GARDP

Global Antibiotic Research & Development Partnership

A joint DND*i* / WHO initiative

ACCOMPANYING NOTES TO REVIVE WEBINAR:

ANTIBACTERIAL DRUGS: CLINICAL DEVELOPMENT FOR NON-DEVELOPERS TRADITIONAL DEVELOPMENT – TIERS A AND B

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Introduction

The Global Antibiotic Research & Development Partnership (GARDP) is a not-for-profit research and development organization that addresses global public health needs by developing and delivering new or improved antibiotic treatments, while endeavouring to ensure their sustainable access. Initiated by the World Health Organization (WHO) and the Drugs for Neglected Diseases *initiative* (DND*i*), GARDP is an important element of WHO's Global Action Plan on Antimicrobial Resistance that calls for new public-private partnerships to encourage research and development of new antimicrobial agents and diagnostics.

GARDP's current R&D strategy focuses on developing and delivering antibiotics for paediatric infections, neonatal sepsis, and sexually-transmitted infections as priority areas of global public health need. The decision to focus on these is based on a prioritization framework that considers the intersection between priority pathogens identified by WHO; specific populations' health needs; and individual diseases and syndromes alongside targeting indications less likely to be developed by other actors.

In addition, GARDP's transversal R&D work to recover knowledge, data, and assets of forgotten or abandoned antibiotics aims to recover candidates and identify new ones for pre-clinical or clinical development to further support its priority areas. GARDP has also created REVIVE to support and connect the antimicrobial R&D community by developing educational events and materials, collating open-access resources, and helping researchers get in touch with each other.

Antibacterial drugs: clinical development for non-developers traditional development – tiers A and B with David Shlaes was the first in a series of REVIVE webinars and is available here. The recording also includes a question and answer session.

If you have questions or comments about this content, please let us know in the REVIVE forum. We will do our best to provide an answer to your questions.

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CAVEATS

- This series of webinars is aimed at providing a perspective upon prioritization based on clinical development risk today
- Under current regulations, there is a high probability that drugs discovered today will not enter the marketplace for at least eight years

Discovery and risk

Every decision made during the discovery phase has a potential effect on the risk that any resulting product will make it to market. The **scientific risk** is the greatest:

- Choice of target – some targets are easier to drug than others
- How to evaluate screening hits and what assays are required to move them forward
- Optimization strategy once a lead was chosen
- Preclinical risk during first safety studies of leads

All of these decisions affect the risks of later clinical development.

Although the greatest risk is during the discovery phase where the vast majority of projects will fail, it is important to understand that there is also a **clinical risk:**

- Failure rate during clinical trials about 80-90% overall
- In the case of antibacterial drugs, this is most often due to unforeseen toxicity or secondary effects (infusion pain, phlebitis, gastro-intestinal (GI) intolerance, etc.)
- Another risk is a lack of efficacy which might be due to
    - Poor dose selection
    - Unanticipated poor pharmacokinetics (PK)
    - Rapid emergence of resistance

Given our ability to predict pharmacokinetics in people based on animal studies, appropriate dosing, and the emergence of drug resistance, these problems should not lead to clinical failure today.

Developing a strategy

One of the most important things to do before embarking on a new discovery project, is to know where you are going.

- Understand **medical need** today but, as drugs developed today will not come to the market for at least eight years, try to project to needs of the future. To do this, you need to enlist the help of a physician specialized in infectious diseases (ID); preferably one who has an understanding of discovery science.
- Based on this create a **target product profile** (TPP). This can be preliminary or general – but it is important that you can live with it and that you can discipline yourself and your team to fulfil its requirements.

THE TARGET PRODUCT PROFILE

A target product profile (TPP) summarizes the desired R&D outcome (e.g. indications, population, clinical efficacy, safety and tolerability, stability, route of administration, dosing frequency). TPPs can play a central role in the entire drug discovery and development process including effective optimization of drug candidates, decision-making within an organization, design of clinical research strategies, and constructive communication with regulatory authorities. TPPs can, to a certain extent, evolve in the course of the development process. TPPs should be based on medical need.

MEDICAL NEED

WHO priority pathogens[1]:

Priority 1: CRITICAL	Priority 2: HIGH
Acinetobacter baumannii, carbapenem-resistant	*Enterococcus faecium*, vancomycin-resistant
Pseudomonas aeruginosa, carbapenem-resistant	*Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
Enterobacteriaceae, carbapenem-resistant, extended spectrum β-lactamase (ESBL)-producing	*Helicobacter pylori*, clarithromycin-resistant
	Campylobacter spp., fluoroquinolone-resistant
	Salmonellae, fluoroquinolone-resistant
	Neisseria gonorrhoeae, cephalosporin-resistant, fluoroquinolone-resistant

Clinical indications with high unmet need:

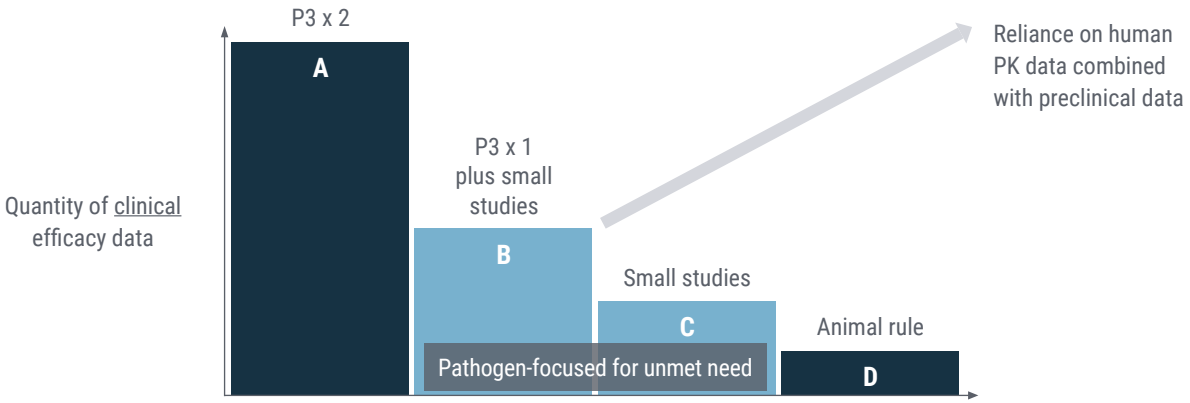
- Hospital-acquired & ventilator-associated pneumonia (HAP/VAP)
- Oral therapy of complicated urinary tract infections (cUTI) in order to prevent the necessity of admitting patients to the hospital for intra venous therapy or to shorten their stay by switching to effective oral therapy.

Basic clinical development pathways

Traditional clinical development pathways have been used for a long time to develop antibiotics. They are the least risky in terms of clinical risk and they are the most straightforward to develop but they require a fair number of patients and a product with a broad or moderately broad spectrum. These pathways will likely not work well for anti-infectives that only target a single species; however, exceptions exist, e.g. Methicillin-resistant *Staphylococcus aureus*.

ADDRESSING UNMET NEED VIA FOUR TIERS

The four tiers of antimicrobial drug development were first described by John Rex and colleagues in 2013[2]. Tier A requires two phase 3 trials and previously, every antibiotic had to be tested in two phase 3 trials for every targeted clinical indication. The other available pathway was tier D. This was developed for diseases that couldn't be studied in humans, such as anthrax. In that case, the drug is tested in an animal model, pharmacokinetics are assessed in people, and the findings from the animal model are bridged to expected results in people based on pharmacokinetics. John Rex and colleagues then proposed intermediate pathways between tier A and tier D which they called tier B and tier C. Tier B includes a phase 3 trial plus one or more other smaller studies, which could be pathogen-focused. Tier C strictly involves smaller studies. To be noted, as the study size is reduced, the risk to encounter problems once the drug gets to the market increases. Nowadays it is very uncommon to conduct two phase 3 trials per indication (current exceptions are Tetraphase and Nabriva). Most other recently developed antibiotics have been based on two trials in different indications or a phase 3 trial plus a small study (Tier B).



Reference: Rex JR et al. Lancet Infect Dis. 2013

The standard, traditional non-inferiority (NI) trial comparing a test article to a "gold standard" comparator is the way most antibiotics have been developed:

- Best for broad-spectrum drugs or for treating staphylococcal infections
- Two trials used to be required for each indication – but –
- Streamlined pathways now exist where a single NI trial per indication is acceptable for antibacterials active against resistant strains or antibacterials which have other properties (improved safety profile) meeting important unmet medical needs

The requirements of the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have evolved considerably in recent years[3,4,5,6]:

FDA pre 2012	FDA post 2012 reboot
In general, two independent NI trials required for each indication.	Single NI trial in ABSSSI plus a single NI trial in CABP - allows for approval in both indications.
Exception - 2 trials in CABP + 1 in HABP	Single NI trial in cUTI plus single NI trial in cIAI - allows for approval in both indications.
NI margins generally 10%	Single NI trial in HABP/VABP plus a trial in a second indication - allows for approval in both.
Exception - HABP - 15-20%	Small, pathogen-specific trials may be allowed. Controls and other parameters for such trials remain to be established for individual products.
AOM, ABS, ABECOPD - placebo controls required	Placebo controls no longer required for AOM.

NI = Non-inferiority; CABP = community acquired bacterial pneumonia; HABP = hospital acquired bacterial pneumonia; ABSSSI = acute bacterial skin and skin structure infection; cUTI = complicated urinary tract infection; cIAI = complicated intraabdominal infection; AOM = acute otitis media; ABS = acute bacterial sinusitis; ABECOPD = acute bacterial exacerabtions of chronic obstructive pulmonary disease

THE NON-INFERIORITY MARGIN

The reason to do non-inferiority trials is because it is statistically impossible to show equivalence. Instead, the aim is to show that the test drug is not inferior to the comparator.

The non-inferiority margin determines the size of the trial (number of patients) and with that, the cost and length of time required to complete. The lower the margin, the greater the number of subjects required. The NI margin required by regulatory authorities is often around 10%.

True or false? If the NI margin is 10%, the test agent can be up to 10% inferior to the comparator drug and still be approved. Answer: It is misleading (at least). Whether one meets the margin is a statistical calculation and may not imply that the test agent is actually 10% inferior to the comparator.

Standardly used margins of FDA and EMA[3,4,5,6]:

Indication	FDA Non-inferiority Margin	EMA Non-inferiority Margin
Skin and skin structure infection	10%	10%
Community-acquired pneumonia	12.5%	10%
Ventilator associated and hospital acquired pneumonia	10%	12.5%
Complicated intra-abdominal infection	10%	10%
Complicated intra-abdominal infection	10%	10%

For innovative antibiotics that would target patients with unmet needs (including those with drug resistant infections), for some indications, the NI margin can increase allowing for a more streamlined trial.

NON-INFERIORITY TRIALS

Restrictions on the use of prior antibiotics and concomitant antibiotics are still problematic in the sense that enrolment is more difficult – especially for trials in pneumonia. But this remains a problem that must be addressed in such trials since prior antibiotics might influence the outcome of the trial. Prospective or early enrolment (also called early consent) might be one approach to work around that. This means, in order to avoid having to enrol a patient in an urgent situation that needs to be treated right away (e.g. HAP), they are pre-enrolled beforehand, agreeing to enrol in the trial in case this urgent situation happens.

Basic clinical development pathways for fixed-dose combinations

Examples for fixed-dose combinations include Trimethoprim-sulfamethoxazole (TMP-SMX) and β-lactam (BLA)-β-lactamase inhibitor (BLI) combinations. For such combinations, non-inferiority designs are okay.

β-lactam (BLA)- β-lactamase inhibitor (BLI):

The BLI must have strong protective effect on the BLA in vitro (and, so far, it always has been the case for the ones which were marketed). For use in daily practice, you will need to show efficacy against BLA-resistant infections who respond to the BLA-BLI combination (where the combination is active). A strong pharmacokinetic-pharmacodynamic (PK/PD) data package supports the argument.

Another pathway available in the US (not Europe) is FDA 505(b)(2)[7]. This provision expressly permits FDA to rely, for approval of a new drug application (NDA), on data not developed by the applicant (e.g. published literature, the Agency's finding of safety and effectiveness for an approved drug). This was done twice, once for meropenem-vaborbactam where meropenem was the previously approved drug, and once for ceftazidime-avibactam, where ceftazidime was the previously approved drug.

Activity of β-lactamase inhibitors against various β-lactamase enzymes[8]:

	Inhibitory activity of ß-lactamase-inhibitors, IC_{50} (µM)	
β-lactamase	**Tazobactam**	**Avibactam**
TEM-1	0.01	0.01
KPC-2	43	0.17
SHV-1	0.07	NR
SHV-4	0.06	0
SHV-5	0.01	NR
CTX-M15	0.01	0.01
AmpC (*P. aeruginosa*)	1.49	0.13
P99	12	0.1
Oxa (*A. baumannii*)	58	NR

NR = not reported

Impact of β-lactamase inhibitors on MIC[8]:

	Minimum inhibitory concentration MIC_{90} (µg/ml)	
Pathogen	**Ceftazidime**	**Ceftazidime-avibactam**
***E. coli* ESBL**	32	0.5
***K. pneumoniae* ESBL**	>32	2
***K. pneumoniae* non-susceptible to carbapenem**	>32	2
***E. cloacae* ceftazidime-resistant**	>32	2
***Enterobactereaceae* multiple β-lactamases**	>256	4

Tier B

Tier B requires an innovative drug that meets an unmet clinical need, such as resistance. This may involve a single NI trial in a traditional indication (e.g. UTI) plus a single trial in a second traditional indication (e.g. intraabdominal infection) or a single trial that may target resistant pathogens (tier C). But in that case, the label will be more restrictive in a sense that it will restrict treatment to patients who have few options. This was the case for both, for the approvals of ceftazidime-avibactam originally, and now for meropenem-vaborbactam.

Example 1 – ceftazidime-avibactam:

- This combination was approved by FDA based on two phase 2 trials: complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI) FDA 505(b)(2).
- 25% of the infections were due to ceftazidime-resistant organisms and the combination was effective in the vast majority of these cases.
- Later, multiple phase 3 NI trials in traditional indications including hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) and a ceftazidime-resistant infection trial comparing to best available therapy in patients in a NI design (REPRISE)[9]
- This is one example for using a tier B pathway to get a drug approved earlier.

Example 2 – plazomicin:

- The company, Achaogen, designed two trials:
  - Single NI trial in cUTI
  - A superiority design trial studying the effect of plazomicin in patients with infections (bloodstream infections (BSI) and HABP/VABP) caused by highly resistant *Enterobacteriaceae*
- The superiority study did not lead to FDA approval for BSI and HABP/VABP – but the company did receive approval for cUTI based on their single trial.

DOES A DRUG NEED TO BE STUDIED IN THE CONTEXT OF HIGHLY RESISTANT BACTERIA?

From a regulatory point of view the answer is no. Studies in usually encountered resistance within the context of a standard clinical trial are acceptable. In vitro data and PK/PD data help to make the argument that the test agent is active against resistant infections clinically.

However, commercially it might be important to have at least some infections with highly resistant organisms studied in order to explain the efficacy of the drug to physicians as they might not be convinced by a PK/PD argument. But these studies do not necessarily have to be pivotal for registration.

Conclusions

- Non-inferiority (NI) trial designs are a necessary and essential part of antibiotic development today.
- Modern design NI studies conducted in the setting of 'usual drug resistance' (UDR) vs. a high-quality comparator produce reliable data.
- Strong in vitro data and complete PK/PD data sets are of increasing importance in allowing streamlined NI studies to take place.
- These trials are the lowest risk designs allowing for antibacterial drug approval
    - But they require relatively broad-spectrum drugs such that trials are feasible
    - Or they must target specific pathogens that are very frequent causes of infection such as MRSA

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