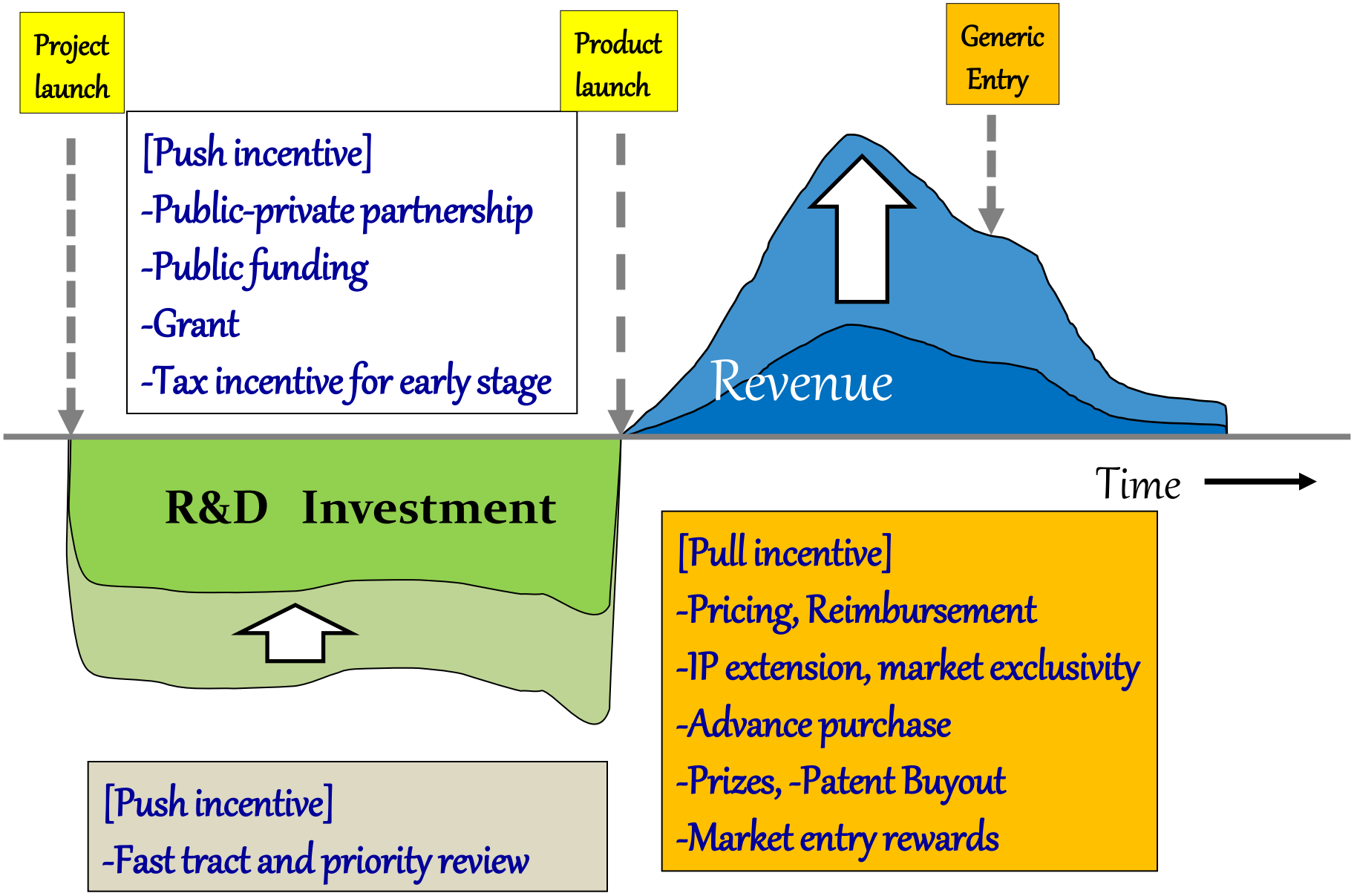
DRIVE-AB REPORT: Revitalizing the antibiotic pipeline (2018)

Challenges on the antibiotic development value chain

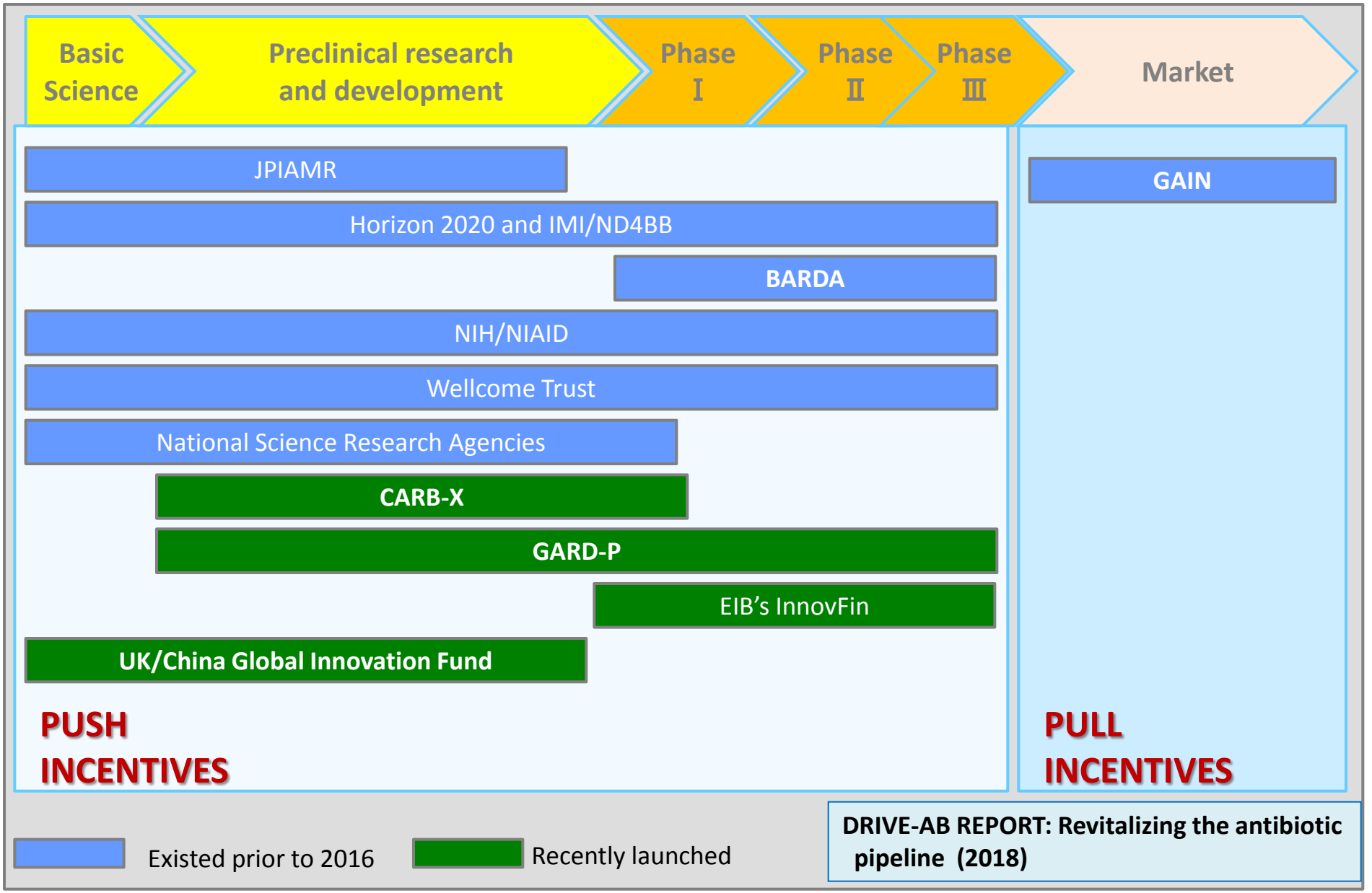
Challenges	Discovery Void	"Valley of Death"	Difficult patient recruitment and high cost	Insufficient alignment between leading agencies worldwide	Low market attractiveness
					Low and highly unpredictable revenue expectations leading to **negative return on investment**

Chorzelski,S. et al., Breaking through the wall: Global Union for Antibiotic Research & Development Initiative (2015)

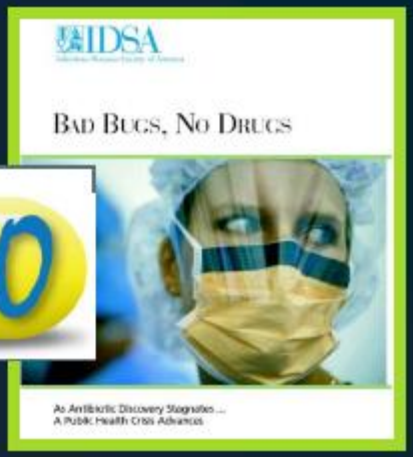
“Push” and “Pull” Incentive for R&D



Major publicly funded incentives, by R&D phases



The 10 x '20 Initiative



- Global Commitment to Develop 10 new systemic antibiotics by 2020 (CID; April 2010)

- Bring together essential leaders: global political, scientific, industrial, economic, intellectual property, policy, medical and philanthropic leaders to determine the right combination of incentives necessary to establish a sustainable R&D enterprise

Senate IDSA Presentation (2011)

The Generating Antibiotic Incentives Now(GAIN) Act

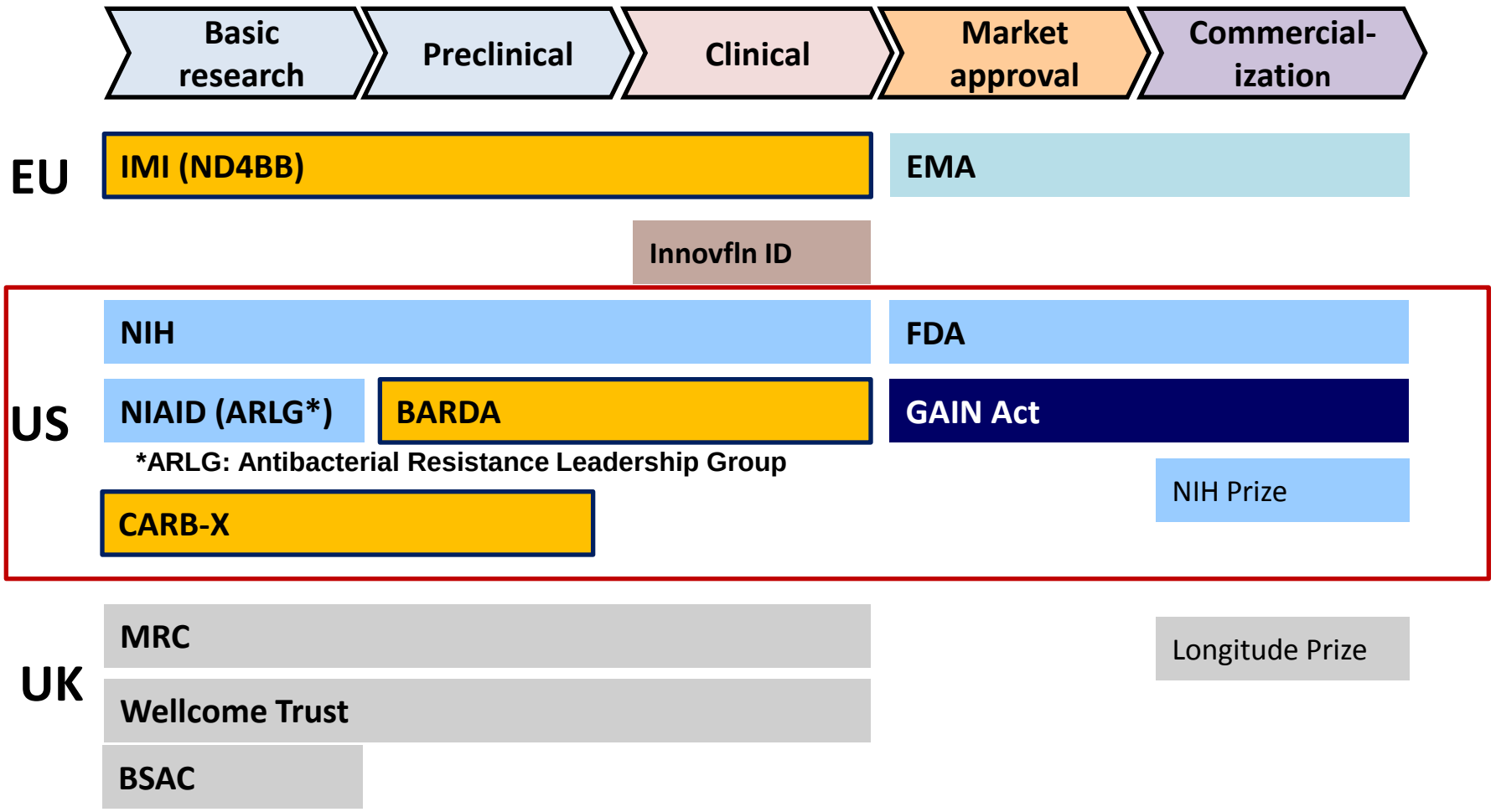
(July 9,2012)

US Congress has recognized the need for action and has taken valuable steps, passing the Generating Antibiotics Incentives Now(GAIN) Act in 2012 , to extent the market exclusivity period for certain Antimicrobials, and creating the Limited Population Antibacterial Drug regulatory approval pathway to facilitate the development of antibiotics for patients who have few or no treatment option.

*** The incentives are granted "Qualified Infectious Disease Product (QIDP)" status.**

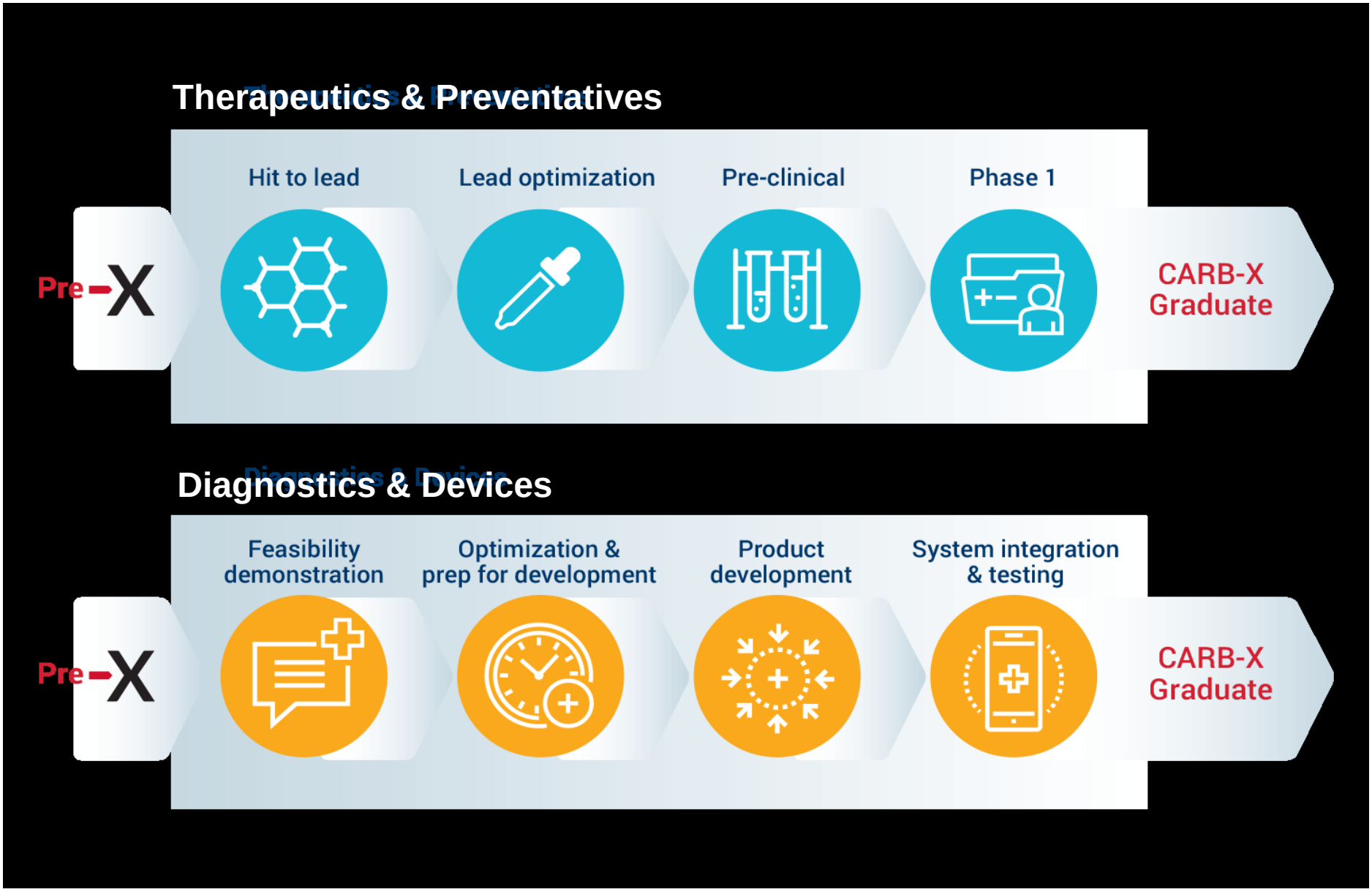
US congress has also increased funding for NIAID and BARDA to support antibiotic R&D, including CARB-X

Antibiotic R&D initiatives across the R&D value chain in EU, US and UK



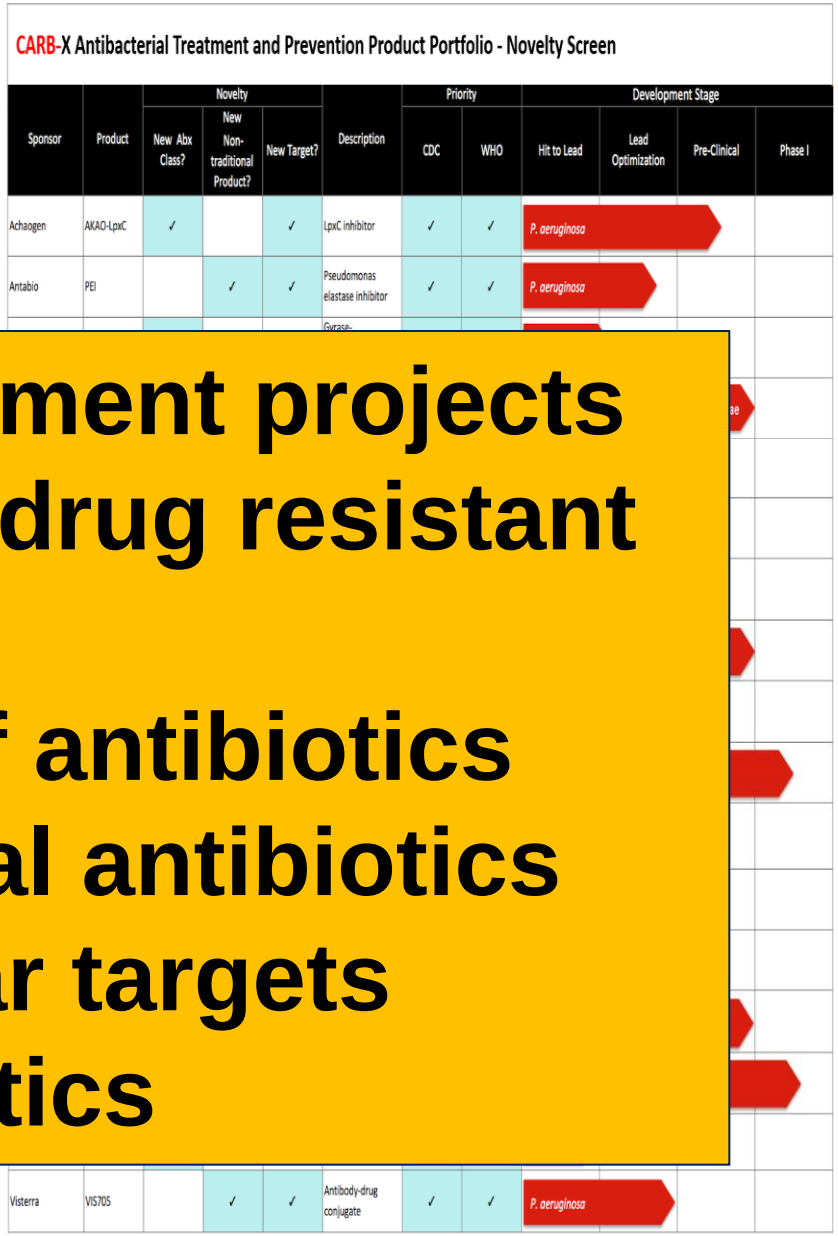
M.J.Renwick, et al. , Targeting innovation in antibiotic drug discovery and development 2016

CARB-X Funds Projects in Early Development



CARB-X Projects

- 33 early development projects targeting serious drug resistant bacteria
- 9 new classes of antibiotics
- 10 non-traditional antibiotics
- 11 new molecular targets
- 6 Rapid diagnostics



The above projects are Powered by CARB-X utilizing non-dilutive funding from BARDA, Wellcome Trust, & NIAID. The stage of development is approximate as of March 2017 (please refer to each company's website for updated information). Characterizations of new Abx Class and New Target by CARB-X, following Pew pipeline analysis. Other characterizations by CARB-X experts and external expert opinion. Abx = traditional small molecule antibiotic. Non-traditional Product = not a traditional small molecule antibiotic.

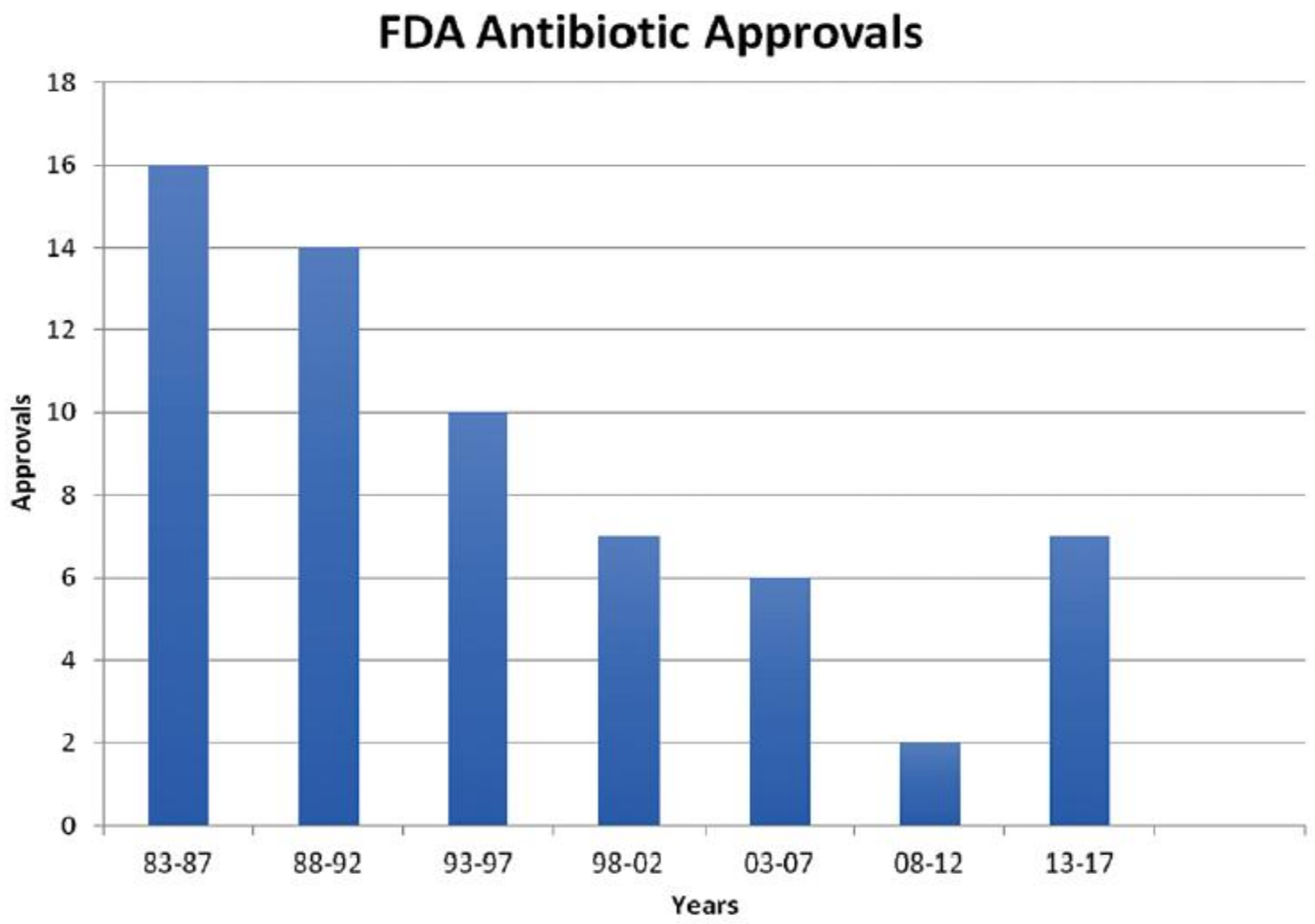


Figure 1. Trend in US Food and Drug Administration new antibiotic approvals. Reproduced with permission of David Shlaes, MD, founder of the Blog "The Perfect Storm." Abbreviation: FDA, US Food and Drug Administration.

Talbot GH, et al. Clinical Infectious Diseases 69: 1, 2019

Eleven(11) New Antibiotics approved since 10X'20 Initiative launched in 2010

• Ceftraroline	2010	Allergan (Activis)
• Dalbavancin	2014	Allergan (Activis)
• Tedizoid	2014	Merck (Cubist)
• Oritavancin	2014	Merck (Cubist)
• Ceftolozane/Tazobactam *	2014	Merck (Cubist)
• Ceftazidime/Avibactam	2015	Allergan (Activis)
• Delafloxacin	2017	Melinda (Rib-X Pharm.)
• Meropenem/Vaborbactam	2017	Melinda
• Plazomicin	2018	Achaogen
• Eravacycline	2018	Tetrapahse
• Omadacycline	2018	Pratek

(*approved in 2019 in Japan)

IDSA : ID week (2018) @ SFO

Current News of New Antimicrobials form USA

Good News:

Two new antibiotics, **Recarbrio** (Merck) and **Xenleta** (Nabriva) were approved the by FDA 7/17/19 and 8/19/19, respectively.

- **Recarbrio (imipenem/relebactam)** was approved for cUTI and cIAI. This drug may be most relevant for CRE and MDR P. aeruginosa.
- **Xenleta (lefamulin, PO/IV)** was approved for Community Acquired Bacterial Pneumonia.

Bad News:

Achaogen files for bankruptcy protection, seeks asset sale.

The US-based biotech had received approval from the FDA for its product Zemdri(Plazomicin) June 2018. Achaogen was not making enough of a profit to stay afloat.

"Pull" incentives are needed to ensure new antibiotics will be profitable and that drug makers will continue developing and producing them.

Is 20 x ’20 a possible?

Although “20 x ‘20” may well be achieved, this success could be the “last hurrah” for robust antibiotic development.

Pharmaceutical sponsor and sustainable antibiotic R&D infrastructure will be bleak in the absence of further economic incentives for antibiotic development.

In the meantime, clinicians must protect currently available antibacterial drugs through robust antibiotic stewardship and infection prevention.

Talbot, GH et al. Clinical Infectious Disease 69: 1-11 (2019) :
The Infectious Disease Society of America’s 10 x ‘20 Initiative (Ten New Systemic Antibacterial Agents FDA-approved by 2020): Is 20 x ‘20 a Possibility?

Current antimicrobials pipeline and future R&D directions for new antimicrobials against AMR

Current Antimicrobials pipeline listed by WHO

Name (synonym)	Phase	Antibiotic class	Developer
• Cefiderocol	3	Siderophore- cephalosporin	Shionogi
• **Relebactam+imipenem****	3	DBO-LBI+ carbapenem	Merck＆Co
• Sulopenem	3	Carbapenem	Iterum
• **Plazomicin***	3	Aminoglycoside	Achaogen
• Lascufloxacin	3	Fluoroquinolone	Kyorin
• **Eravacycline***	3	Tetracycline	Tetraphase
• **Omadacycline***	3	Tetracycline	Paratek
• Solithromycin	3	Macrolide	Cempra
• Iclaprim	3	DHFR-inhibitor	Motif Bio
• **Lefamulin****	3	Pleuromutilin	Nabriva
• MRX-I/MRX-4	2/3	Oxazolidinone	MicuRx
•Gepotidacin	2	NBTI (Triazaacenaphthylene)	GSK
•Zoliflodacin	2	NBTI (Spiropyrimidenetrione)	Entasis
•Murepavidin (POL-7080)	2	Novel membrane targeing AB	Polyphor
•Brilacidin	2	Novel membrane targeting AB	Innovation
•Nafithromycin	2	Macrolide	Wockhardt
•Afabicin (Debio-1450)	2	FabI inhibitor	Debiopharm

(*approved in 2018, **approved in 2019)

WHO: Antibacterial Agents in Clinical Development (2017)

Future directions for new antimicrobials R&D against AMR

1. Novel chemical classes acts at a new targets
2. New agents act at a known target but exploit a new mechanism of action or binding site
   (e.g., novel topoisomerase inhibitor)
3. New agents modify an existing chemical scaffold that overcome resistance
   (e.g., cephalosporins,TC, AG)
4. Combination therapy
   - combination with antibiotic therapy
     (beta-lactamase inhibitor, old antibiotic)
   - combination with antibiotic resistance breaker
5. Non-antibiotic (Non-traditional therapies)
   monoclonal antibody, phage therapy, anti-toxin

Current situation to promote antimicrobials R&D against AMR in Japan

- Establish new "Public- private partnership (PPP)" for discovery research and development for novel antimicrobials against AMR
  - Collaboration of AMED, Industry (JPMA), and academia

- Publish international clinical evaluation guidelines to develop new antimicrobials against AMR
  - Alignment between leading agencies (PMDA, FDA, EMA)

- Develop incentives for new antimicrobials against AMR
  - Discussion on the "pull-incentives" (NHW, JPMA)
    model delinked from sales :
    -market entry rewards
    -Transferable Exclusivity Extensions

Conclusion

Better and well balanced push and pull incentives are necessary to promote antimicrobials R&D and investment for new drugs and improving existing ones for AMR in present circumstances