# An introduction to antibiotic research and development (R&D)

Guest speakers: Alan Hennessy, Mo Yin & Herbert Wetli

Moderator: Rosemary Dorrington

Host: Victor Kouassi

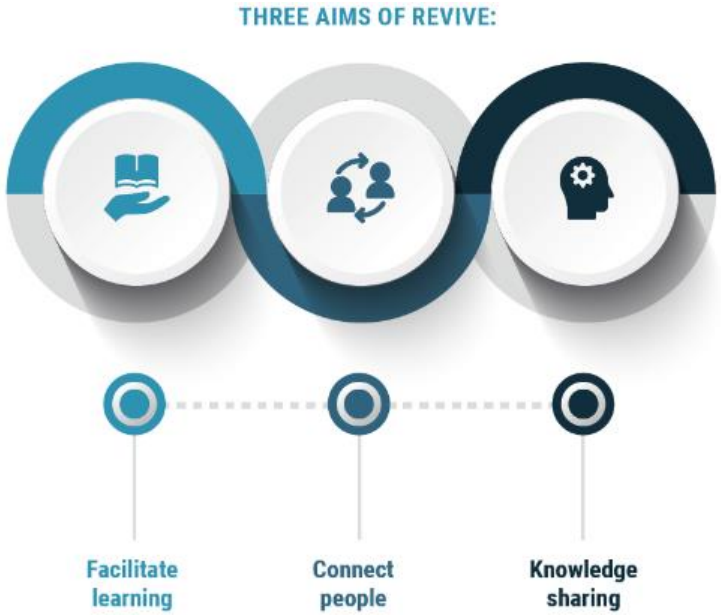
**19 September 2024**

GARDP

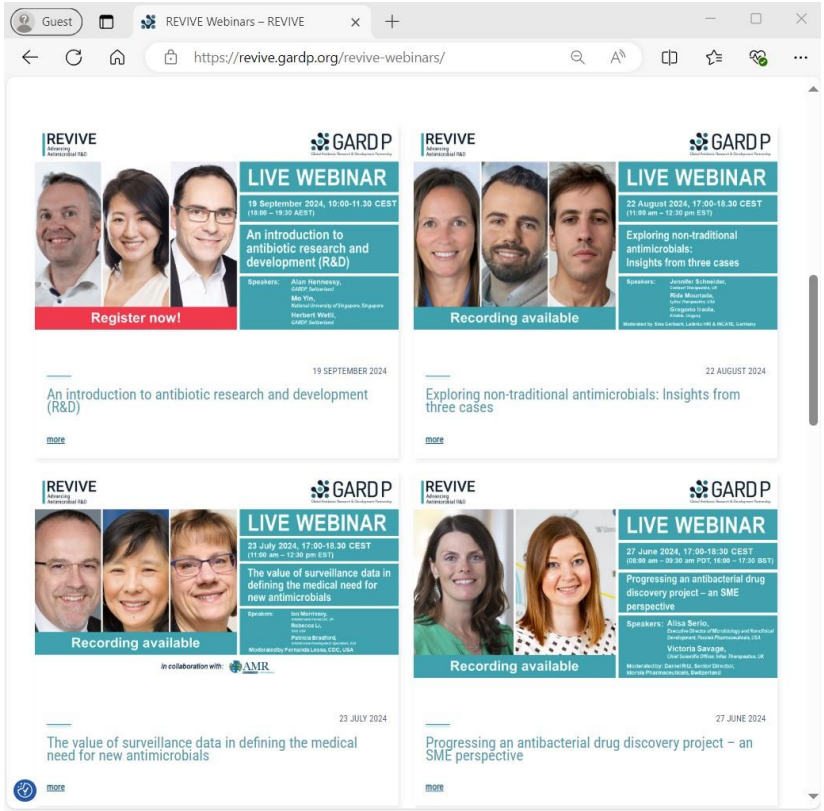
Global Antibiotic Research & Development Partnership

# REVIVE

Capture essential R&D technical knowledge and share expertise with the global community through the REVIVE website (revive.gardp.org).

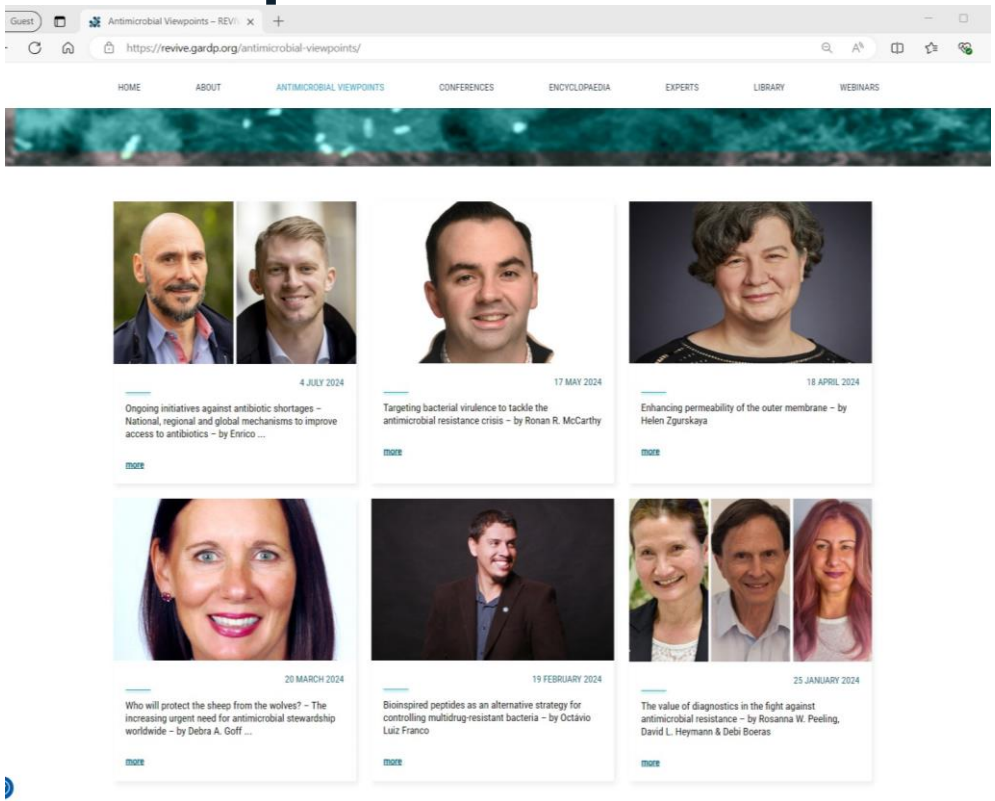


# Webinar recordings




revive.gardp.org/webinars

# Antimicrobial Viewpoints

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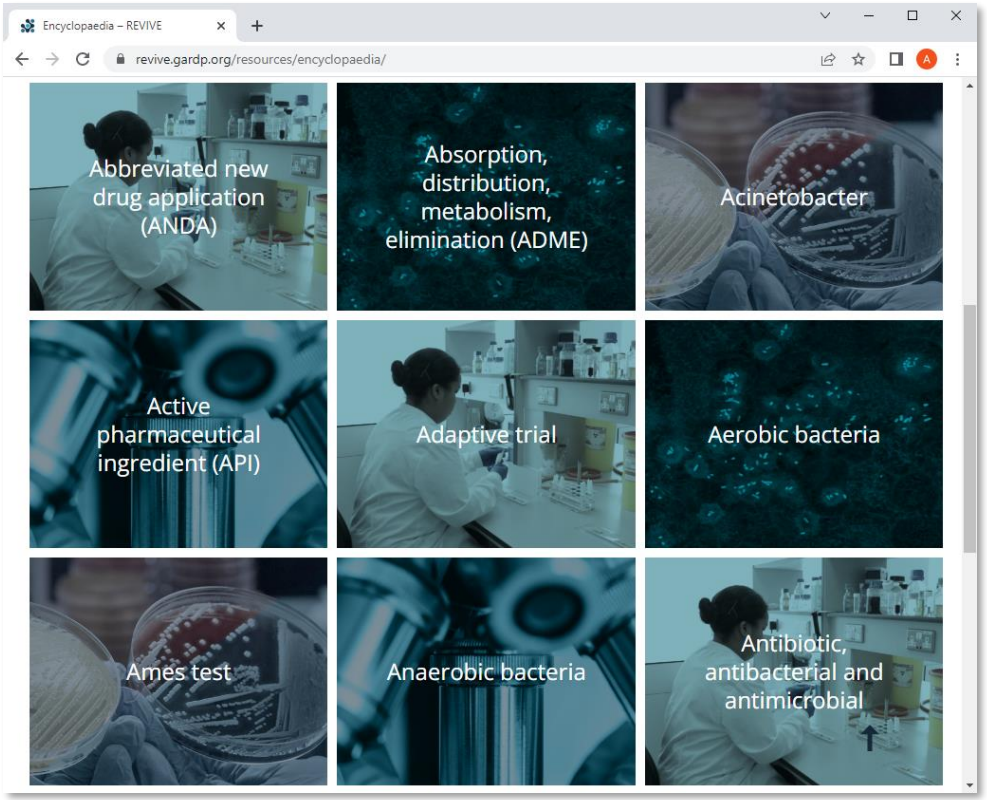
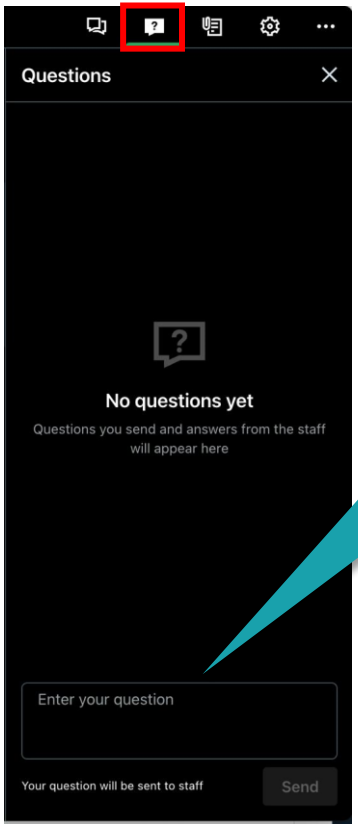
# Antimicrobial Encyclopaedia




revive.gardp.org/resources/encyclopaedia

# How to submit your questions

If your question is addressed to a specific speaker, please include their name when submitting the question.




The presentation will be followed by an interactive Q&A session.

Please submit your questions through the box provided after clicking the ‘questions’ button. We will review all questions and respond to as many as possible after the presentation.

# Today’s speakers

## An introduction to antibiotic research and development (R&D)

**Alan Hennessy**
Discovery & Exploratory Team Lead
*GARDP (Switzerland)*

**Mo Yin**
Consultant, ADVANCE-ID
*National University Hospital (Singapore)*

**Herbert Wetli**
Head of Pharmaceutical Development
*GARDP (Switzerland)*

**Moderator:**
**Rosemary Dorrington**
DSI/NRF SARChI Professor:
Marine Natural Products Research
*Rhodes University (South Africa)*

# Alan Hennessy

**Alan Hennessy** has been the Discovery and Exploratory Research Team Lead at GARDP since June 2023. Prior to this, Alan was head of lead generation and group leader at Syngenta, UK. During this time, several of the research projects he led successfully transitioned into development. Metproxybicyclone is the most advanced compound from these projects and is now in late development.

Alan also worked in anti-bacterial research for almost 10 years at GSK, leading diverse medicinal chemistry teams. He is an inventor on over 50 published patents including the key patent for GSK's Phase III clinical candidate gepotidacin. He received his BSc and PhD from University College Dublin, Ireland and completed his postdoctoral research at Imperial College London, UK.

# Antibiotic Research

## - a medicinal chemistry viewpoint

19th September 2024

Alan Hennessy
GARDP, Discovery and Exploratory Team Lead

GARDP
Global Antibiotic Research & Development Partnership

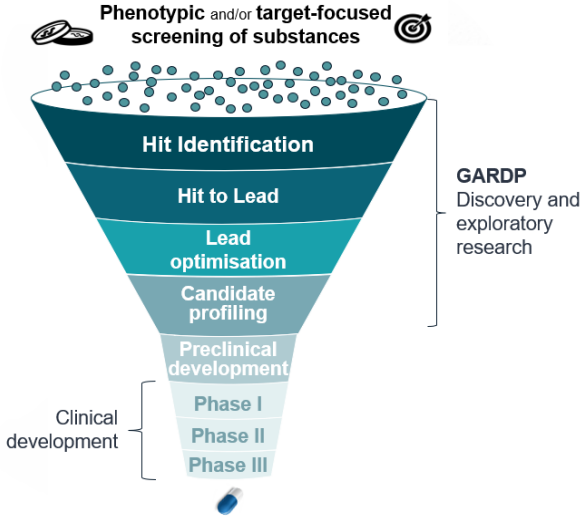
# Antibiotic R&D has fallen behind

**Half of all antibiotics used today were discovered over 60 years ago.**

Since then, **R&D has slowed**, whilst drug-resistant infections continue to increase

# Outline

- An overview of antibacterial discovery
- Examples of the discovery approach for products, clinical compounds etc.
- Recent trends in antibacterial discovery





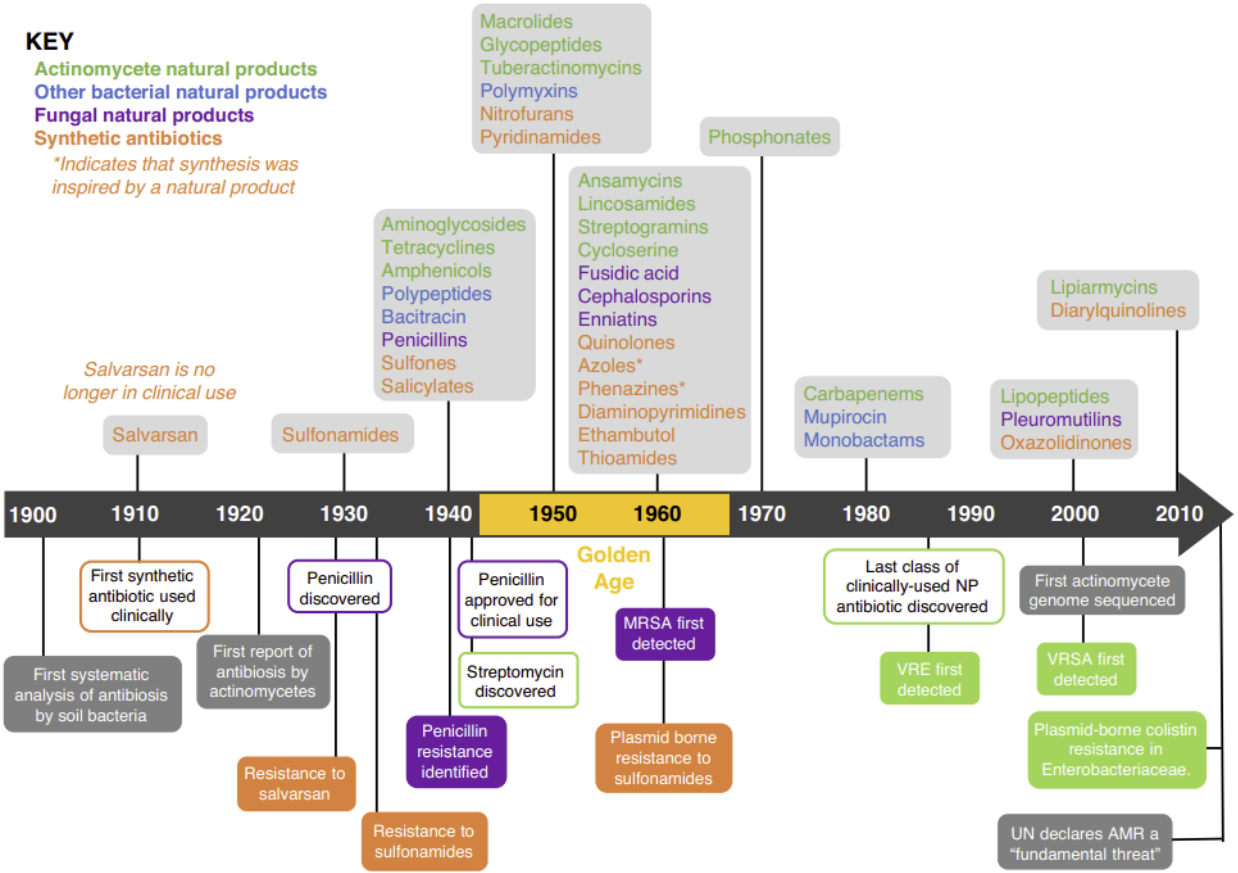

Best Practices in Medicinal Chemistry (efmc.info)

# Research stages of the antibacterial journey


- Attrition rates are extremely high for innovative approaches (1)
- In 2022, 90% of pre-clinical compounds were estimated to be discontinued (2)
- An IND application was only submitted for 0.6% discovered compounds; this includes NCEs discovered in academia that are undeveloped (3)
- To populate the preclinical and clinical pipelines there needs 1000s NCEs discovered and >100 projects/candidates in the preclinical phase and to ensure that sufficient enter clinical development *and eventually* come to market (4)

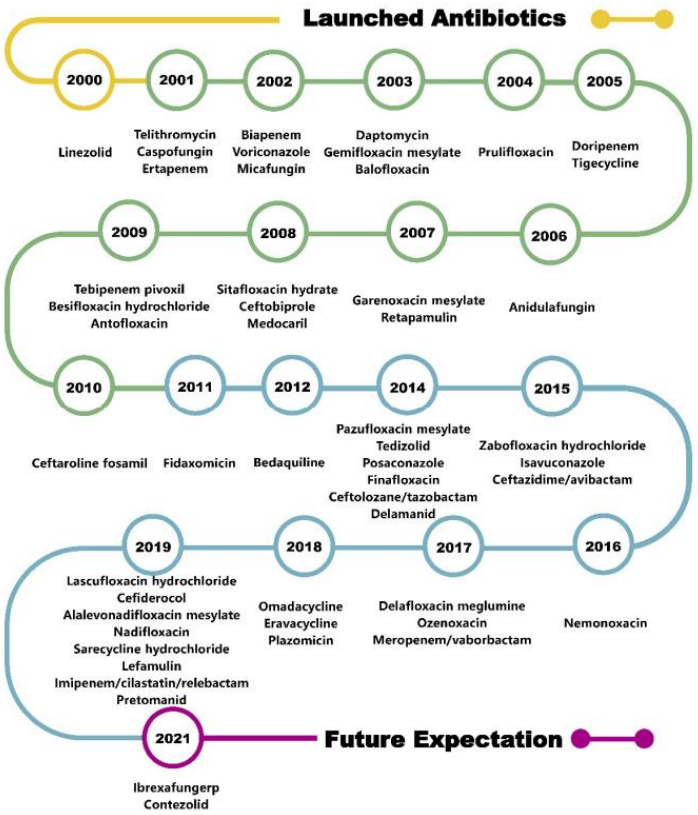
(1) Bradford (ex-AZ, Novartis and Wyeth); (2) Farrell *et al.*, J Antimicrob Chemother, 2018; (3) WHO, 2019

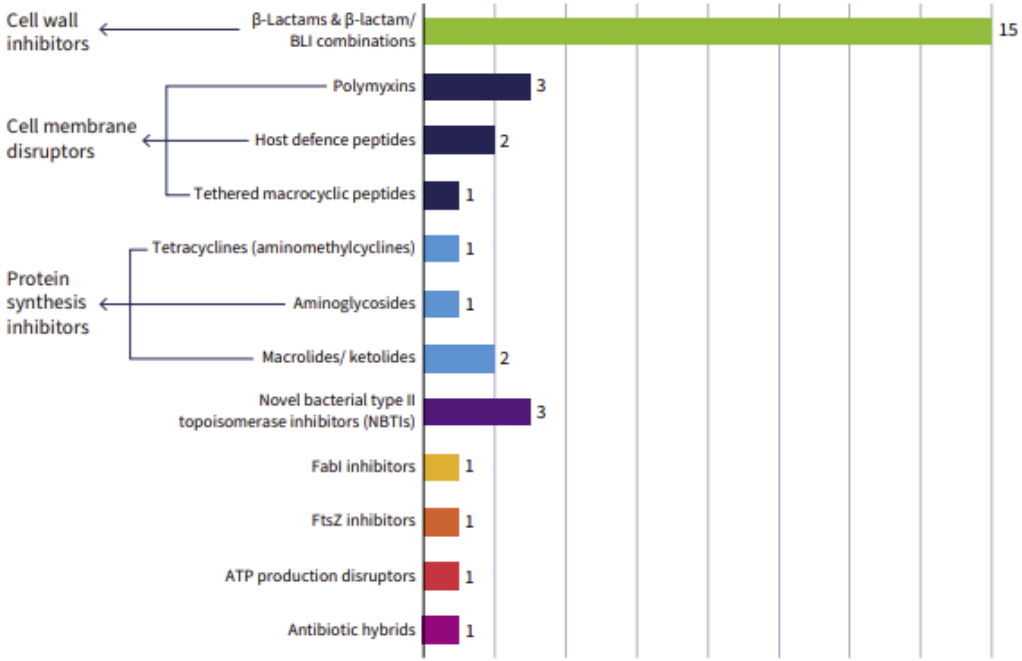
# Timeline of discovery of major antibacterial classes




Hutchings *et al.*, Current Opinion in Microbiology, 2019

# Limited innovation in modern era




Shi *et al.*, Molecules, 2023

WHO, 2023 Antibacterial agents in clinical and preclinical

# Project Selection

# Starting with the desired outcome:

**TPP for oral therapy of acute uncomplicated UTI (cystitis)**

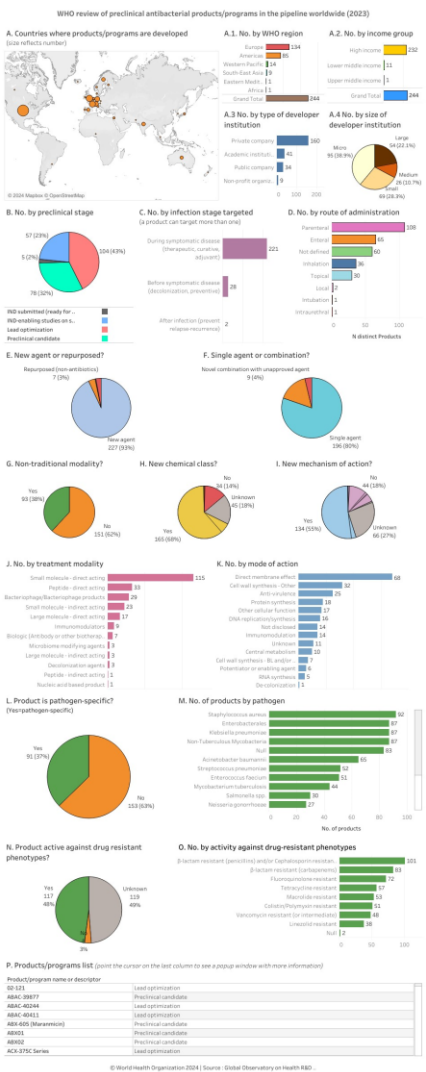
| | Minimal TPP | Preferred TPP |
|---|---|---|
| **Indication for use** | Treatment of acute uncomplicated community-acquired lower UTI in women (cystitis). | Treatment of acute uncomplicated community-acquired lower UTI (cystitis) in women with confirmed or increased risk for multidrug-resistant (MDR) Gram-negative (incl. ESBL-producing) pathogens, or in need of an alternative therapy to nitrofurantoin, fosfomycin or pivmecillinam. |
| **Target population** | Adolescents and adults (women) with suspected MDR Gram-negative pathogens. | Adolescents and adults (women) with suspected MDR Gram-negative pathogens. |
| **Access and affordability** | See Introduction and paragraph on Access and affordability. | See Introduction and paragraph on Access and affordability. |
| **Safety/tolerability** | Comparable to current therapies with β-lactams, no toxicity signals in preclinical reproduction toxicity studies. | Comparable to current therapies with β-lactams, no indication for toxicity signals in preclinical reproduction toxicity studies. |
| **In vitro activity** | Activity against Enterobacteriaceae (especially *E. coli*, *Klebsiella* and *Proteus*, including ESBL producers); low cross-resistance to known antibiotic classes (new class/target/ mode of action), especially β-lactams, fluoroquinolones, co-trimoxazole, fosfomycin, nitrofurantoin; low propensity for mutational resistance development. | Activity against Enterobacteriaceae (especially *E. coli*, *Klebsiella* and *Proteus*, including ESBL producers); no cross-resistance to known antibiotic classes (new class/new target/new mode of action), especially β-lactams, fluoroquinolones, co-trimoxazole; low propensity for mutational resistance development. |
| **Clinical efficacy** | Non-inferior clinical activity to current therapies in acute infections with susceptible pathogens: ciprofloxacin, pivmecillinam and co-trimoxazole. Clinical trials should include elderly patients (> 65 years). | Non-inferior clinical activity to current therapies in acute infections with susceptible pathogens: ciprofloxacin, pivmecillinam and co-trimoxazole. Clinical trials should include elderly patients (> 65 years). |
| **Formulation/ presentation** | Suggestion: tablets/capsules/sachet | Suggestion: tablets/capsules/sachet |
| **Dose regimen** | 1–3x daily, treatment duration 1–5 days | 1–2x daily, treatment duration 1–5 days |
| **Route of administration** | Oral | Oral |
| **Product stability and storage** | Heat stable, 1-year shelf life in hot tropic/ humid climate (simulated with 30°C and 65% relative humidity). | Heat stable, 3-year shelf life in hot tropic/ humid climate (simulated with 30°C and 65% relative humidity). |
| **Pharmacokinetics** | Pharmacokinetic data available to support use in lower UTI (renal elimination), activity in urine. | Pharmacokinetic data available to support use in lower UTI (adequate concentrations and activity in urine, potentially concentrations in blood). |
| **Drug interactions** | Comparable to current therapies | Comparable to current therapies |

- Defining your optimal **Target product profile** (TPP)
- Since many features will be unknown until much later in development a **Target Candidate Profile** (TCP) indicates the idealized profile of a future preclinical candidate
- Process builds increasing knowledge on key features of project across multiple areas

Target product profiles for needed antibacterial agents: WHO website

# Project options

- Positioning of project versus current preclinical pipeline
- **Which pathogens** to focus upon to align to TPP?

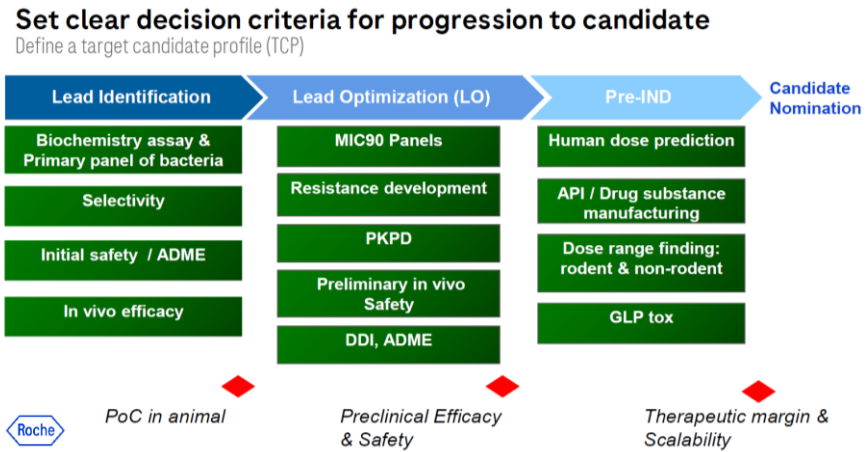


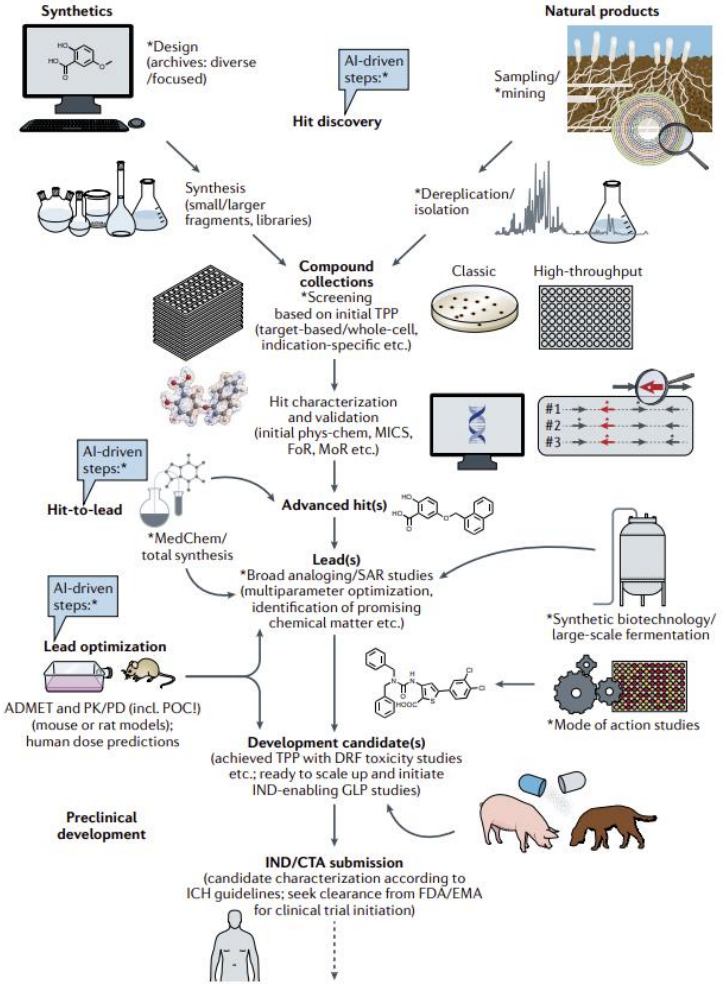


WHO bacterial priority pathogens list
WHO antibacterial preclinical pipeline review

# Discovery Cascade

- For antibacterials, especial consideration can be given to resistance, market, dosing, safety, cost of goods, activity translation.
- Critical to think about biology, chemistry, toxicology in a holistic way from the outset.



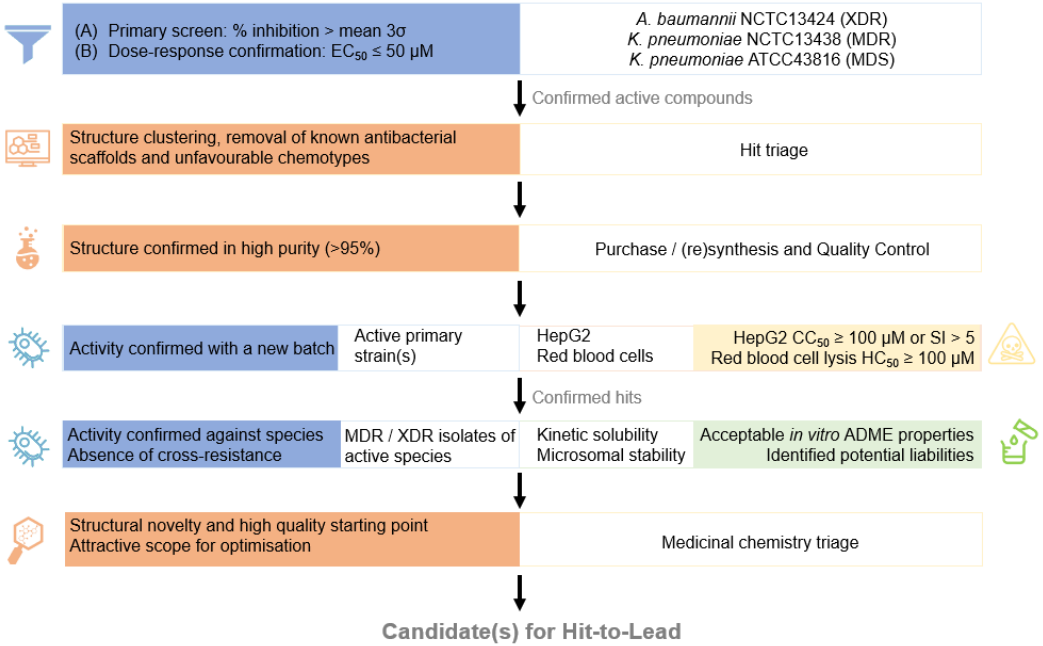

Miethke *et al*, Nature Reviews Chemistry, 2021

# Phenotypic screening

## High-throughput screening of small-molecules libraries identified antibacterials against clinically relevant multidrug-resistant *A. baumannii* and *K. pneumoniae*


Benjamin Blasco,[a] Soojin Jang,[b] Hiroki Terauchi,[c,k] Naoki Kobayashi,[c,k] Shuichi Suzuki,[c,k] Yuichiro Akao,[d,k] Atsuko Ochida,[d,k] Nao Morishita,[d,k] Terufumi Takagi,[d,k] Hiroyuki Nagamiya,[d,k] Yamato Suzuki,[e,k] Toshiaki Watanabe,[e,k] Hyunjung Lee,[b] Sol Lee,[b] David Shum,[b] Ahreum Cho,[b] Dahae Koh,[b] Soonju Park,[b] Honggun Lee,[b] Kideok Kim,[b,l] Henni-Karoliina Ropponen,[a,l] Renata Maria Augusto da Costa,[a] Steven Dunn,[f] Sunil Ghosh,[g] Peter Sjö,[h] and Laura J. V. Piddock[a,*]

[a]Global Antibiotic Research and Development Partnership (GARDP), 15 Chemin Camille-Vidart, 1202, Geneva, Switzerland
[b]Institut Pasteur Korea, 16, Daewangpangyo-ro 712 beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do, South Korea
[c]Eisai Co., Ltd., Tsukuba Research Laboratories, 5-1-3 Tokodai, Tsukuba, Ibaraki, 300-2635, Japan
[d]Takeda Pharmaceutical Company Ltd, 261, Muraoka-Higashi 2-chome, Fujisawa, Kanagawa, 251-8555, Japan
[e]Daiichi Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo, 140-8710, Japan
[f]Dunn Genomics, United Kingdom
[g]TCG Lifesciences Private Limited, Block BN, Plot 7, Salt Lake Electronics Complex, Sector V, Kolkata, 700091, West Bengal, India
[h]Drugs for Neglected Diseases Initiative, 15 Chemin Camille-Vidart, 1202, Geneva, Switzerland


Blasco *et al.*, EBioMedicine, 2024

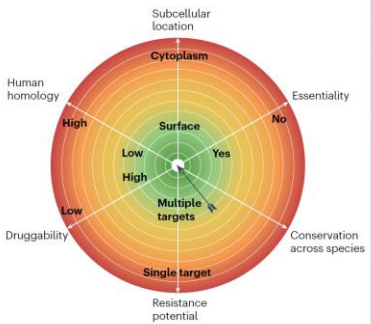
# Target based screens:

- Opportunities for hit finding on novel targets and optimization of existing chemotypes active against novel targets

nature reviews drug discovery

## Unrealized targets in the discovery of antibiotics for Gram-negative bacterial infections

Ursula Theuretzbacher[1], Benjamin Blasco[2], Maëlle Duffey[2] & Laura J. V. Piddock[2]




| Level of target validation | Clinical | In vivo | In vitro |
|---|---|---|---|
| Target term category | Old | Unrealized | Under-explored |
| Degree of risk/innovation for a discovery programme | + | ++ | +++ |
| Discovery approches to bring chemical innovation | Identify a new chemical class binding to a new site not covered by an existing antibiotic in an old target | Identify a new chemical class addressing liabilities known from previously investigated cognate inhibitors acting on target | Bring target to next level of validation by demonstrating chemical validation in in vivo proof-of-concept studies |
| | Convert Gram-positive-only antibiotics of an old target conserved in Gram-positive and Gram-negative bacteria into broad-spectrum anitbiotics | Convert Gram-positive-only antibiotics of an under-exploited target conserved in Gram-positive and Gram-negative bacteria into broad-spectrum antibiotics | |

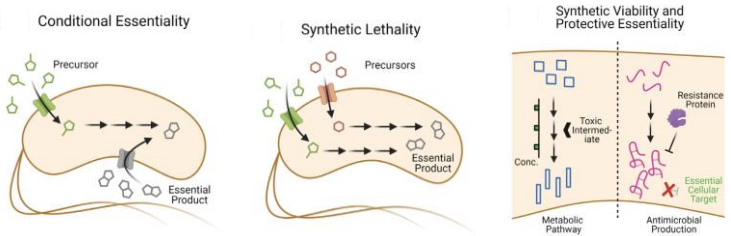
Theuretzbacher *et al.*, Nat Rev Drug Discov., 2023

FEMS

## Gradients in gene essentiality reshape antibacterial research

Andrew M. Hogan[1] and Silvia T. Cardona[1,2,*]

'Quantification' of gene essentiality based on Gene-Environment and Gene-Gene interactions

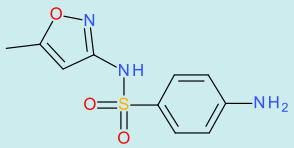
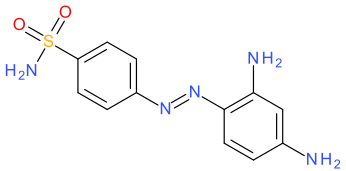



Hogen *et al.*, FEMS Microbiology Reviews, 2022

# Examples of discovery approaches

# Marketed antibacterials of synthetic origin

## Hit Identification strategy – phenotypic screening

| | |
|---|---|
| **Structure of example Product** |  |
| **Product, organisation, year of disclosure** | **Sulfamethoxazole**, Shionogi, 1957 |
| **Target** | Dihydropteroate synthetase |
| **Structure of Hit** |  |
| **Organisation, year of disclosure** | **Prontosil**, Bayer, 1932 |
| **Type of screen / approach used to discover** | Testing thousands of compounds related to azo dyes. |

# Marketed antibacterials of synthetic origin

## Hit Identification strategy – phenotypic screening

| | | |
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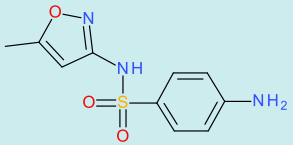
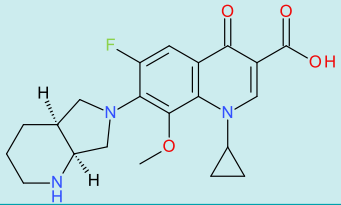
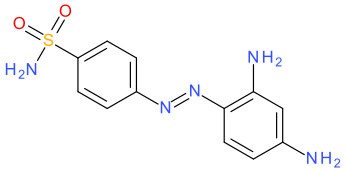
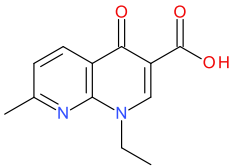
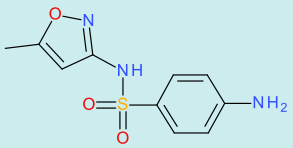
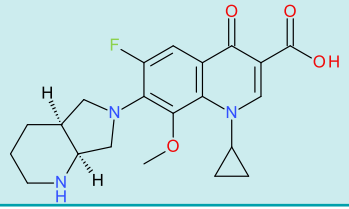
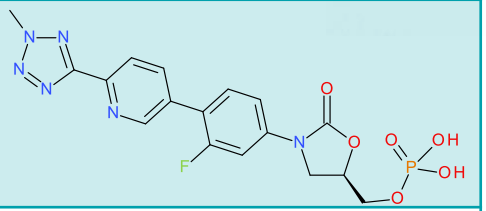
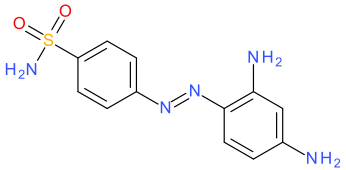
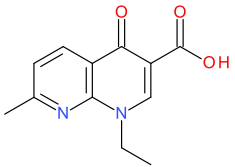
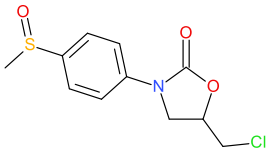
| **Structure of example Product** |  |  |
| **Product, organisation, year of disclosure** | **Sulfamethoxazole**, Shionogi, 1957 | **Moxifloxacin**, Bayer, 1993 |
| **Target** | Dihydropteroate synthetase | DNA gyrase, topoisomerase IV |
| **Structure of Hit** |  |  |
| **Organisation, year of disclosure** | **Prontosil**, Bayer, 1932 | **Nalidixic acid**, Sterling-Winthrop, 1962 |
| **Type of screen / approach used to discover** | Testing thousands of compounds related to azo dyes. | Nalidixic acid discovered as a chloroquine synthetic by-product. |

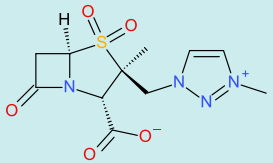
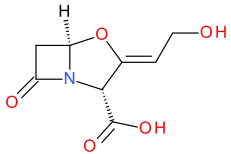
# Marketed antibacterials of synthetic origin

## Hit Identification strategy – phenotypic screening

| | | | |
|---|---|---|---|
| **Structure of example Product** |  |  |  |
| **Product, organisation, year of disclosure** | **Sulfamethoxazole**, Shionogi, 1957 | **Moxifloxacin**, Bayer, 1993 | **Tedizolid phosphate**, Dong-A Pharm, 2005 |
| **Target** | Dihydropteroate synthetase | DNA gyrase, topoisomerase IV | Protein synthesis inhibitor (50S subunit) |
| **Structure of Hit** |  |  |  |
| **Organisation, year of disclosure** | **Prontosil**, Bayer, 1932 | **Nalidixic acid**, Sterling-Winthrop, 1962 | DuPont, 1978 |
| **Type of screen / approach used to discover** | Testing thousands of compounds related to azo dyes | Nalidixic acid discovered as a chloroquine synthetic by-product. | Testing racemic oxazolidinones invented by plant disease researchers. |

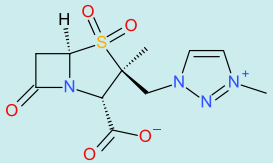
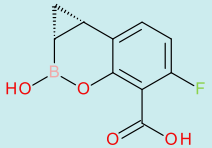
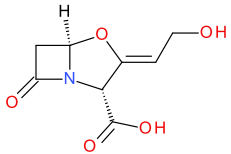
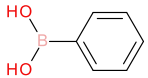
# Beta-lactamase inhibitors

## Hit Identification strategy – multiple origins

| | |
|---|---|
| **Structure of example Product/Lead** |  |
| **Product, organisation, year of disclosure** | **Enmetazobactam**, Orchid, 2008 |
| **Target** | Beta-lactamases |
| **Structure of Hit** |  |
| **Organisation, year of disclosure** | **Clavulanic acid**, Beecham, 1974, |
| **Type of screen / approach used to discover** | Natural product isolation and testing (*Streptomyces clavuligerus*) |

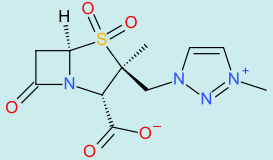
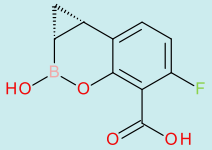
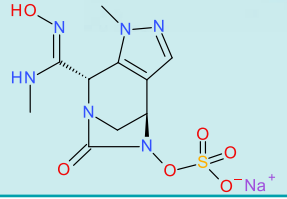
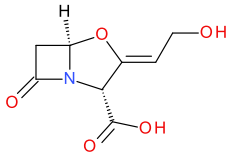
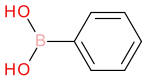
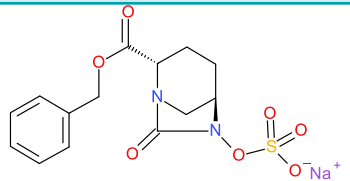
# Beta-lactamase inhibitors

## Hit Identification strategy – multiple origins

| | | |
|---|---|---|
| **Structure of example Product/Lead** |  |  |
| **Product, organisation, year of disclosure** | **Enmetazobactam**, Orchid, 2008 | **QPX7728**, Qpex, 2020 |
| **Target** | Beta-lactamases | Serine and metallo-beta-lactamase inhibitor |
| **Structure of Hit** |  |  |
| **Organisation, year of disclosure** | **Clavulanic acid**, Beecham, 1974, | University of Oxford,1978 |
| **Type of screen / approach used to discover** | Natural product isolation and testing (*Streptomyces clavuligerus*) | Basic biochemical research – UK and Hungary. |

# Beta-lactamase inhibitors

## Hit Identification strategy – multiple origins

| | | | |
|---|---|---|---|
| **Structure of example Product/Lead** |  |  |  |
| **Product, organisation, year of disclosure** | **Enmetazobactam**, Orchid, 2008 | **QPX7728**, Qpex, 2020 | **ETX0462**, Entasis, 2021 |
| **Target** | Beta-lactamases | Serine and metallo-beta-lactamase inhibitor | PBP2 |
| **Structure of Hit** |  |  |  |
| **Organisation, year of disclosure** | **Clavulanic acid**, Beecham, 1974, | University of Oxford,1978 | Hoechst Marion Roussel (HMR), 1990s |
| **Type of screen / approach used to discover** | Natural product isolation and testing (*Streptomyces clavuligerus*) | Basic biochemical research – UK and Hungary. | Researchers proposed that DBOs might act to acylate nucleophilic enzymes in a manner analogous to β-lactams. |

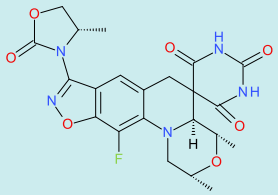
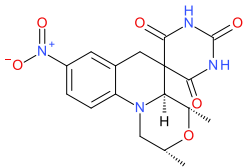
# Hits to Products

## Take-home messages

- Multiple hit finding strategies have been successful in finding initial hits that eventually result in a product(s).
- The organization that finds the hit is not always the one that develops the product.
- Similarity of original hit to product is variable but thousands of compounds are designed, synthesized, tested and analyzed in iterative cycles to develop candidates from initial hits.
- There is high attrition in such projects – only showing successful outcomes!

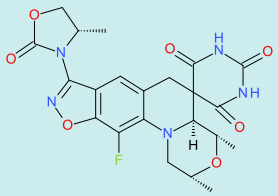
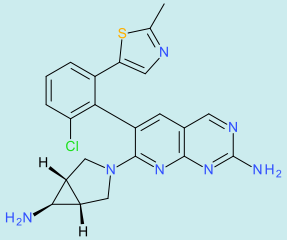
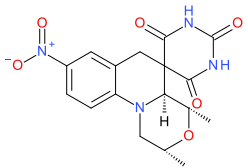
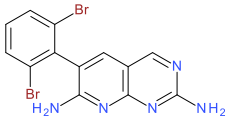
# Leads against novel targets

## From phenotypic screening of synthetic compounds

| | |
|---|---|
| **Structure of Lead** |  |
| **Organisation, year of disclosure** | Astra-Zeneca, 2014 (**Zoliflodacin**) |
| **Target** | Gyrase and TopoIV |
| **Structure of Hit** |  |
| **Organisation, year of disclosure** | Pharmacia, 2008 |
| **Type of screen / approach used to discover** | High-throughput MIC screens of the (~250,000 compounds) |

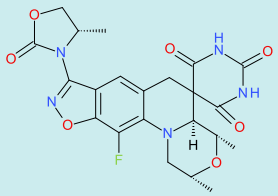
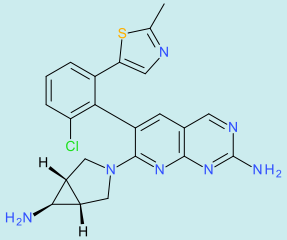
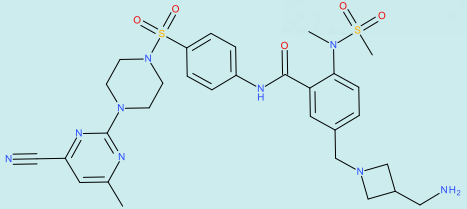
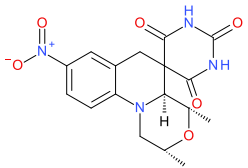
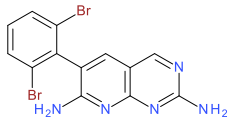
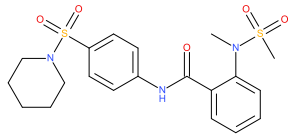
# Leads against novel targets

## From phenotypic screening of synthetic compounds

| | | |
|---|---|---|
| **Structure of Lead** |  |  |
| **Organisation, year of disclosure** | Astra-Zeneca, 2014 (**Zoliflodacin**) | Achaogen, 2018 |
| **Target** | Gyrase and TopoIV | Biotin Carboxylase |
| **Structure of Hit** |  |  |
| **Organisation, year of disclosure** | Pharmacia, 2008 | Pfizer, 2009 |
| **Type of screen / approach used to discover** | High-throughput MIC screens of the (~250,000 compounds) | High-throughput screen of a membrane-compromised, efflux pump-deficient strain of *E. coli* |

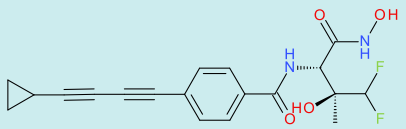
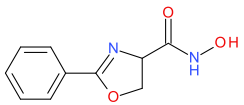
# Leads against novel targets

## From phenotypic screening of synthetic compounds

| | | | |
|---|---|---|---|
| **Structure of Lead** |  |  |  |
| **Organisation, year of disclosure** | Astra-Zeneca, 2014 (**Zoliflodacin**) | Achaogen, 2018 | Uppsala University, 2024 |
| **Target** | Gyrase and TopoIV | Biotin Carboxylase | LpxH |
| **Structure of Hit** |  |  |  |
| **Organisation, year of disclosure** | Pharmacia, 2008 | Pfizer, 2009 | Astra-Zeneca 2015, Uppsala University, 2024 |
| **Type of screen / approach used to discover** | High-throughput MIC screens of the (~250,000 compounds) | High-throughput screen of a membrane-compromised, efflux pump-deficient strain of *E. coli* | Merging screening hits from a TolC-*E. coli* screen and reporter-based screen |

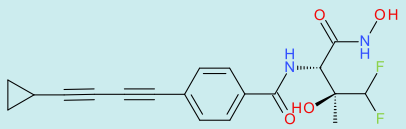
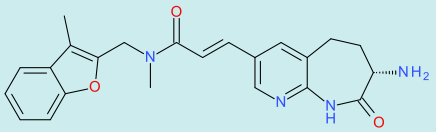
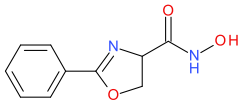
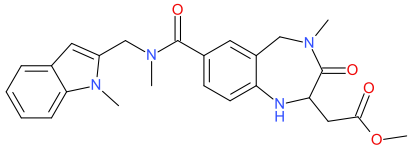
# Leads against novel targets

## From target-based screening of synthetic compounds

| | |
|---|---|
| **Structure of Lead** |  |
| **Organisation, year of disclosure** | Duke University, 2023 |
| **Target** | LpxC |
| **Structure of Hit** |  |
| **Organisation, year of disclosure** | Merck, 1996 |
| **Type of screen / approach used to discover** | Measuring LPS synthesis by monitoring incorporation of radiolabeled galactose into a galE *Salmonella* mutant |

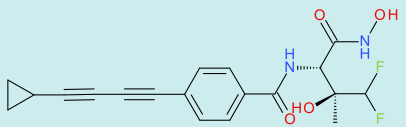
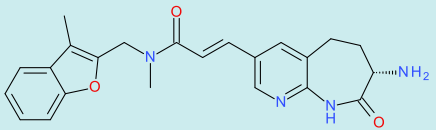
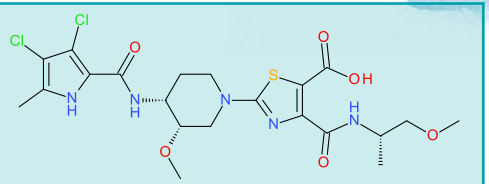
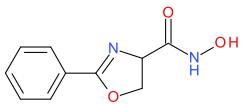
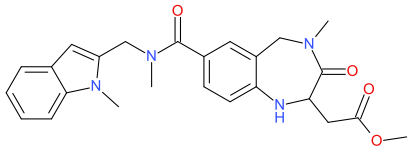
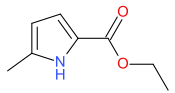
# Leads against novel targets

## From target-based screening of synthetic compounds

| | | |
|---|---|---|
| **Structure of Lead** |  |  |
| **Organisation, year of disclosure** | Duke University, 2023 | Debiopharm, Uni of Illinois, 2021/2022 |
| **Target** | LpxC | FabI |
| **Structure of Hit** |  |  |
| **Organisation, year of disclosure** | Merck, 1996 | GSK, 2001 |
| **Type of screen / approach used to discover** | Measuring LPS synthesis by monitoring incorporation of radiolabeled galactose into a galE *Salmonella* mutant | HTS campaigns with SmithKline Beecham compound collection (260,000+ compounds) - *S. aureus* FabI. |

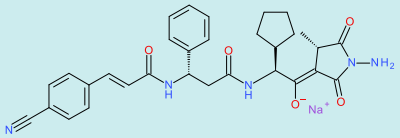
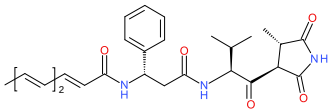
# Leads against novel targets

## From target-based screening of synthetic compounds

| | | | |
|---|---|---|---|
| **Structure of Lead** |  |  |  |
| **Organisation, year of disclosure** | Duke University, 2023 | Debiopharm, Uni of Illinois, 2021/2022 | Astra-Zeneca, 2014 |
| **Target** | LpxC | FabI | GyrB – A-Z fragment |
| **Structure of Hit** |  |  |  |
| **Organisation, year of disclosure** | Merck, 1996 | GSK, 2001 | Astra-Zeneca, 2012 |
| **Type of screen / approach used to discover** | Measuring LPS synthesis by monitoring incorporation of radiolabeled galactose into a galE *Salmonella* mutant | HTS campaigns with SmithKline Beecham compound collection (260,000+ compounds) - *S. aureus* FabI. | Fragment-based approach targeting the ATP binding site of bacterial type II topoisomerases – related to clorobiocin |

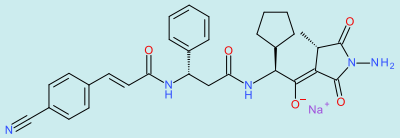
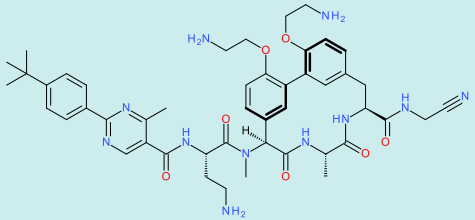
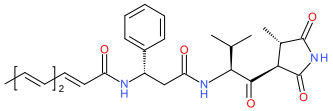
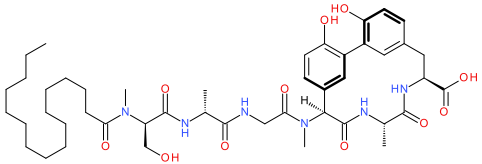
# Leads against novel targets

## From phenotypic screening of natural products

| | |
|---|---|
| **Structure of Lead** |  |
| **Organisation, year of disclosure** | Bayer, 2006 |
| **Target** | Acetyl-CoA carboxylase |
| **Structure of Hit** |  |
| **Organisation, year of disclosure** | **Andrimid**, Suntory institute and others, 1987 |
| **Type of screen / approach used to discover** | Isolated from of an intracellular symbiont (*Enterobacter*) present in the eggs of the brown planthopper |

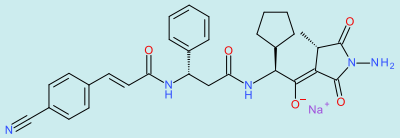
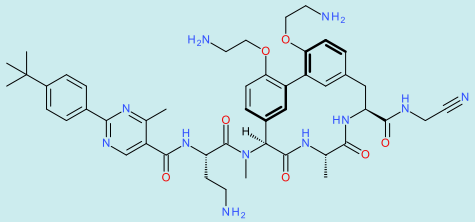
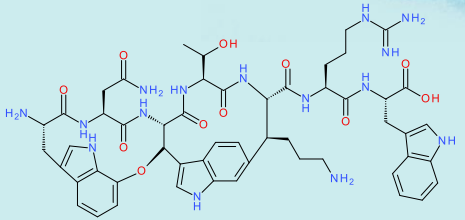
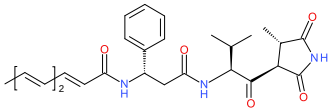
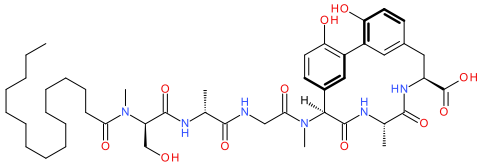
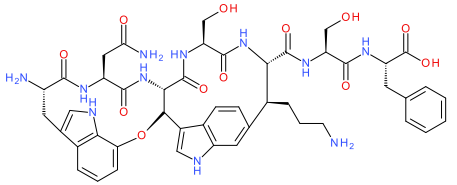
# Leads against novel targets

## From phenotypic screening of natural products

| | | |
|---|---|---|
| **Structure of Lead** |  |  |
| **Organisation, year of disclosure** | Bayer, 2006 | G0775, Genentech, 2018 |
| **Target** | Acetyl-CoA carboxylase | LepB (Type I signal peptidase) |
| **Structure of Hit** |  |  |
| **Organisation, year of disclosure** | **Andrimid**, Suntory institute and others, 1987 | **Arylomycin A-C16**, University of Tübingen, 2002 |
| **Type of screen / approach used to discover** | Isolated from of an intracellular symbiont (*Enterobacter*) present in the eggs of the brown planthopper | Detected in the extracts of *Streptomyces* strain from Ghana, then isolated and tested |

# Leads against novel targets

## From phenotypic screening of natural products

| | | | |
|---|---|---|---|
| **Structure of Lead** |  |  |  |
| **Organisation, year of disclosure** | Bayer, 2006 | G0775, Genentech, 2018 | HIPS, 2023 |
| **Target** | Acetyl-CoA carboxylase | LepB (Type I signal peptidase) | BamA (outer membrane protein) |
| **Structure of Hit** |  |  |  |
| **Organisation, year of disclosure** | **Andrimid**, Suntory institute and others, 1987 | **Arylomycin A-C16**, University of Tübingen, 2002 | **Darobactin**, Northeastern University and others, 2019 |
| **Type of screen / approach used to discover** | Isolated from of an intracellular symbiont (*Enterobacter*) present in the eggs of the brown planthopper | Detected in the extracts of *Streptomyces* strain from Ghana, then isolated and tested | Screening *Photorhabdus* isolates (nematode symbionts) |

# Hits to Leads for novel targets

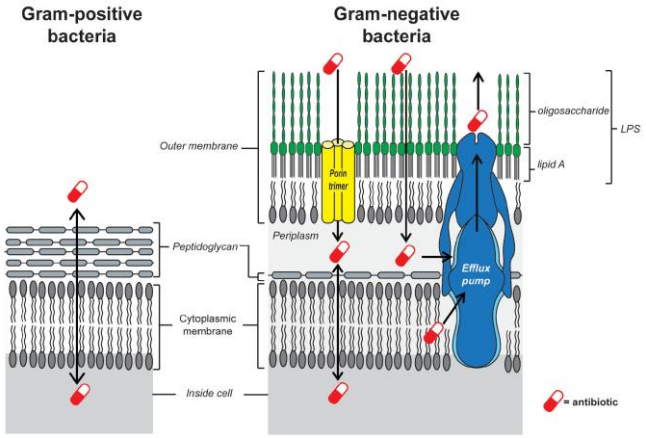
## Take-home messages

- Similar hit-finding strategies continue to deliver innovative starting points.
- Opportunities to optimize phenotypic screening of both synthetics and natural products as well as target-based screening.
- Need to increase these efforts substantially to refill pipeline
- Can this be done more efficiently than in the past?

# Selected recent trends in antibacterial discovery

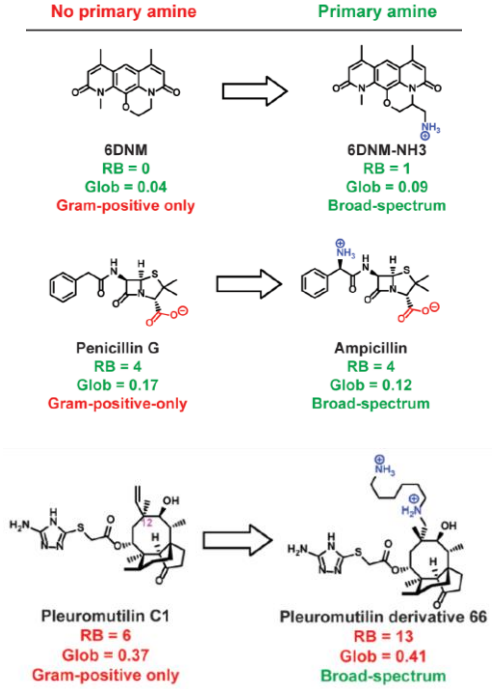
# Physical property understanding

- Advances in understanding and measuring accumulation and then formalizing strategies to enhance it in Gram-negative bacteria have been transformational.




**eNTRY Rules**
**N**itrogen (1° > 2° > 3° amine)
**T**hree-dimensionality (Glob ≤ 0.25)
**R**igidity (RB ≤ 5)

- Conversion of Gram-positive-only compounds into broad-spectrum antibiotics by applying the eNTRY rules:




RB = rotatable bonds
Glob = globularity

Richter *et al.*, Ann N Y Acad Sci., 2019

# Synthetic compounds with natural product features

Article

## A novel antibiotic class targeting the lipopolysaccharide transporter

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- Libraries **of unconventional small molecules** (macrocycles, peptides...) enable identification of interesting new antibacterial clinical candidates – Zosurabalpin
- Integrated drug discovery process

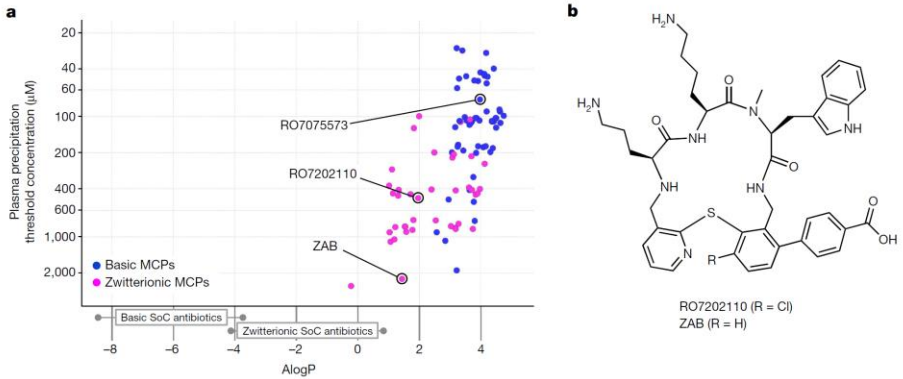



**Fig. 2 | The second-generation lead zosurabalpin demonstrates low lipid plasma precipitation. a**, The drug lipophilicity (AlogP) of basic MCPs and zwitterionic MCPs in correlation with plasma precipitation. The standard of care (SoC) antibiotics and their AlogP lipophilicities are described in Extended Data Table 5. **b**, The chemical structure of the second-generation tethered macrocyclic peptides: zwitterions RO7202110 and zosurabalpin (ZAB).

Zampaloni *et al.*, Nature, 2024

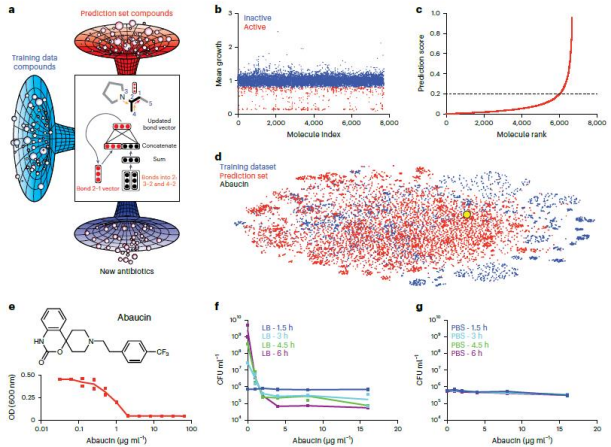
# AI/ML for discovery

## Examples of utilization for both hit finding and AI generative chemistry for optimization of hits

nature chemical biology

**Deep learning-guided discovery of an antibiotic targeting *Acinetobacter baumannii***

Gary Liu[1,10], Denise B. Catacutan[1,10], Khushi Rathod[1,10], Kyle Swanson[2], Wengong Jin[2], Jody C. Mohammed[3], Anush Chiappino-Pepe[3,4], Saad A. Syed[5], Meghan Fragis[1,6], Kenneth Rachwalski[1], Jakob Magolan[1,6], Michael G. Surette[5], Brian K. Coombes[1], Tommi Jaakkola[2], Regina Barzilay[2,7], James J. Collins[3,7,8,9] & Jonathan M. Stokes[1]



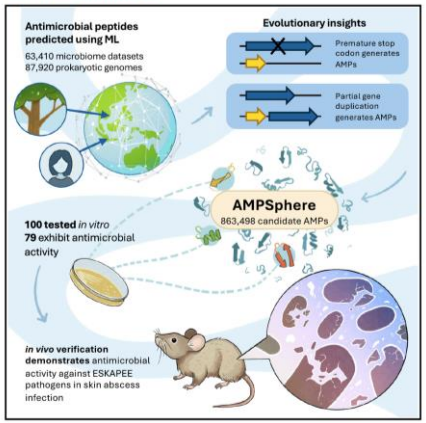

Liu *et al.*, Nat Chem Biol, 2023

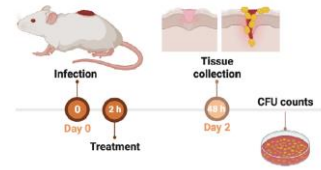
Cell

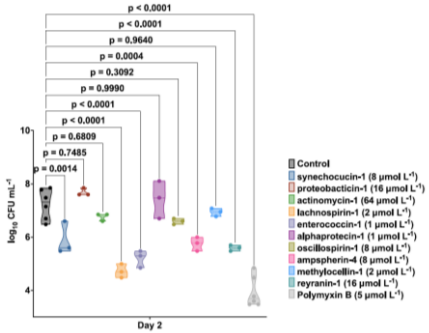
**Discovery of antimicrobial peptides in the global microbiome with machine learning**

Authors
Célio Dias Santos-Júnior,
Marcelo D.T. Torres, Yiqian Duan, ...,
Jaime Huerta-Cepas,
Cesar de la Fuente-Nunez,
Luis Pedro Coelho

Graphical abstract



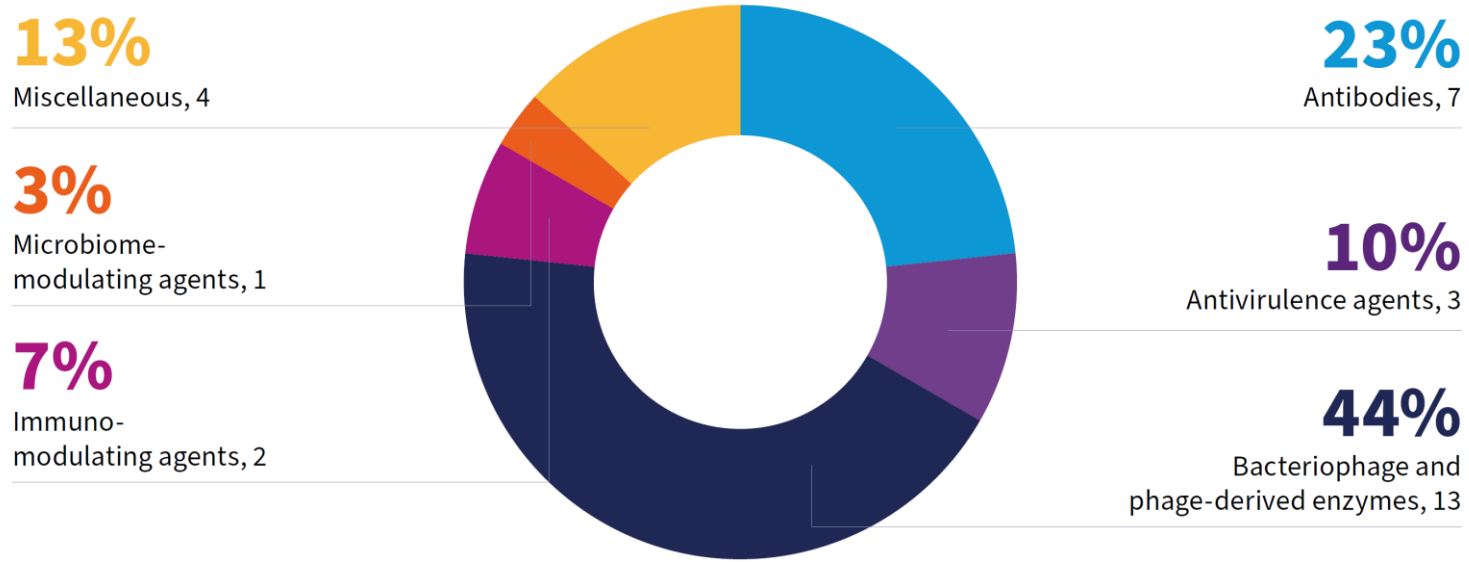




Dias Santos-Júnior *et al.*, Cell, 2024

# Non-traditional approaches

## Non-traditional antibacterials in the clinical pipeline


2023 Antibacterial agents in clinical and preclinical development: an overview and analysis (who.int)

# Conclusion:

- There is a critical need for **innovative antibacterial products** but also a well documented lack of such options in the pipeline.
- Recent products and leads show a diversity in their initial discovery approach but all required **extensive optimization of chemistry, microbiology and toxicology**.
- Early discovery continues to provide new options but this **process needs to be accelerated,** and these later assets need to be carefully nurtured.

# Mo Yin

**Mo Yin** is an Infectious Diseases physician and a clinician scientist based at the National University Hospital in Singapore. Her research interests include antimicrobial resistance and emerging infectious diseases. Mo designs and leads large multinational clinical trials which focus on pragmatic clinical solutions. In addition, Mo has expertise in mathematical modelling, statistics, bioinformatics and qualitative research.

She is the deputy director of the ADVANCE-ID, a large clinical trial network consisting of over 60 hospitals globally. She has served as an external consultant to the World Health Organisation and Public Health England. Mo Yin obtained her MBBS from the National University of Singapore and doctorate degree from the University of Oxford, UK.

# Phase 1 - 3 trials for Antibiotic Development

Mo Yin
MBBS, DPhil

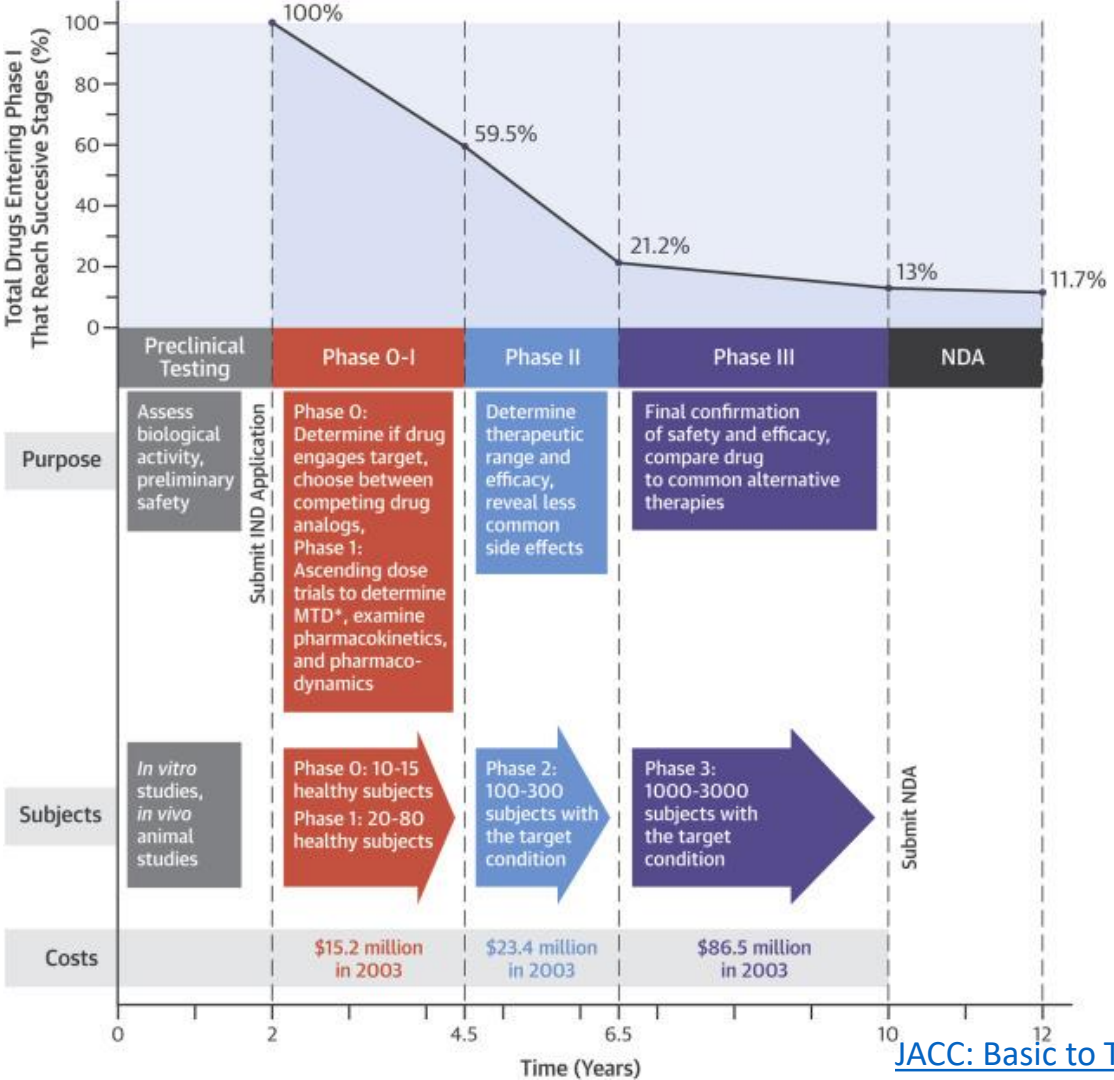
# Conflicts of interest

- Research funding from Pfizer, bioMérieux
- Honoraria for speaking for Pfizer

# Overview

- Introduction to Phase 1– 3 trials for novel antibiotics
- Antibiotic-specific challenges
  - Methodology considerations
  - Regulatory / approval issues

# Introduction to Phase 1– 3 trials for novel antibiotics




JACC: Basic to Translational Science, 2016

# Phase I – **Safety and Tolerability**

- Healthy volunteers, small sample size <100
- Open label, single/few centres, quick
- Pharmacodynamics
  - Biological and physiological effects on humans, mechanisms of action
- Pharmacokinetics
  - Half life, plasma concentration
- Dose-Escalation Study Design
  - Receive increasing dose until a maximum tolerated dose is identified
- Early signals of efficacy

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

CLINICAL THERAPEUTICS

# A Phase 1, Randomized, Single-Ascending-Dose Study To Investigate the Safety, Tolerability, and Pharmacokinetics of DSTA4637S, an Anti-*Staphylococcus aureus* Thiomab Antibody-Antibiotic Conjugate, in Healthy Volunteers

**Melicent Peck,[a] Michael E. Rothenberg,[a] Rong Deng,[a] Nicholas Lewin-Koh,[a] Gaohong She,[a] Amrita V. Kamath,[a] Montserrat Carrasco-Triguero,[a] Ola Saad,[a] Aide Castro,[a]* Lisa Teufel,[a]* Daniel S. Dickerson,[b] Marisa Leonardelli,[b] Jorge A. Tavel[a]**

[a]Genentech, Inc., South San Francisco, California, USA
[b]PRA Health Sciences, Lenexa, Kansas, USA

**ABSTRACT** *Staphylococcus aureus* causes serious bacterial infections with high morbidity and mortality, necessitating the discovery of new antibiotics. DSTA4637S is a novel antibody-antibiotic conjugate designed to target intracellular *S. aureus* that is not adequately eliminated by current standard-of-care antibiotics. DSTA4637S is composed of an anti-*S. aureus* Thiomab human immunoglobulin G1 (IgG1) monoclonal antibody linked to a novel rifamycin-class antibiotic (4-dimethylaminopiperidino-hydroxybenzoxazino rifamycin [dmDNA31]) via a protease-cleavable linker. Phagocytic cells ingest DSTA4637S-bound *S. aureus*, and intracellular cathepsins cleave the linker, releasing dmDNA31and killing intracellular *S. aureus*. This first-in-human, randomized, double-blind, placebo-controlled, single-ascending-dose phase 1 trial analyzed the safety, pharmacokinetics, and immunogenicity of DSTA4637S in healthy volunteers. Thirty healthy male and female volunteers, 18–65 years old, were randomized into five cohorts receiving single intravenous (i.v.) doses of 5, 15, 50, 100, and 150 mg/kg of DSTA4637S or placebo (4 active:2 placebo). Subjects were followed for 85 days after dosing. No subject withdrew from the study, and no serious or severe adverse events occurred. One moderate infusion-related reaction (150 mg/kg DSTA4637S) occurred. No clinically meaningful or dose-related changes in laboratory parameters or vital signs occurred. Pharmacokinetics of plasma DSTA4637S conjugate and serum DSTA4637S total antibody were dose proportional. Systemic exposure of unconjugated dmDNA31 was low. No DSTA4637S-induced anti-drug antibody responses were observed. DSTA4637S was generally safe and well tolerated as a single i.v. dose in healthy volunteers. DSTA4637S has a favorable safety and pharmacokinetic profile that supports future development as a novel therapeutic for *S. aureus* infections. (This study has been registered at ClinicalTrials.gov under identifier NCT02596399.)

**Citation** Peck M, Rothenberg ME, Deng R, Lewin-Koh N, She G, Kamath AV, Carrasco-Triguero M, Saad O, Castro A, Teufel L, Dickerson DS, Leonardelli M, Tavel JA. 2019. A phase 1, randomized, single-ascending-dose study to investigate the safety, tolerability, and pharmacokinetics of DSTA4637S, an anti-*Staphylococcus aureus* Thiomab antibody-antibiotic conjugate, in healthy volunteers. Antimicrob Agents Chemother 63:e02588-18. https://doi.org/10.1128/AAC.02588-18.

# Phase II – **Efficacy and Safety**

- Diseased patients >100
- Phase II A
  - ”Proof-of-concept" - **explore** efficacy in a relatively small group of patients
  - Preliminary dose-response relationship
  - Surrogate or exploratory end points
  - Dose ranging
- Phase II B
  - More rigorous - **confirm** efficacy at doses to be used in phase III trials
  - Definitive endpoints aligned with phase III
  - Critical in making “Go/ No go” decision for phase III

ARTICLES · Volume 18, Issue 12, P1319-1328, December 2018 Download Full Issue

# Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial

Simon Portsmouth, MD [a] · David van Veenhuyzen, MBChB [a] · Roger Echols, MD [b] · Mitsuaki Machida, MS [c] · Juan Camilo Arjona Ferreira, MD [a] · Mari Ariyasu, BPharm [c] · et al. Show more

## Methods

We did a phase 2, multicentre, double-blind, parallel-group non-inferiority trial at 67 hospitals in 15 countries. Adults (≥18 years) admitted to hospital with a clinical diagnosis of complicated urinary tract infection with or without pyelonephritis or those with acute uncomplicated pyelonephritis were randomly assigned (2:1) by an interactive web or voice response system to receive 1 h intravenous infusions of cefiderocol (2 g) or imipenem-cilastatin (1 g each) three times daily, every 8 h for 7–14 days. Patients were excluded if they had a baseline urine culture with more than two uropathogens, a fungal urinary tract infection, or pathogens known to be carbapenem resistant. The primary endpoint was the composite of clinical and microbiological outcomes at test of cure (ie, 7 days after treatment cessation), which was used to establish non-inferiority (15% and 20% margins) of cefiderocol versus imipenem-cilastatin. The primary efficacy analysis was done on a modified intention-to-treat population, which included all randomly assigned individuals who received at least one dose of study drug and had a qualifying Gram-negative uropathogen (≥1 × $10^5$ colony-forming units [CFU]/mL). Safety was assessed in all randomly assigned individuals who received at least one dose of study drug, according to the treatment they received. This study is registered with ClinicalTrials.gov, number NCT02321800.

## Findings

Between Feb 5, 2015, and Aug 16, 2016, 452 patients were randomly assigned to cefiderocol (n=303) or imipenem-cilastatin (n=149), of whom 448 patients (n=300 in the cefiderocol group; n=148 in the imipenem-cilastatin group) received treatment. 371 patients (n=252 patients in the cefiderocol group; n=119 patients in the imipenem-cilastatin group) had qualifying Gram-negative uropathogen (≥1 × $10^5$ CFU/mL) and were included in the primary efficacy analysis. At test of cure, the primary efficacy endpoint was achieved by 183 (73%) of 252 patients in the cefiderocol group and 65 (55%) of 119 patients in the imipenem-cilastatin group, with an adjusted treatment difference of 18·58% (95% CI 8·23–28·92; p=0·0004), establishing the non-inferiority of cefiderocol. Cefiderocol was well tolerated. Adverse events occurred in 122 (41%) of 300 patients in the cefiderocol group and 76 (51%) of 148 patients in the imipenem-cilastatin group, with gastrointestinal disorders (ie, diarrhoea, constipation, nausea, vomiting, and abdominal pain) the most common adverse events for both treatment groups (35 [12%] patients in the cefiderocol group and 27 [18%] patients in the imipenem-cilastatin group).

# Phase III – **Efficacy and approval**

- Diseased patients, large sample size, multicentre
- Blinding
  - May not be feasible
- Definitive clinical end points
- For regulatory approvals

ARTICLES | VOLUME 23, ISSUE 9, P1072-1084, SEPTEMBER 2023 Download Full Issue

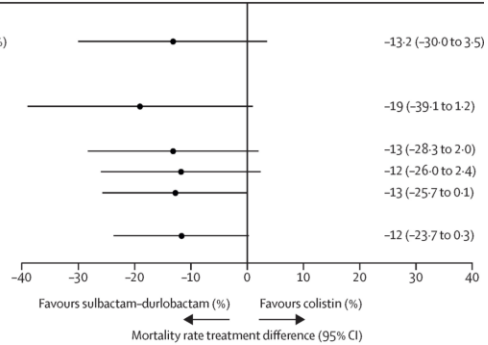
# Efficacy and safety of sulbactam–durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii–calcoaceticus* complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK)

Prof Keith S Kaye, MD • Prof Andrew F Shorr, MD • Prof Richard G Wunderink, MD • Prof Bin Du, MD • Gabrielle E Poirier, BS • Khurram Rana, PharmD • et al. Show all authors

Published: May 11, 2023 • DOI: https://doi.org/10.1016/S1473-3099(23)00184-6 • Check for updates

A

| | Sulbactam–durlobactam, n/N (%) | Colistin, n/N (%) | Treatment difference, % (95% CI) |
|---|---|---|---|
| **Primary endpoint** | | | |
| 28-day ACM: carbapenem-resistant ABC microbiologically modified ITT | 12/63 (19·0%) | 20/62 (32·3%) | −13·2 (−30·0 to 3·5) |
| **Secondary endpoints** | | | |
| 28-day ACM: carbapenem-resistant ABC microbiologically evaluable | 8/46 (17%) | 16/44 (36%) | −19 (−39·1 to 1·2) |
| 28-day ACM: microbiologically modified ITT | 15/76 (20%) | 25/76 (33%) | −13 (−28·3 to 2·0) |
| 28-day ACM: ITT | 19/90 (21%) | 28/85 (33%) | −12 (−26·0 to 2·4) |
| 14-day ACM: carbapenem-resistant ABC microbiologically modified ITT | 4/64 (6%) | 12/63 (19%) | −13 (−25·7 to 0·1) |
| 14-day ACM: microbiologically modified ITT | 6/77 (8%) | 15/77 (20%) | −12 (−23·7 to 0·3) |




## Methods

The ATTACK trial was done at 59 clinical sites in 16 countries. Adults aged 18 years or older with ABC-confirmed hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, ventilated pneumonia, or bloodstream infections were randomised 1:1 using a block size of four to sulbactam–durlobactam (1·0 g of each drug in combination over 3 h every 6 h) or colistin (2·5 mg/kg over 30 min every 12 h) for 7–14 days. All patients received imipenem–cilastatin (1·0 g of each drug in combination over 1 h every 6 h) as background therapy. The primary efficacy endpoint was 28-day all-cause mortality in patients with laboratory-confirmed carbapenem-resistant ABC (the carbapenem-resistant ABC microbiologically modified intention-to-treat population). Non-inferiority was concluded if the upper bound of the 95% CI for the treatment difference was less than +20%. The primary safety endpoint was incidence of nephrotoxicity assessed using modified Risk, Injury, Failure, Loss, End-stage renal disease criteria measured by creatinine level or glomerular filtration rate through day 42. This trial is registered at ClinicalTrials.gov, NCT03894046.

RESEARCH SUMMARY

# Oral Tebipenem Pivoxil Hydrobromide in Complicated Urinary Tract Infection

Eckburg PB et al. DOI: 10.1056/NEJMoa2105462

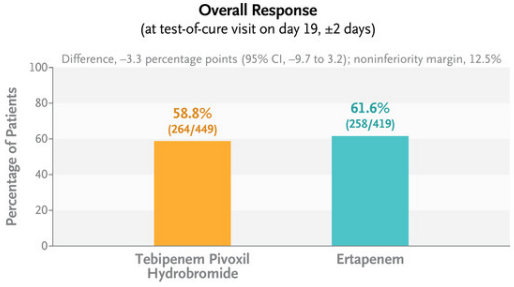
## CLINICAL PROBLEM

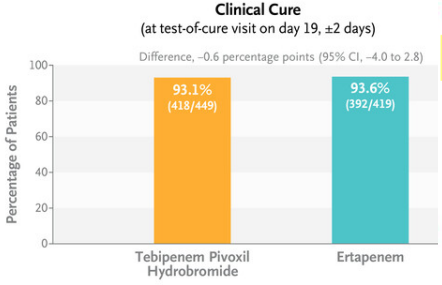
Complicated urinary tract infection and acute pyelonephritis are increasingly treated in the inpatient setting with intravenous agents for antibiotic-resistant pathogens, a situation that indicates the need for effective oral treatments. Tebipenem pivoxil hydrobromide — an orally bioavailable carbapenem prodrug with broad-spectrum activity against multidrug-resistant gram-negative pathogens — is one potential option.

## CLINICAL TRIAL

**Design:** A phase 3, international, randomized, double-blind, double-dummy trial examined whether oral tebipenem pivoxil hydrobromide was noninferior to intravenous ertapenem for complicated urinary tract infection or acute pyelonephritis.

**Intervention:** 1372 hospitalized adults were assigned to receive either oral tebipenem pivoxil hydrobromide (two 300-mg tablets every 8 hours) plus dummy ertapenem infusion every 24 hours or intravenous ertapenem (1 g every 24 hours) plus dummy tebipenem pivoxil hydrobromide for 7 to 10 days (up to 14 days in patients with bacteremia). The primary efficacy end point — overall response (clinical cure plus microbiologic response) at the test-of-cure visit — was assessed among 868 patients with confirmed complicated urinary tract infection or acute pyelonephritis.

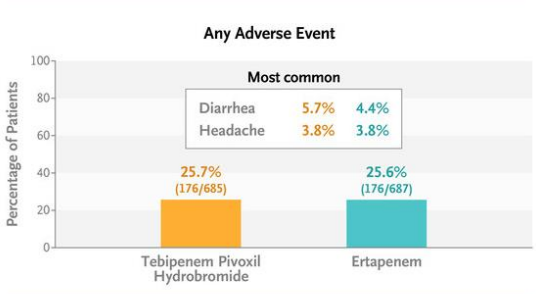



## RESULTS

**Efficacy:** Oral tebipenem pivoxil hydrobromide was noninferior to intravenous ertapenem with respect to overall response.

**Safety:** The incidence of adverse events was nearly identical in the two groups. Mild diarrhea and headache were the most common adverse events.




## LIMITATIONS AND REMAINING QUESTIONS

- The trial mandated at least a 7-day inpatient stay for antibiotic treatment, which may not reflect the standard of care in the United States.
- Patients who had immunocompromise, severe renal impairment, or infection with confirmed or suspected carbapenem-resistant pathogens were excluded.
- Most patients were White and most had been enrolled in Central and Eastern Europe.

**Links: Full Article | NEJM Quick Take**

## CONCLUSIONS

Among patients with complicated urinary tract infection or acute pyelonephritis, oral tebipenem pivoxil hydrobromide was noninferior to intravenous ertapenem in terms of overall response and had a similar safety profile.

# FDA says oral UTI treatment application is insufficient for approval

June 28, 2022
By Jason M. Broderick

*Article*

The FDA has sent a complete response letter to Spero Therapeutics saying its New Drug Application (NDA) lacked sufficient data to support the approval of tebipenem pivoxil hydrobromide (tebipenem HBr), the company's oral agent for the treatment of adult patients with complicated urinary tract infection (cUTI), including pyelonephritis.[1]

The NDA was supported by data from the phase 3 ADAPT-PO trial showing that tebipenem HBr has noninferior efficacy and safety compared to intravenous ertapenem in this setting.[2]

"We are disappointed with the FDA's decision, but we look forward to our continued dialogue, addressing the agency's concerns and outlining a clear path forward for tebipenem HBr," Ankit Mahadevia, MD, Chief Executive Officer of Spero Therapeutics, stated in a news release "With this development, we continue to believe that tebipenem HBr offers patients and their providers an important new treatment option, that if approved, has the potential to address the critical unmet need for a new oral antibiotic for patients with cUTI."

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

# Cefepime–Taniborbactam in Complicated Urinary Tract Infection

Wagenlehner FM et al. DOI: 10.1056/NEJMoa2304748

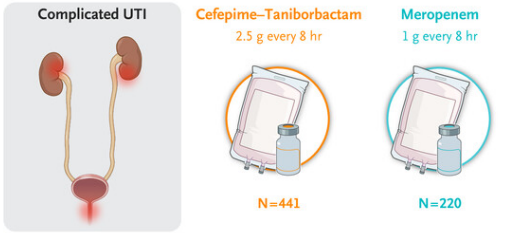
## CLINICAL PROBLEM

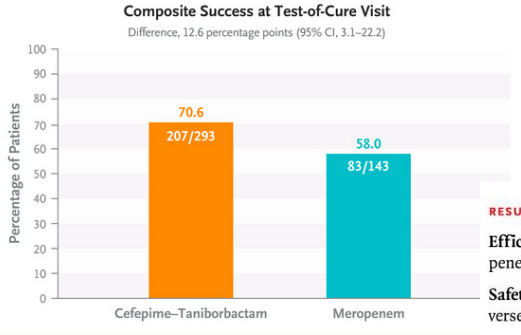
Complicated urinary tract infection (UTI), including acute pyelonephritis, is responsible for ≥600,000 hospital admissions per year in the United States, with considerable health care costs. The efficacy and safety of cefepime–taniborbactam, an investigational $\beta$-lactam and $\beta$-lactamase inhibitor combination, in comparison with standard treatment with meropenem, are unknown.

## CLINICAL TRIAL

**Design:** A phase 3, international, randomized trial compared cefepime–taniborbactam with meropenem in hospitalized adults with complicated UTI, including acute pyelonephritis.

**Intervention:** 661 patients were randomly assigned in a 2:1 ratio to receive 2.5 g of cefepime–taniborbactam intravenously every 8 hours (plus meropenem placebo) or 1 g of meropenem intravenously every 8 hours (plus cefepime–taniborbactam placebo) for 7 days (up to 14 days for patients with bacteremia). The primary outcome was composite (microbiologic and clinical) success at the test-of-cure visit (trial days 19 to 23) in the microbiologic intention-to-treat population, which included patients who had a qualifying gram-negative pathogen against which both treatments had antibacterial activity. Cefepime–taniborbactam was tested for superiority to meropenem after noninferiority had been confirmed.




Adverse Events

## RESULTS

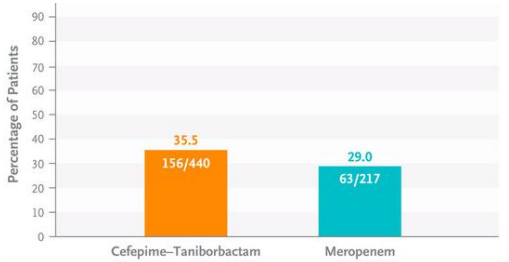
**Efficacy:** Cefepime–taniborbactam was superior to meropenem with respect to composite success.

**Safety:** The frequencies of adverse events and serious adverse events were similar in the two groups.

## LIMITATIONS AND REMAINING QUESTIONS

- Lack of oral step-down antibiotics, the fixed duration of intravenous therapy, and the requirement for inpatient participation may not reflect clinical practice in all regions of the world.
- The composite outcome classifies patients who have asymptomatic bacteriuria as having composite failure, which is inconsistent with clinical practice.

**Links: Full Article | NEJM Quick Take**




## CONCLUSIONS

In patients with complicated UTI, including acute pyelonephritis, cefepime–taniborbactam was superior to meropenem with respect to microbiologic and clinical success, with a similar safety profile.

# FDA rejects new drug application for cefepime-taniborbactam

*News brief* | *February 28, 2024*

*Chris Dall, MA*

*Topics: Antimicrobial Stewardship*

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SHARE

Manufacturing issues have led the US Food and Drug Administration (FDA) to reject a New Drug Application (NDA) for cefepime-taniborbactam, a combination antibiotic under review as a potential treatment for urinary tract infections (UTIs) caused by multidrug-resistant bacteria.

In a **press release** late last week, Venatorx Pharmaceutical and Melinta Therapeutics said the FDA issued a Complete Response Letter to the NDA requesting additional chemistry, manufacturing, and controls (CMC) and related data about the drug, testing methods, and manufacturing process. The companies said the FDA did not identify clinical safety or efficacy issues, nor did it request any new clinical trials.

Developed by Venatorx, of Malvern, Pennsylvania, cefepime-taniborbactam combines a fourth-generation cephalosporin antibiotic with a beta-lactamase inhibitor. The results of a **phase 3 trial** recently published in the *New England Journal of Medicine* found the combination antibiotic was superior to meropenem in patients with complicated UTIs. Venatorx submitted the NDA to the FDA in August 2023 based on the results of that trial.

# Antibiotic-specific challenges for clinical trials

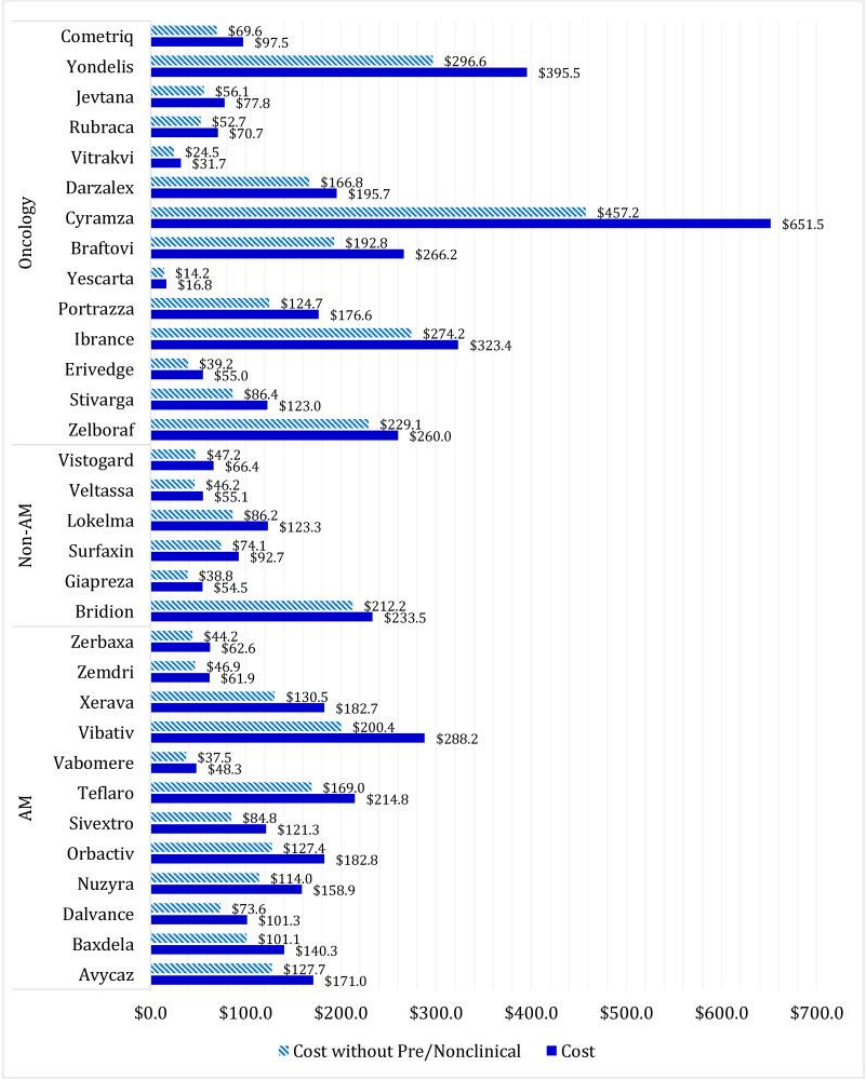
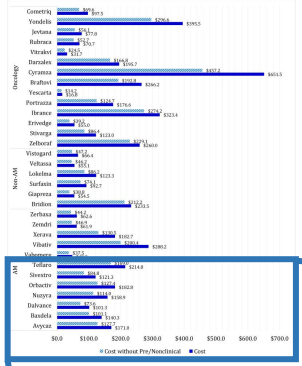

Oncology
Cometriq $69.6 $97.5
Yondelis $296.6 $395.5
Jevtana $56.1 $77.8
Rubraca $52.7 $70.7
Vitrakvi $24.5 $31.7
Darzalex $166.8 $195.7
Cyramza $457.2 $651.5
Braftovi $192.8 $266.2
Yescarta $14.2 $16.8
Portrazza $124.7 $176.6
Ibrance $274.2 $323.4
Erivedge $39.2 $55.0
Stivarga $86.4 $123.0
Zelboraf $229.1 $260.0
Non-AM
Vistogard $47.2 $66.4
Veltassa $46.2 $55.1
Lokelma $86.2 $123.3
Surfaxin $74.1 $92.7
Giapreza $38.8 $54.5
Bridion $212.2 $233.5
AM
Zerbaxa $44.2 $62.6
Zemdri $46.9 $61.9
Xerava $130.5 $182.7
Vibativ $200.4 $288.2
Vabomere $37.5 $48.3
Teflaro $169.0 $214.8
Sivextro $84.8 $121.3
Orbactiv $127.4 $182.8
Nuzyra $114.0 $158.9
Dalvance $73.6 $101.3
Baxdela $101.1 $140.3
Avycaz $127.7 $171.0
$0.0 $100.0 $200.0 $300.0 $400.0 $500.0 $600.0 $700.0
Cost without Pre/Nonclinical
Cost

Table 7. Average Number of Patients Enrolled, by Phase and Drug Cohort

| Phase | AM Cohort Drugs | Non-AM Comparator Cohort Drugs | Oncology Cohort Drugs |
|---|---|---|---|
| Clinical | | | |
| Phase 1 | 270 (156 – 507) | 155 (27 – 367) | 145 (8 – 454) |
| Phase 2 | 237 (88 – 430) | 244 (2 – 770) | 396 (97 – 1,613) |
| Phase 3 | 1,948 (627 – 3,532) | 1,031 (243 – 1,886) | 2,257 (330 – 5,054) |
| *Clinical Total* | *2,413 (889 – 4,046)* | *1,430 (562 – 2,416)* | *2,314 (119 – 6,763)* |
| Post-approval | | | |
| Phase 4 | 1,293 (12 – 7,923) | 2,193 (20 – 8,615) | 462 (65 – 1,623) |
| **Overall Total** | **3,706 (1,399 – 10,916)** | **3,623 (622 – 11,031)** | **2,777 (581 – 7,225)** |



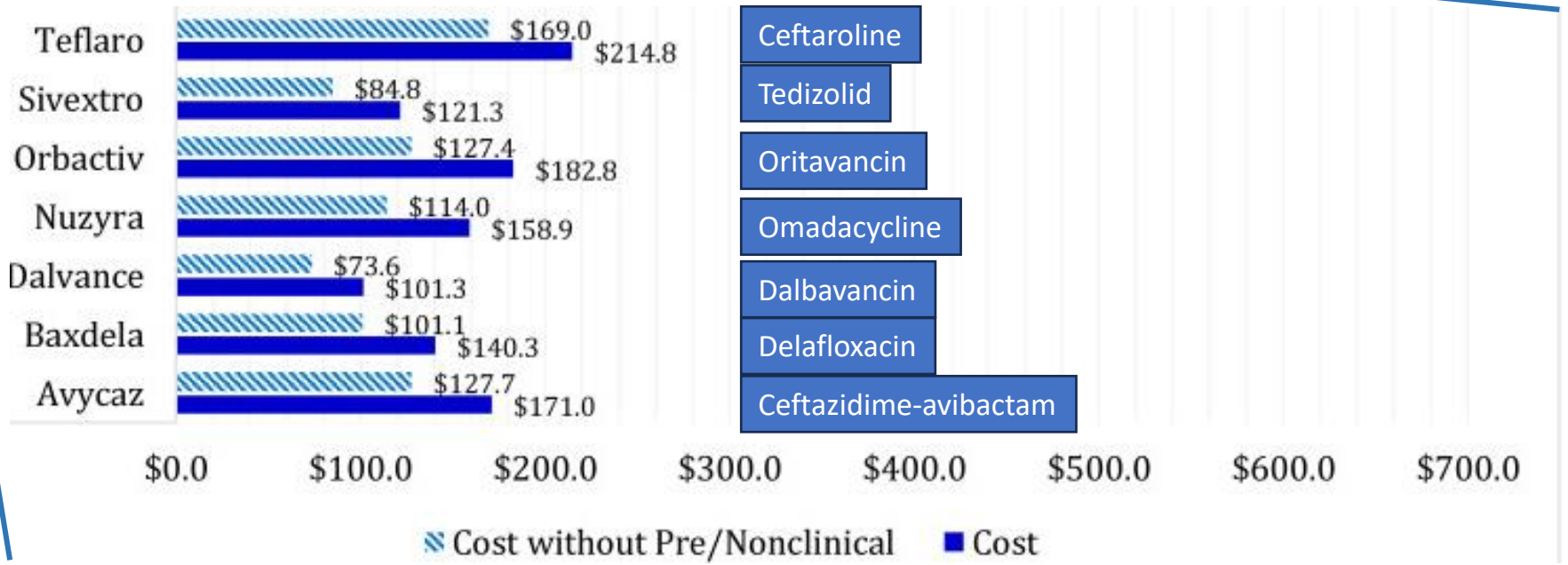
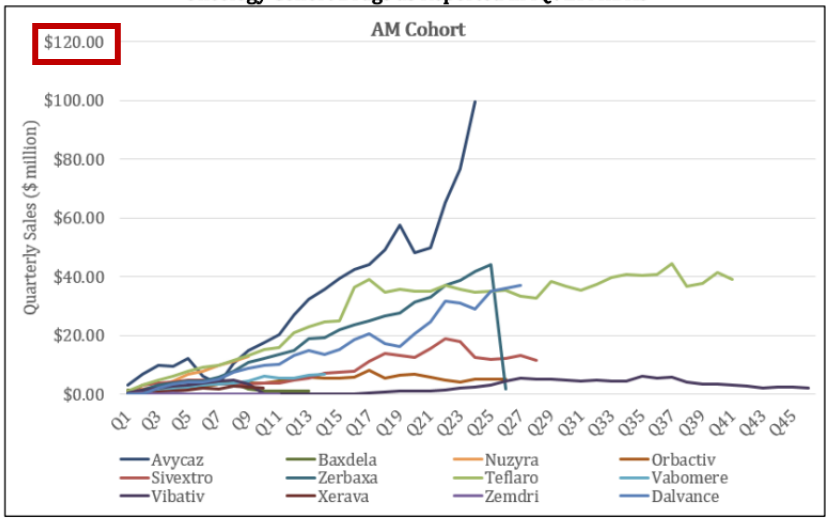
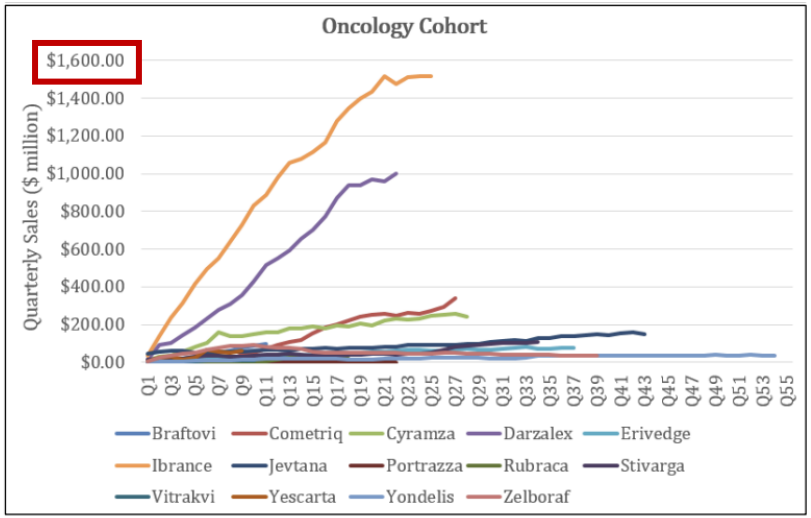
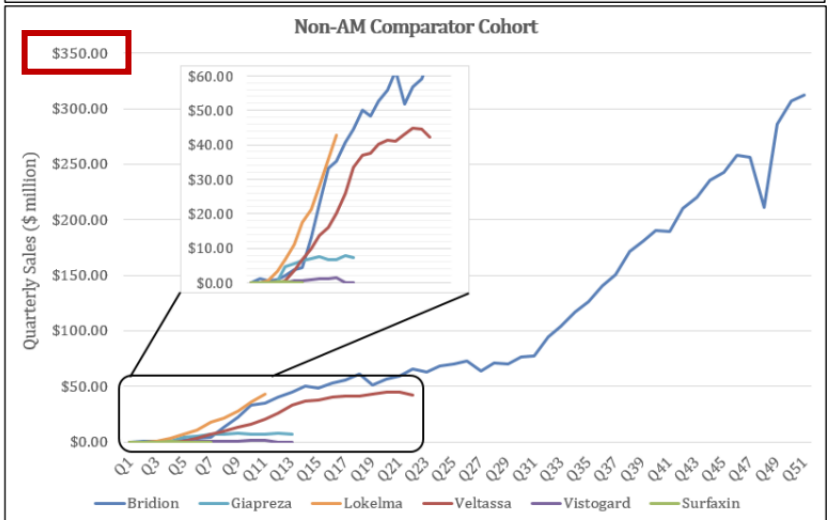


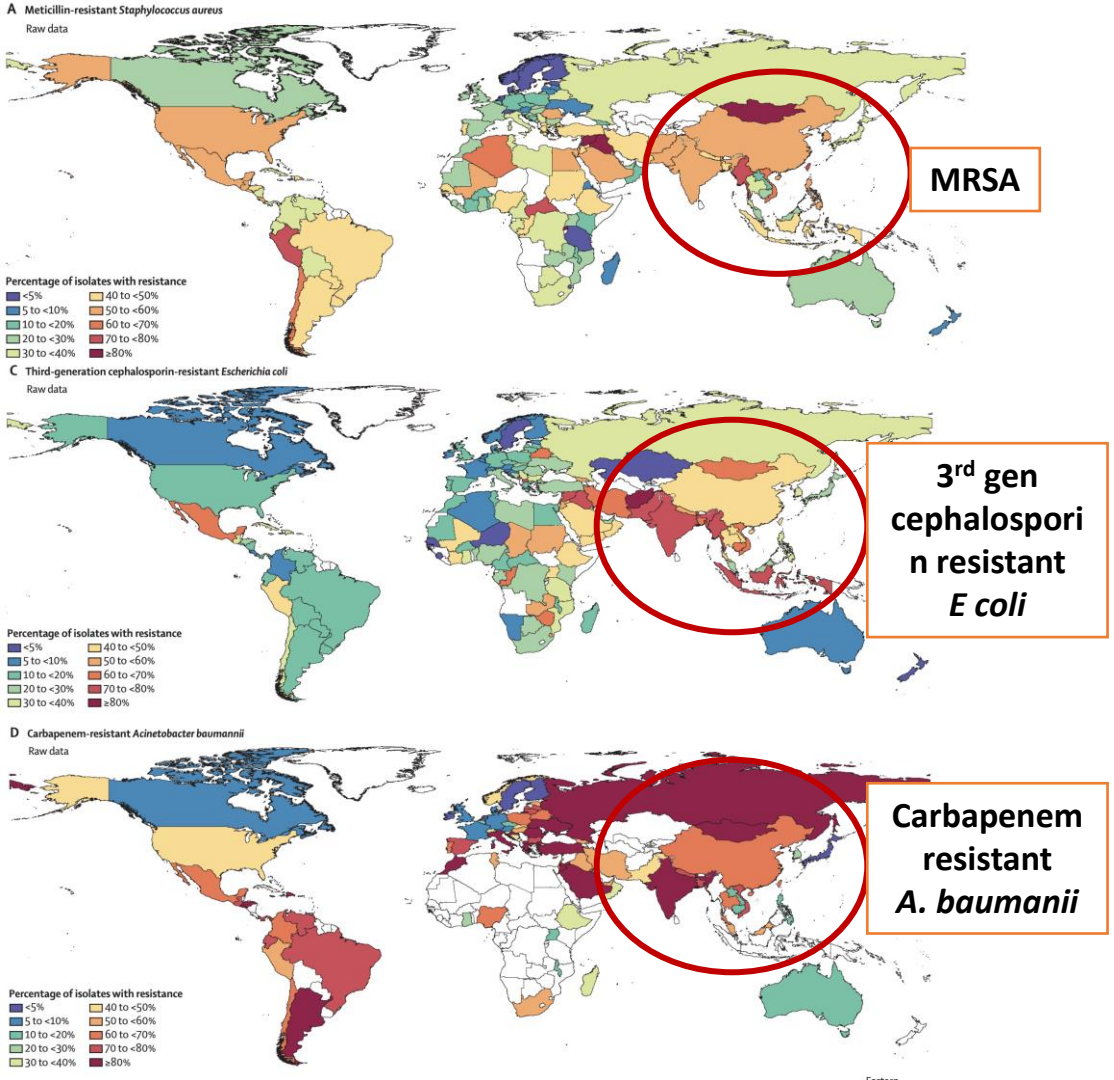
**Figure 7. Quarterly Global Sales Since Launch (in $ Million) for AM, Non-AM Comparator, and Oncology Cohort Drugs as Reported in IQVIA MIDAS**




***Cost of developing an antibiotic is ~2X less than an oncology drug, but the returns are ~10X less than an oncology drug in the first year.***




**MRSA**

**3rd gen cephalosporin resistant *E coli***

**Carbapenem resistant *A. baumanii***

# Antimicrobial resistance **3rd** cause of death in global disease burden in 2019

Lancet, 2022

# Antibiotic R&D

- Since 1990, antibiotic development shifted from large pharmaceutical companies (18 → 4) to smaller companies
- Investments from governments, philanthropy, global health bodies in the recent years offset a large portion of R&D expenditures incurred by the developers

Review

# Antibacterial agents active against Gram Negative Bacilli in phase I, II, or III clinical trials

David L. Paterson

Pages 371-387 | Received 07 Jan 2024, Accepted 28 Feb 2024, Published online: 06 Mar 2024

Nearly 50 antimicrobial agents (28 small molecules and 21 non-traditional antimicrobial agents) active against Gram-negative bacilli are currently in clinical trials. These have the potential to provide substantial improvements to the antimicrobial armamentarium, although it is known that 'leakage' from the pipeline occurs due to findings of toxicity during clinical trials.

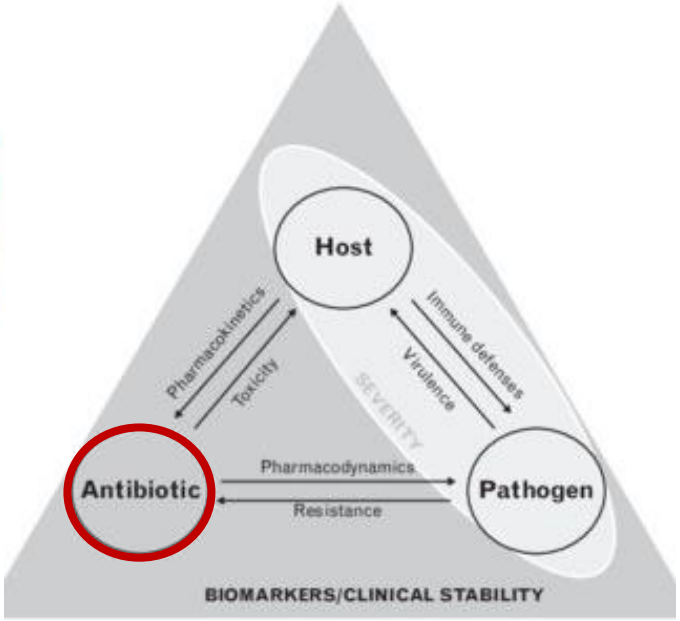
## Downstream challenges persist..

# Implementation challenges in enrolling infected patients into trials - **Antibiotic**

| Antibiotic | Enterobacteriaceae (e.g. E. coli, Klebsiella spp.) | | | | | *Pseudomonas* spp. | | *Acinetobacter* spp. |
|---|---|---|---|---|---|---|---|---|
| | ESBL | AmpC | KPC | OXA-48 | NDM | Efflux | AmpC | |
| Ceftolozane-tazobactam | | | | | | | | |
| Ceftazidime-avibactam | | | | | | | | |
| Meropenem-vaborbactam | | | | | | | | |
| Imipenem-relebactam | | | | | | | | |
| Aztreonam-avibactam | | | | | | | | |
| Eravacycline | | | | | | | | |
| Plazomicin | | | | | | | | |
| Cefiderocol | | | | | | | | |

ESBL – Extended spectrum beta-lactamase
AmpC – Ambler class C beta-lactamase (the Amp probably stands for Ampicillin)
KPC - Klebsiella pneumoniae carbapenemase
OXA - Oxacillin carbapenemase number 48
NDM - New Delhi metallo-beta-lactamase

Lack of standard-of-care



# Antibiotic resistance mechanisms are complex

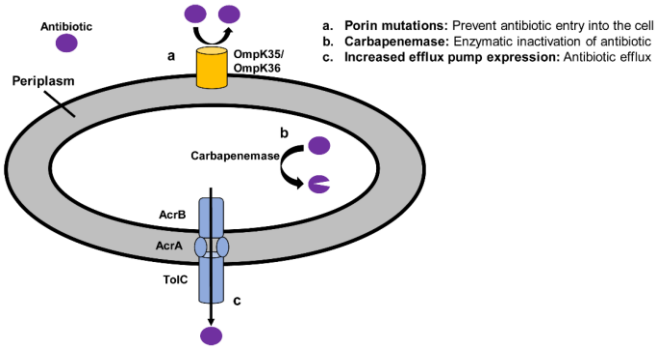
- Example: Carbapenem-resistance

- Mechanisms:
  - Carbapenamase production
  - Others in combination:
    - extended spectrum β-lactamases, overexpression of ampC
    - loss of porin channels
    - efflux pumps

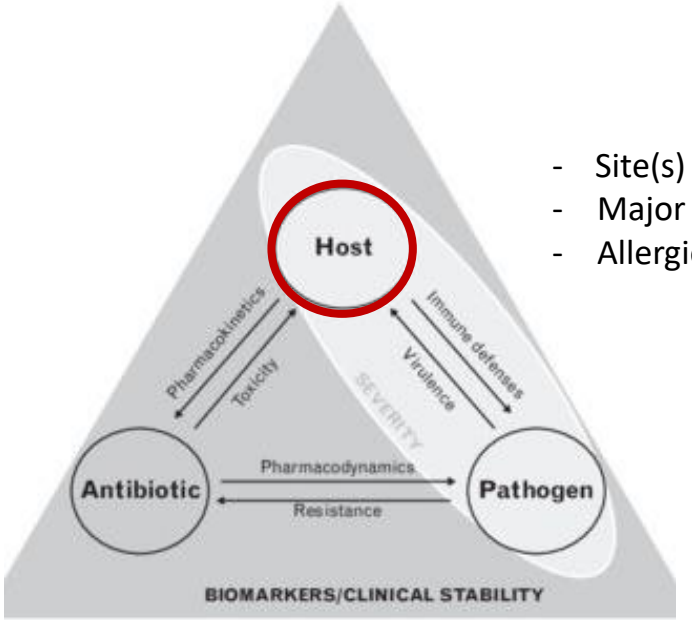
**Carbapenemases**/β-lactamases

| Serine-β-lactamases | Metallo-β-lactamases |
|---|---|
| Class A: **KPC**, **IMI**, **SME**, CTX-M, GES*, SHV, TEM | |
| | Class B: **NDM, VIM, IMP** |
| Class C: AmpC, ACT, CMY, DHA, FOX | |
| Class D: **OXA-48, OXA-181, OXA-23, OXA-40, OXA-58** OXA-1, OXA-2, OXA-9, OXA-10 | |

* Some variants may possess carbapenemase activity

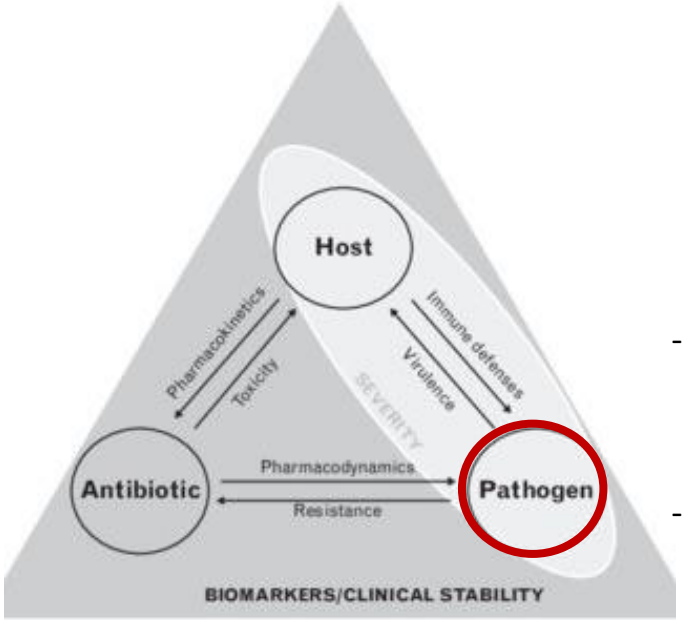


# Implementation challenges in enrolling infected patients into trials - **Host**



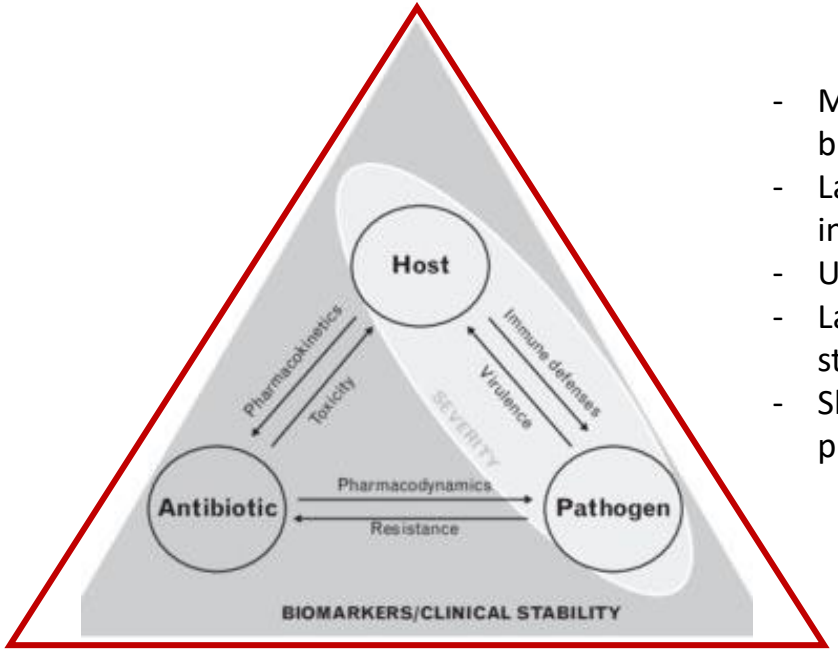

- Site(s) of infection
- Major organ functions
- Allergies

# Implementation challenges in enrolling infected patients into trials - **Pathogen**




- Resistance emergence – short term within-host selection / increase transmissibility vs longer term *de novo* mutations
- Differentiation of colonisers vs true pathogens

# Implementation challenges in enrolling infected patients into trials – **System / infrastructure**




- Mismatch between disease burden and clinical trial capacity
- Lack of antibiotic stewardship / infection prevention and control
- Unreliable diagnostics
- Lack of surveillance data to inform study site selection
- Skepticism for research in general public

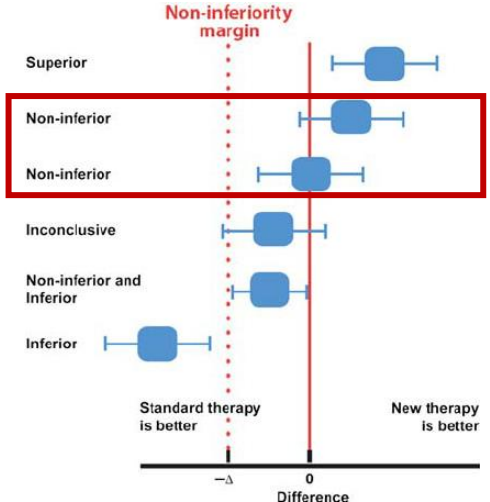
# advanceid.

**47** sites in **20** countries


1. Shared Resources
2. Protocol Standardisation
3. Patient Recruitment
4. Data and Results Sharing

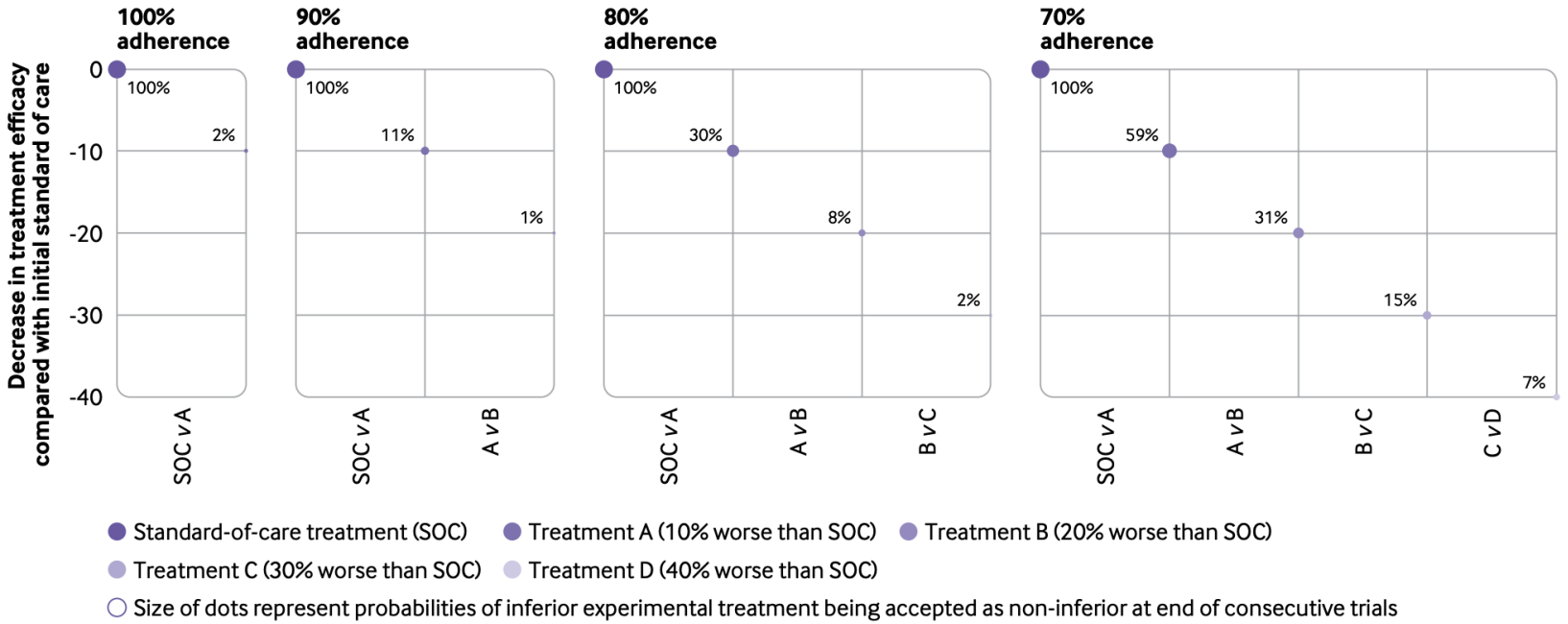
# Non-inferiority *vs* Superiority trials

- Most phase 3 trials for novel antibiotics are of non-inferiority in design
- Unethical to conduct placebo-controlled trials for antibiotics
- Existing antibiotics are efficacious




***'not too bad'***

# Easier to show non-inferiority when trials are poorly performed




Mo, BMJ 2022

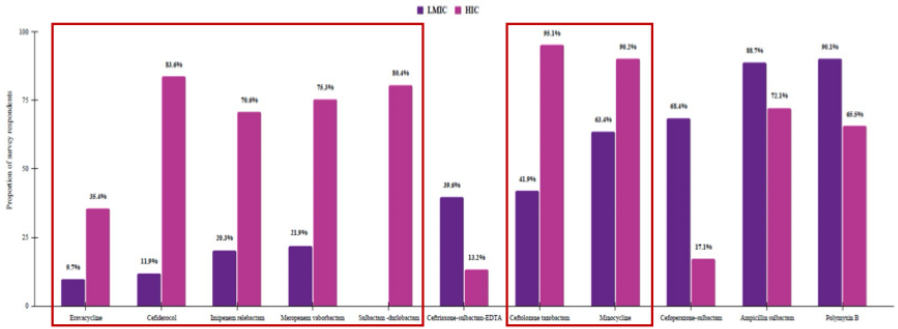
# How to conduct superiority trials for novel antibiotics?

- Target patients with extensively resistant infections e.g. carbapenem-resistant Gram-negative bacterial infections
- Innovative designs
  - Ranking instead of comparisons based on arbitrary p values
    - “PRACTical” design
  - Incorporate categorical outcomes instead of just mortality
    - DOOR/ RADAR, win ratio
- Combinations of old and new

# Conclusion

- Despite market failures, novel antibiotics are being developed with joint incentivisation
- However, funding limited for phase 3/ 4 trials
- Antibiotic access in LMICs

Access to newer antibiotics is limited in LMICs




Manesh, under review

# *Food for thought…*

## Antimicrobial resistance and the great divide: inequity in priorities and agendas between the Global North and the Global South threatens global mitigation of antimicrobial resistance

*Marc Mendelson, Ramanan Laxminarayan, Direk Limmathurotsakul, Samuel Kariuki, Martha Gyansa-Lutterodt, Esmita Charani, Sanjeev Singh, Kamini Walia, Ana C Gales, Mirfin Mpundu*

**To limit the catastrophic effects of the increasing bacterial resistance to antimicrobials on health, food, environmental, and geopolitical security, and ensure that no country or region is left behind, a coordinated global approach is required. In this Viewpoint, we argue that the diverging resource availabilities, needs, and priorities of the Global North and the Global South in terms of the actions required to mitigate the antimicrobial resistance pandemic are a direct threat to success. We argue that evidence suggests a need to prioritise and support infection prevention interventions (ie, clean water and safe sanitation, increased vaccine coverage, and enhanced infection prevention measures for food production in the Global South contrary to the focus on research and development of new antibiotics in the Global North) and to recalibrate global funding resources to address this need. We call on global leaders to redress the current response, which threatens mitigation of the antimicrobial resistance pandemic.**

*Lancet Glob Health* 2024; 12: e516–21

Published Online January 23, 2024 https://doi.org/10.1016/S2214-109X(23)00554-5

Division of Infectious Diseases and HIV Medicine, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town,

# THANK YOU

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# Herbert Wetli

**Herbert Wetli** is head of Pharmaceutical Development at GARDP, in this role he is responsible for the assessment of new drug product opportunities, as well as the coordination of all chemistry, manufacturing and controls (CMC) activities across the lifecycle of drug products.

Herbert has over 20 years of professional experience in the pharmaceutical development and manufacturing arena across all stages of development. He has a master's degree in pharmaceutical sciences from the University of Basel and a doctorate degree in analytical chemistry and pharmacology from the University of Bern, Switzerland.

# Chemistry, Manufacturing and Controls (CMC) in Drug Development

The important role that CMC plays throughout the development and commercialization of a pharmaceutical product

GARDP
Global Antibiotic Research & Development Partnership

# What is Chemistry, Manufacturing and Controls (CMC)?

"CMC" is a group of *integrated* functions that are collectively responsible for delivering an acceptable product to the patient

| API | Drug Product | Analytical | Regulatory |
|---|---|---|---|
| • Active Pharmaceutical Ingredient | • A solid oral or a sterile dosage form | • In-process testing<br>• Final release testing | • Health authority filings<br>• Updates |

| Quality | Manufacturing | Packaging |
|---|---|---|
| • Adherence to GMPs | • Lab scale<br>• Pilot plant<br>• Commercial | • Clinical supplies<br>• Primary<br>• Secondary |

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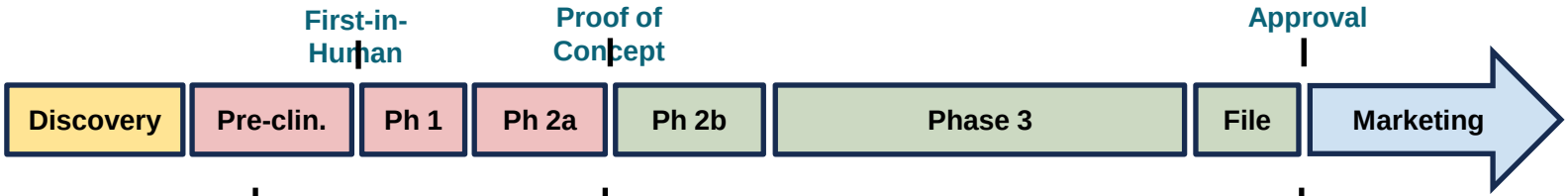
# Key CMC activities along the drug development path




### *"Late Discovery"*

- Aid in the selection of a developable drug candidate

### *"Early Development"*

- Pre-clinical and clinical supply manufacture
- Focus on speed to enable quick go/no-go decision-making
- API synthesis, clinical formulation and analytical methods are "enabling"

### *"Late Development"*

- Clinical supply manufacture
- Commercial process development – robust, safe, economically viable, efficient, sustainable
- Tech transfer to commercial manufacturing site(s)
- Final process, final site product included in Phase 3 trials
- Process validation

### *"Lifecycle"*

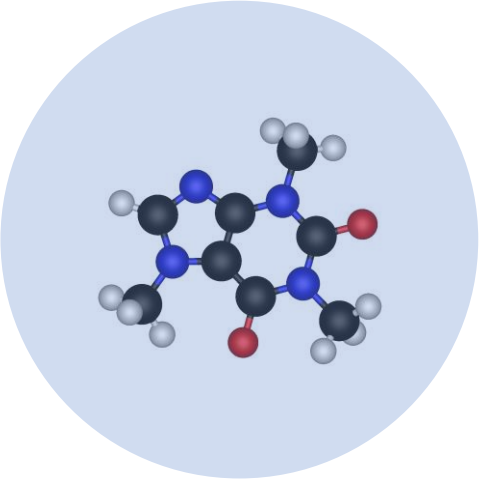
- New market introductions
- Possible new indications and dosage forms
- Process (cost) improvements

# Late Discovery and Early Development

Selecting a developable drug candidate and building a body of CMC knowledge and understanding

# Selection of the Active Pharmaceutical Ingredient (API)

A drug candidate is selected based on its activity against a biological target



**Drug candidate/API**

However, if salt formation is possible, a salt screen **must** be done:

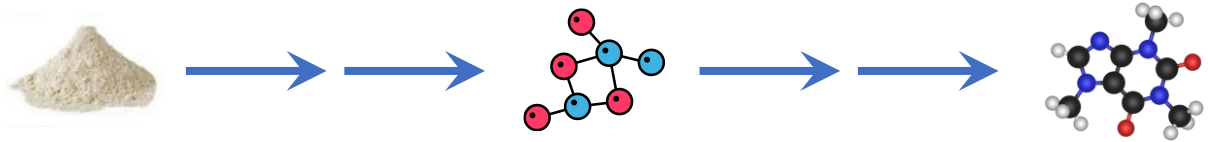
API salt form(s)

- Defines the physical and chemical properties of the API
  - Solubility, stability, hygroscopicity, etc.
- Affects bioavailability
- Impacts developability
- Offers patentability

***Salt selection is a key development decision***

# API Synthesis in Early Development

**Drug development cannot begin until API becomes available (on critical path) – *and API lead times can be 3 to 12+ months, depending on synthetic complexity!***



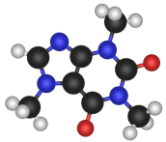
starting materials | intermediates | final API

Speed is of the essence:

- Use enabling chemistry (safe, reproducible and scalable) to prepare Phase 1 and 2 API
- Limited process development at this stage
- If possible, “lock” the final chemical and isolation step to assure consistent API quality
- Progressive scale-up to move off critical path:
  - ~100-500 g non-GMP (lab) → use for API characterization, analytical and formulation dev., Tox studies
  - ~1-5 kg GMP (pilot plant) → use for drug product scale-up, First-in-human supplies

*GMP = Good Manufacturing Practices

# Analytical requirements for the API



## In-process testing

- Methods to support the API synthesis and manufacture

## API Analysis

- API Characterization
- Purity, impurities (may require chiral methods)
- Residual solvents, H2O; residual heavy metals
- Stability indicating methods
  - Every unique lot of API needs to be placed on stability
- Release specifications and a justification of specifications
- Reference standard
- Container closure system specified (bag + secondary package, bottle, etc.)

# Drug product considerations in Early Development

As with API, key aspects of the formulation must be considered and managed early on

**Drug product**

Formulation and excipients

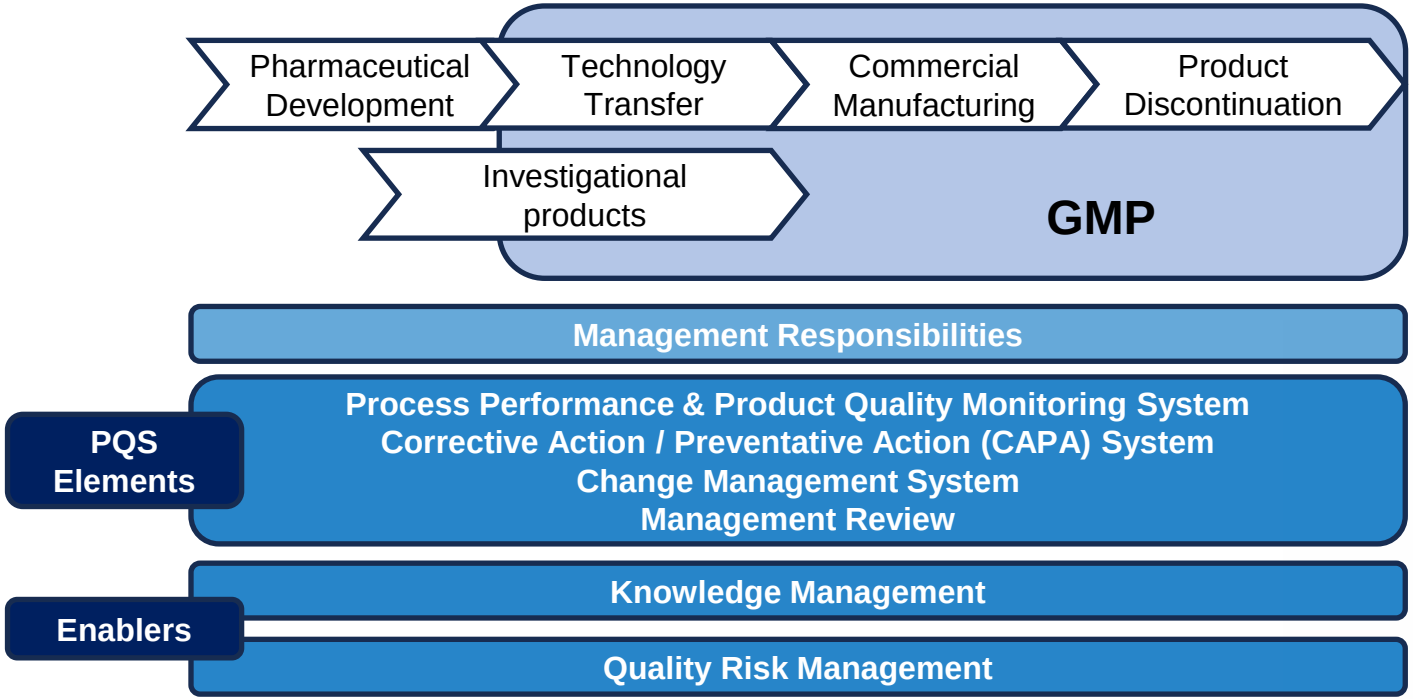
- Affects bioavailability
- Use animal pharmacokinetic (PK) models
- Impacts dissolution, stability

Food effects

- Affects bioavailability
- Based on clinical data

# Quality considerations

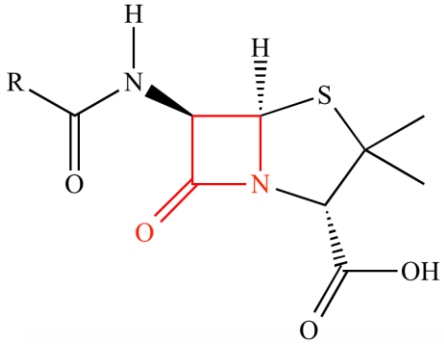
## ICH Q10 Pharmaceutical Quality System



# Specific considerations for beta-lactams

## Regulatory situation

- Many antibiotics contain a beta-lactam moiety and can lead to drug-induced anaphylaxis
- Pharmaceutical technologies to develop and manufacture beta-lactam antibiotics are the same as for non-beta-lactam APIs, but:
- Major regulatory agencies require that beta-lactams and pharmaceutical products containing beta-lactams are manufactured in dedicated and segregated facilities, separated from non-beta-lactam products
- An official license to handle beta-lactams is required from local governments




An amide contained within a four-membered ring

# The Target Product Profile as a development roadmap

**A Target Product Profile (TPP) is a regulatory (FDA) expectation in drug development. At the same time, it can serve as an important internal "contract" to align on CMC-related expectations and final deliverables.**

***Sample CMC TPP:***

| Attribute | Essential (required) | Ideal (desired) |
|---|---|---|
| Administration | Intramuscular (IM) | Oral |
| Treatment regimen* | Two tablets, twice-a-day dosing (BID) | Single tablet, once-a-day dosing (QD) |
| Palatability | Acceptable taste (including pediatric patients) | No taste or pleasant taste |
| Packaging | 30 count bottles in US, 28 count blisters in EU | 90 count bottles worldwide |
| Shelf life | 18 months at refrigerated conditions | 3 years at room temperature |
| … | | |

* Also dependent upon dose/efficacy

# Development risks and trade-off decisions

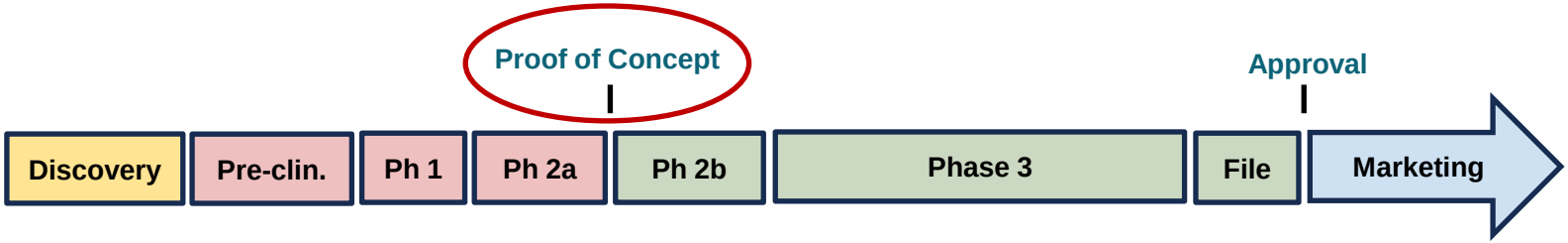
**To stay off critical path, CMC work needs to occur one phase ahead of clinical development. This will require at-risk investments and trade-off decisions.**

| | |
|---|---|
| Continue with enabling technologies? | Invest in process development? |
| Prepare clinical material in advance? | Wait for a positive pre-clinical/clinical result? |
| Time | Cost, resources |

# Late Development and Lifecycle Management

Developing commercially viable manufacturing processes and supporting new markets, indications and product requirements

# Preparing for commercialization and market approval

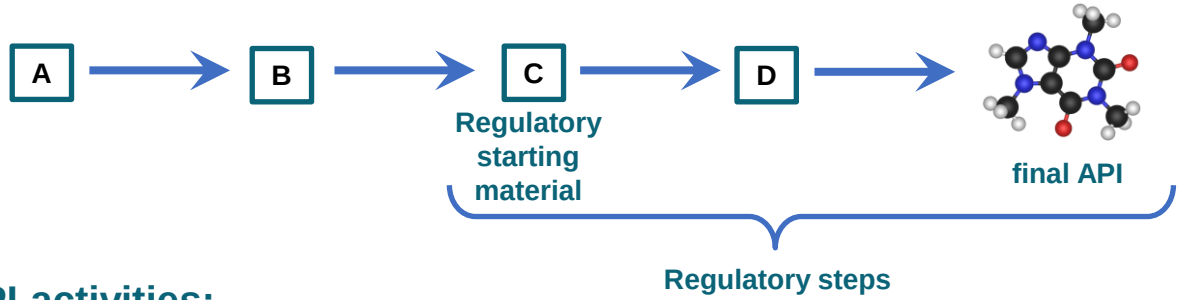



**A positive Proof-of-concept result is an inflection point in drug development**

**The probability of clinical and regulatory success has now increased significantly**

**CMC development shifts towards commercialization and launch readiness**

# API Commercial process development




## Key API activities:

- Final process development – robust, safe, cost effective, sustainable (i.e., Green Chemistry). Lead time can be 2-3+ years.
- Identification of commercial manufacturing site(s) and technology transfer
- Final process, final site API included in Phase 3 trials
- Decisions on the filed regulatory steps (health authority discussion)
- Data generation (batch data, specs, stability, etc.) for regulatory filings
- Process validation prior to launch (typically 3 batches)

# Sustainability

**Sustainability concepts offer environmental *and* economic benefits. Considerations include:**

- Following the 12 Principles of Green Chemistry
- Yield optimization and maximization
- Solvent/volume efficiency (increased reaction concentrations)
- Use of alternate solvents (e.g., water)
- Flow chemistry, continuous manufacturing
- Heavy metal reduction/avoidance
- Less energy intensive processing (lower reaction temperatures)
- Reduction/elimination of toxic waste streams
- For antibiotics, pre-treatment of waste streams

# Drug product commercial process development

## Key formulation activities:

- Final formulation and process development – meeting TPP requirements (lead time can be 1-2+ years)
- Demonstration of bioequivalence
- Identification of commercial manufacturing site(s) and technology transfer
- Final process, final site drug product included in Phase 3 trials
- Data generation (batch data, specs, real-time stability, etc.) for regulatory filings
- Process validation prior to launch (typically 3 batches)

# Considerations in CDMO selection and partnering

**Without internal manufacturing capabilities, effective partnering with Contract Development Manufacturing Organizations (CDMO) is essential for a successful commercial product**

## Considerations and expectations:

- Expect to work with more than one CDMO (no “one size fits all”)
- Geographic location (trouble-shooting, inspections, audits, Market access, etc.)
- Where will the technical oversight and support come from?
- Access to manufacturing documentation and technical reports
- Develop a good relationship with your CDMOs (expect to manage your partner to your desired endpoints and deliverables)
- Release testing – at the CDMO, in-house or other?

- As the sponsor, you will be accountable for the quality of the product

# Post-approval, lifecycle management

**After the primary market approvals and launch, CMC support (and possibly additional new development) will be required throughout a product's life**

**Possible lifecycle activities include:**

- Launching the product in secondary markets
- New presentation (e.g., long-acting)
- New indication(s) requiring a change in formulation (e.g., new dosage strength, fixed-dose combination)
- Regulatory file updates (e.g., minor process changes, shelf-life extensions)
- 2nd Generation process improvements
- Supply chain changes (e.g., adding/removing a CDMO)

# Key CMC development takeaways

- With advance planning and at-risk investment, CMC can avoid being on critical path
- There are important CMC decisions that need to be carefully considered and taken early to allow for successful drug development
- Trade-off decisions (balancing time, resources and expense) will be required and are unique to each product and the business environment
- Speed is the driver in Early development, to support rapid decision-making. Late development focus is directed towards optimization and commercialization.
- Quality underpins all CMC activities throughout a product's entire life

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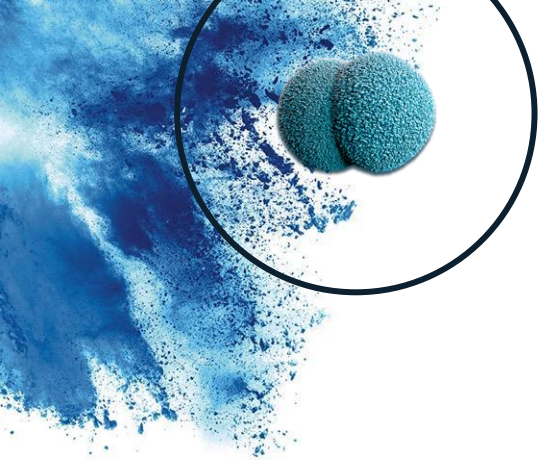
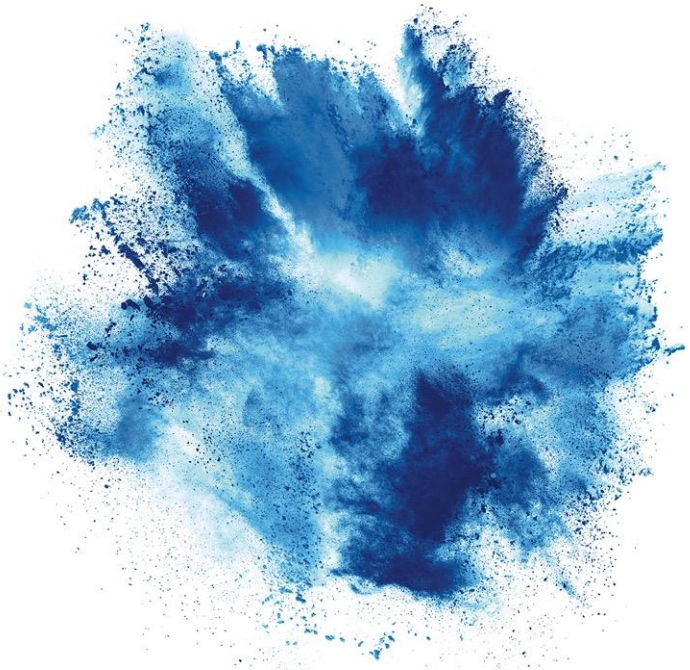


# Thank you



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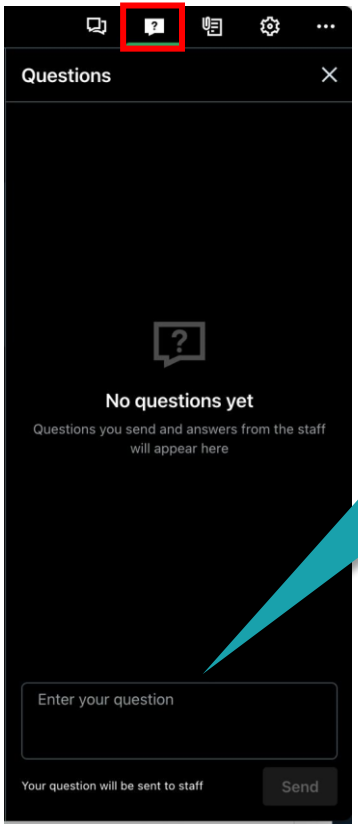
# How to submit your questions

If your question is addressed to a specific speaker, please include their name when submitting the question.




The presentation will be followed by an interactive Q&A session.

Please submit your questions through the box provided after clicking the ‘questions’ button. We will review all questions and respond to as many as possible after the presentation.

# Today’s speakers

## An introduction to antibiotic research and development (R&D)

**Alan Hennessy**
Discovery & Exploratory Team Lead
*GARDP (Switzerland)*

**Mo Yin**
Consultant, ADVANCE-ID
*National University Hospital (Singapore)*

**Herbert Wetli**
Head of Pharmaceutical Development
GARDP *(Switzerland)*

**Moderator:**
**Rosemary Dorrington**
DSI/NRF SARChI Professor:
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# Antimicrobial Chemotherapy Conference

## 4-5 February 2025 | Online conference

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