Written responses to open questions of the webinar 'An introduction to antibiotic research and development (R&D)' by Alan Hennessy (speaker), Mo Yin (speaker), Herbert Wetli (speaker), and Rosemary Dorrington (moderator) originally broadcast on 19 September 2024.

See the recordings of the presentations here: https://revive.gardp.org/an-introduction-to-antibiotic-rd/

Question asked	Response from the speakers
Are there any leads or products that target restoring antimicrobial sensitivity to a drug?	Yes, the beta-lactamase inhibitor class has been commercialized and also has several clinical candidates. The beta-lactamase inhibitor is paired with an appropriate beta-lactamase to restore its effect. There are only research phase agents from other classes e.g., efflux inhibitors.
Alan: what efforts are put in understanding better resistance itself (mechanisms, evolution, impact, transmission) and to what extent do you think this knowledge could help designing new efficient antibiotics?	There is extensive literature on all aspects of antimicrobial resistance and designing new antibiotics with this in mind is crucial. Such as determining which strains to screen against to estimate the eventual utility of the new agent.
Do you have any insights regarding the threat of multi-resistant fungal pathogens?	Due to time constraints, this was not covered in the webinar but here is a useful place to start: WHO fungal priority pathogens list to guide research, development and public health action
What are the panel's thoughts on developing NCEs using an old class of antibiotics? Will an NCE with better safety or improved resistance profile than older SoC, not be associated with significantly less risk? (both during discovery/development phases, CMC, and importantly for investors)	Several generations of the major classes of antibiotics have already been developed e.g., fourth-generation fluoroquinolones or 4th generation cephalosporin all with improvements in certain aspects over earlier options in terms of spectrum, toxicity, route of administration etc. While more products may very well still be possible with this route, there are mechanisms of resistance which are general to the entire class and may be challenging for any new analogue to overcome.
As WHO indicated, there is an increase in resistance to multiple pathogens to the vast majority of antibiotics. What can we do better to avoid this issue in the future and what must we focus on in respect to drug discovery?	Prevention of infection, monitoring of usage, accurate diagnosis are some aspects needed to protect overuse/inappropriate usage of current and future antibiotics. As discussed in the talk, all stages of the drug discovery pipeline require replenishment.
Herbert: What legislation currently exists for implementing green chemistry? Is it guidance or is it strictly enforced?	Available guidances and ISO standards are not mandatory, they are only recommended. For example: - PSCI (pscinitiative.org) - Guidance on wastewater and solid waste management for manufacturing of antibiotics (who.int)

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	- ISO - Building a sustainable path to ESG reporting
Alan: The research into new therapeutics in academia seems quite inefficient if not being carried out in commercial partnerships or in a large institution. Has any effort been made to form links between smaller academic institutions that currently do great work in a detached manner to produce a pipeline.	There continues to be fantastic work done by all types of organisations in AMR – from academia to biotech to pharma. Continuing to link this work together, especially in the pre-competitive space would be beneficial to the whole discovery community.
How should we modify DBO core to act more sensitively to restore parent beta lactams?	Avibactam and relebactam are two commercialized examples from this class while several others are in clinical development.
Mo: ACORN is a very helpful standardized protocol for surveillance. Do you see a role for this protocol in forming the basis of standardizing indicators for post-market and implementation science studies also?	ACORN is an individual-based surveillance study for the main purpose of quantifying attributable mortality for multidrug-resistant bacterial infections. If standardized, this can be a useful tool for various interventions targeting AMR including post-market and implementation science studies.
Herbert: What are some of the ways that new medicines can be made affordably?	There are various approaches, the below list is not exhaustive: a) Increase of the batch size b) Improve the manufacturing robustness to reduce the number of scrapped batches c) Improve the manufacturing process to increase the yields d) Selection of more affordable raw materials, consumables and packaging materials e) Working in manufacturing campaigns f) Transfer to more affordable manufacturing sites; however, this is only recommended if the longevity of the product is ensured since a transfer means a lot of costs, resources and risks. In this case, a return of investment calculation should be prepared very carefully.
Alan: What organisations are most active in discovery research at the moment?	In pharma, we still have examples such as Roche, Genentech, Merck, GSK, Shionogi. But with the departure of many other major pharma companies, biotech and academic organisations have filled some gaps. GARDP is an example of a not-for-profit organization which performs its own discovery research. There is an urgent need for more.
Alan: Which approaches (phenotypic screening (natural product or synthetic) or target-based) are most likely to lead to success?	There is no perfect approach and for now there is value in multiple approaches and examples of success from both.

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Alan: Do we need to find many new validated protein targets or concentrate on delivering products from the ones we have?	We need to refill all areas of the pipeline to ultimately deliver novel and diverse solutions to address AMR.
Alan: What is the likely cost of new agents compared to older ones?	To ensure equitable global access to antibacterials, consideration should be given to the likely ultimate costs of products in all geographies. The cost of a small molecule antibacterial may currently be more predictable that new biological modalities where there is greater uncertainty.
Mo: How are non-inferiority trials used in antibiotic development, and what are the key methodological challenges?	Non inferiority trials are increasingly used in antibiotic approval trials because current antibiotics have a high efficacy for antibiotic susceptible infections, and most phase 3 trials include patients with antibiotic susceptible infections. The key challenges are the determination of non-inferiority margin and ensuring robust trial implementation.
Mo: Could you elaborate on the PRACTical design?	The PRACTical design is a noval trial design with allows personalisable randomization lists. The analysis is likened to that of a network meta-analysis.
Mo: What challenges arise when selecting a patient population for efficacy testing in phase 3 trials?	Countries with high AMR burden tend to have low trial capacity. Hence many Phase 3 trials tend to include patients with susceptible infections. This increases the chance of showing non-inferiority.
Herbert: You mentioned that CDMOs can be located in distant geographies. How do you ensure the quality of the deliverables and that the work is done?	By having: a) bi-annual face-to-face meetings with the CDMOs b) quality, technical and development agreements c) regular weekly or bi-weekly virtual calls with the CDMOs d) escalation mechanisms in place in case of serious issues
Herbert: As you explained, chemistry, manufacturing and controls consist of many different disciplines, you mentioned pharmaceutical development, chemical synthesis, pharmaceutical manufacturing and packaging, chemical analytics, etc. How do you manage all of that? Do you have a team?	Yes, you need a multi-disciplinary team to be able to manage these kind of projects. The included functions are: - Pharmaceutical development expert - Analytical chemistry expert - Expert in organic chemistry or process chemistry - Statistician in case of statistical approaches - Packaging engineer (depending on the project)

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