

Strategies for Early R&D: Plumbing, Phase 3, and Durable Value

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NIAID - Early R&D Strategies for Novel Antibacterial and Antifungal Drugs

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Please note these details!

I've put a link to a copy of the slides in the entry for this meeting on the Meetings page of AMR.Solutions: **https://amr.solutions/meetings/**

Slides happily shared … drop me a note!

Executive Summary (& Agenda)



- We really need new antibiotics! Glad you are here!
  - Focus on antibacterials and antifungals: WHO Priority Pathogens
  - We need you to get busy! AMR is killing us!
  - I can't cover everything in 30 minutes!
  - Further resources: Read, Listen, and Learn!
- Attend to the plumbing: Avoid leaks in the pipe(line)
- Anticipate Phase 3: Is your product developable?
- If you build it, will they come? Embed durable value
- Summary

Pathogen (WHO category)	WHO (2017)	Indian* (2021)	CDC (2019)	CDC (2013)	ESKAPE (2008-9)
Acinetobacter baumannii, carbapenem-R	Critical	Critical	Urgent (carbapenem-R)	Serious (MDR)	Yes
Pseudomonas aeruginosa, carbapenem-R	Critical	Critical	Serious (MDR)	Serious (MDR)	Yes
Enterobacteriaceae, carbapenem-R, 3rd-gen ceph-R (ESBL+)	Critical	Critical	Urgent (carbapenem-R) Serious (ESBL+)	Urgent (carbapenem-R) Serious (ESBL+)	Yes
Enterococcus faecium, vancomycin-R	High	High	Serious (VRE)	Serious (VRE)	Yes
Staphylococcus aureus, methicillin-R, vancomycin-I/R	High	High	Serious (MRSA)	Serious (MRSA) Concerning (VRSA)	Yes
Helicobacter pylori, clarithromycin-R	High				
Campylobacter spp., fluoroquinolone-R	High		Serious (drug-R)	Serious (drug-R)	
Salmonellae spp., fluoroquinolone-R	High	High (drug-R)	Serious (drug-R, Typhi & non-typhoidal)	Serious (drug-R)	
Neisseria gonorrhoeae, 3rd-gen ceph-R, fluoroquinolone-R	High		Urgent (drug-R)	Urgent (drug-R)	
***Neisseria meningitidis*, 3rd-gen ceph-R, fluoroquinolone-R**		Medium			
Streptococcus pneumoniae, penicillin-NS	Medium	Medium	Serious (drug-R)	Serious (drug-R)	
Haemophilus influenzae, ampicillin-R	Medium	Medium			
Shigella spp., fluoroquinolone-R	Medium	Medium	Serious (drug-R)	Serious	
Staphylococcus, coagulase-neg, Van/Lzd-R		Medium			
Clostridium difficile			Urgent	Urgent	
Candida spp. fluconazole-R			Urgent (C. auris) Serious (Drug-resistant)	Serious (Flu-R)	
M. tuberculosis			Serious (drug-R)	Serious (drug-R)	
Group A *Streptococcus*			Concerning (erythro-R)	Concerning (erythro-R)	
Group B *Streptococcus*			Concerning (clinda-R)	Concerning (clinda-R)	
Aspergillus fumigatus			Watch (azole-R)		
Mycoplasma genitalium			Watch (drug-R)		
Bordetella pertussis			Watch (drug-R)		

*Note that the Indian PPL sometimes differs slightly from WHO in terms of precise patterns of qualifying R.

Priority Pathogen Lists compared
https://amr.solutions/pathogens-and-pipelines/
Last updated 18 Mar 2021

Pathogen (WHO category)	WHO (2017)	Indian* (2021)	CDC (2019)	CDC (2013)	ESKAPE (2008-9)
Acinetobacter baumannii, carbapenem-R	Critical	Critical	Urgent (carbapenem-R)	Serious (MDR)	Yes
Pseudomonas aeruginosa, carbapenem-R	Critical	Critical	Serious (MDR)	Serious (MDR)	Yes
Enterobacteriaceae, carbapenem-R, 3rd-gen ceph-R (ESBL+)	Critical	Critical	Urgent (carbapenem-R) Serious (ESBL+)	Urgent (carbapenem-R) Serious (ESBL+)	Yes
Enterococcus faecium, vancomycin-R	High	High	Serious (VRE)	Serious (VRE)	Yes
Staphylococcus aureus vancomycin-I/R					Yes
Helicobacter pylori,					
Campylobacter spp.					
Salmonellae spp., fl					
Neisseria gonorrhoe fluoroquinolone-R					
Neisseria meningiti fluoroquinolone-R					
Streptococcus pneu					
Haemophilus influe					
Shigella spp., fluoro					
Staphylococcus, coa					
Clostridium difficile					
Candida spp. fluconaz					
M. tuberculosis			Serious (drug-R)	Serious (drug-R)	
Group A *Streptococcus*			Concerning (erythro-R)	Concerning (erythro-R)	
Group B *Streptococcus*			Concerning (clinda-R)	Concerning (clinda-R)	
Aspergillus fumigatus			Watch (azole-R)		
Mycoplasma genitalium			Watch (drug-R)		
Bordetella pertussis			Watch (drug-R)		

#AMRSOS! GRAM Report: "At Least 1.27m Deaths/Year Directly Attributable To AMR"

Murray et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet: https://doi.org/10.1016/S0140-6736(21)02724-0

*Note that the Indian PPL sometimes differs slightly from WHO in terms of precise patterns of qualifying R.

Priority Pathogen Lists compared
https://amr.solutions/pathogens-and-pipelines/
Last updated 18 Mar 2021

The entire P3 pipeline… *fits on one slide*



Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Expected activity against priority pathogens				Innovation			
					CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Solithromycin (T-4288)	NDA[2]	Macrolide	iv & oral	iFUJIFILM Toyama Chemical	/	/	/	●[1]	-	-	-	-
Sulopenem, Sulopenem etzadroxil/ probenecid	NDA[3]	β-Lactam (penem)	iv & oral	Iterum	○	○	○[4]	/	-	-	-	-
Durlobactam (ETX-2514) + sulbactam	3	DBO-BLI/PBP2 binder + β-lactam-BLI/PBP1,3 binder	iv	Entasis	●	○	○	/	-	-	-	-
Taniborbactam (VNRX-5133) + cefepime	3	Boronate BLI + β-lactam (cephalosporin)	iv	VenatoRx/ GARDP	○	●	●	/	?	✓	-	-
Enmetazobactam (AAI-101) + cefepime	3	BLI + β-lactam (cephalosporin)	iv	Allecra	○	○	○[5]	/	-	-	-	-
Zoliflodacin	3	Spiropyrimidenetrione (topoisomerase inhibitor)	oral	Entasis/GARDP	/	/	/	●[1]	✓	✓	-	✓
Gepotidacin	3	Triazaacenaphthylene (topoisomerase inhibitor)	iv & oral	GSK	/	/	/	●[1]	?	✓/?[6]	-	✓
Nafithromycin (WCK-4873)	3	Macrolide	oral	Wockhardt	/	/	/	●[1]	-	-	-	-
Benapenem	2/3	β-Lactam (carbapenem)	iv	Sichuan Pharmaceutical	○	○	○	/	-	-	-	-

Butler et al. 2022 Antimicrob Ag Chemother (doi:10.1128/AAC.01991-21)

The entire P3 pipeline… *isn't very broad*



Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Expected activity against priority pathogens				Innovation			
					CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Solithromycin (T-4288)	NDA[2]	Macrolide	iv & oral	iFUJIFILM Toyama Chemical	/	/	/	●[1]	-	-	-	-
Sulopenem, Sulopenem etzadroxil/ probenecid	NDA[3]	β-Lactam (penem)	iv & oral	Iterum	○	○	○[4]	/	-	-	-	-
Durlobactam (ETX-2514) + sulbactam	3	DBO-BLI/PB β-lactam-BLI/PBP1,3 binder			●	○	○	/	-	-	-	-
Taniborbactam (VNRX-5133) + cefepime	3	Boronate BLI + β-lactam (cephalosporin)	iv	VenatoRx/ GARDP	○	●	●	/	?	✓	-	-
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Gepotidacin	3	Triazaacenaphthylene (topoisomerase inhibitor)	iv & oral	GSK	/	/	/	●[1]	?	✓/?[6]	-	✓
Nafithromycin (WCK-4873)	3	Macrolide	oral	Wockhardt	/	/	/	●[1]	-	-	-	-
Benapenem	2/3	β-Lactam (carbapenem)	iv	Sichuan Pharmaceutical	○	○	○	/	-	-	-	-

Acinetobacter baumannii

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Solithromycin (T-4288)	NDA[2]	Macrolide	iv & oral	iFUJIFILM Toyama Chemical	/	/	/	●[1]	-	-	-	-
Sulopenem, Sulopenem etzadroxil/ probenecid	NDA[3]	β-Lactam (penem)	iv & oral	Iterum	○	○	○[4]	/	-	-	-	-
Durlobactam (ETX-2514) + sulbactam	3	DBO-BLI/PBP2 binder + β-lactam-BLI/PBP1,3 binder	iv	Entasis	●	○	○	/	-	-	-	-
Taniborbactam (VNRX-5133) + cefepime	3	Boronate BL (cephalospo			○	●	●	/	?	✓	-	-
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Benapenem	2/3	β-Lactam (carbapenem)	iv	Sichuan Pharmaceutical	○	○	○	/	-	-	-	-

Carbepenem-R
P. aerug, Enterobacteriaceae

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The entire P3 pipeline… *isn't very novel*



Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Expected activity against priority pathogens				Innovation			
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Solithromycin (T-4288)	NDA[2]	Macrolide	iv & oral	iFUJIFILM Toyama Chemical	/	/	/	●[1]	-	-	-	-
Sulopenem, Sulopenem etzadroxil/ probenecid	NDA[3]	β-Lactam (penem)	iv & oral	Iterum	○	○	○[4]	/	-	-	-	-
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Taniborbactam (VNRX-5133) + cefepime	3	Boronate BLI + β-lactam (cephalosporin)	iv	VenatoRx/ GARDP	○	●	●	/	?	✓	-	-
Enmetazobactam (AAI-101) + cefepime	3	BLI + β-lactam (cephalosporin)	iv				○[5]	/	-	-	-	-
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Gepotidacin	3	Triazaacenaphthylene (topoisomerase inhibitor)	iv & oral	GSK	/	/	/	●[1]	?	✓/?[6]	-	✓
Nafithromycin (WCK-4873)	3	Macrolide	oral	Wockhardt	/	/	/	●[1]	-	-	-	-
Benapenem	2/3	β-Lactam (carbapenem)	iv	Sichuan Pharmaceutical	○	○	○	/	-	-	-	-

Novel chemical class

Butler et al. 2022 Antimicrob Ag Chemother (doi:10.1128/AAC.01991-21)

The entire P3 pipeline… *isn't very novel*

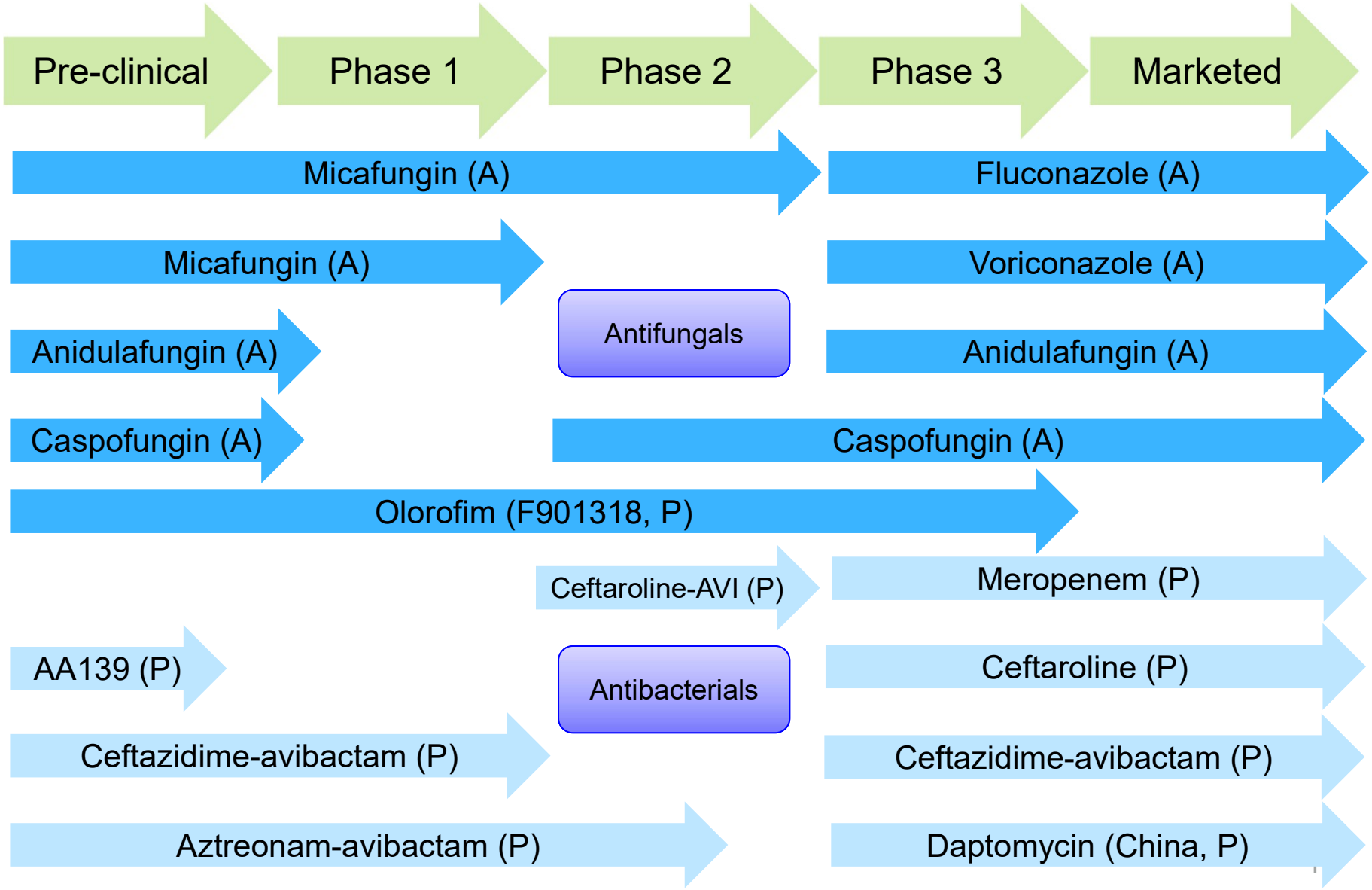


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Taniborbactam (VNRX-5133) + cefepime	3	Boronate BLI + β-lactam (cephalosporin)	iv	VenatoRx/ GARDP	○	●	●	/	?	✓	-	-
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Benapenem	2/3	β-Lactam (carbapenem)	iv	Sichuan Pharmaceutical	○	○	○	/	-	-	-	-

Novel MoA

Butler et al. 2022 Antimicrob Ag Chemother (doi:10.1128/AAC.01991-21)

At heart, I'm an ID doc who wants new antibacterials and antifungals. My comments come from this experience:



Rex JH - Drug Development History, (A)cademia & (P)harma

Scope, Disclosures



- This workshop is good start, but there's more to learn!
  - **Read & listen**: See materials on the next slide
  - Patrice Courvalin's **ICARe course** is a great jump-start opportunity
    - https://www.icarecourse.org/
  - *(blatant plug)* Subscribe to the (free!) **AMR.Solutions newsletter**
- Non-traditional approaches *are* encompassed
  - They follow the same pathways as any other agent
  - But they are confusing! See materials on next slide for a deep dive
- Finally, and for avoidance of doubt, note that I work at a company that has novel antifungal in development (F901318, olorofim)
  - I won't be discussing it at all today
  - But, I will note that new antifungals are needed and their development follows the same principles as antibacterial R&D!

Read, Listen, & Learn



- FDA guidances
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents
    - Set filters to Organization = "Center for Drug Research and Evaluation" and Topic = "Clinical Antimicrobial
  - In particular, be sure to review the Unmet Need and LPAD guidances. See also the newsletter cited below for the EMA guidances.
- FDA Advisory Committees: Attend or listen by webcast to **every AdComm**. These are free master classes. I can't emphasize this one strongly enough.
- EMA guidances
  - These have been re-arranged/updated … please see this 27 May 2022 newsletter for a tour: https://amr.solutions/2022/05/27/antibacterial-guidance-including-pediatrics-parallel-emafda-updates/
- Papers
  - Rex, Talbot et al. Progress in the fight against multidrug-resistant bacteria 2005-2016: Modern non-inferiority trial designs enable antibiotic development in advance of epidemic bacterial resistance. CID. 2017;65:141-6.
  - Boucher, Ambrose, et al. White Paper: Developing Antimicrobial Drugs for Resistant Pathogens, Narrow-spectrum Indications, and Unmet Needs. JID. 2017;216:228-36.
  - Hope, Drusano, & Rex. Pharmacodynamics for antifungal drug development: an approach for acceleration, risk minimization and demonstration of causality. JAC 2016;71(11):3008-19.
  - Rex JH, Fernandez Lynch H, Cohen IG, Darrow JJ, Outterson K. Designing development programs for **non-traditional antibacterial agents**. Nature Communications. 2019;10(1):3416.
- Prior meetings
  - 8 Sep 2016: FDA workshop: "Facilitating Antibacterial Drug Development for Patients with Unmet Need and Developing Antibacterial Drugs that Target a Single Species" https://www.fda.gov/drugs/news-events-human-drugs/facilitating-antibacterial-drug-development-patients-unmet-need-and-developing-antibacterial-drugs . Note here the discussion of Drug X-1, a narrow-spectrum agent for P. aeruginosa
  - 2017 GARDP + CARB-X Bootcamp on CMC: https://amr.solutions/2017/09/06/summary-slides-video-from-the-carb-x-gardp-bootcamps-5-8-sep-2017-asm-escmid-conference/
  - 14 May 2018: Duke-Margolis workshop on **Non-Traditional Antibiotics**: https://amr.solutions/2018/05/14/14-june-duke-margolis-workshop-a-taxonomy-for-non-traditional-non-fleming-antimicrobials/
  - 21-22 Aug 2018: FDA workshop: "**Non-Traditional** Therapies for Bacterial Infections" https://amr.solutions/2018/08/23/fda-workshop-on-non-traditional-antibacterials-21-22-aug-2018/ . See discussion of Z-3, a hypothetical compound for prevention of acquisition of resistance.
  - 29 Mar 2019: AAC Podcast on "Developing **Non-Traditional Antibiotics**": https://www.youtube.com/watch?v=9YKb_RWx1MA

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Executive Summary (& Agenda)



- We really need new antibiotics! Glad you are here!
- Attend to the plumbing: Avoid leaks in the pipe(line)
  - Manufacturing, PK, ADME, PK-PD, Toxicology, Clinical, Regulatory
- Anticipate Phase 3: Is your product developable?
- If you build it, will they come? Embed durable value
- Summary

Biology: The role of Academia



Drakeman 2014[1]: Origins of priority review NMEs, 1998-2012

Sector	NBEs	NCEs	Fast track
Biotech	24 (92%)	65 (48%)	49 (70%)
Pharma	2 (8%)	71 (52%)	21 (30%
Totals	26	136	70

In short, **small companies** (often launched from academic insights) **really power the pharmaceutical industry**.

But, the move from Biology to Pharmaceuticals is a big leap!

[1]Drakeman DL. Benchmarking biotech and pharmaceutical product development. Nat Biotechnol. 2014;32(7):621-5.
NME = New Molecular Entity; NBE = New Biological Entity; NCE = New Chemical Entity

The big question: Is it a drug?

- It's easy to kill bacteria and fungi
  - Steam, fire, and bleach are very effective
- **Selective killing is a subtle art**
  - Good checklist: AAC Instructions to Authors
    - https://journals.asm.org/journal/aac/scope
  - This 3-part newsletter series on halicin
    - https://amr.solutions/2020/02/21/chemicals-vs-drugs-the-end-of-bacitracin-the-buzz-around-halicin/
    - https://amr.solutions/2020/02/24/chemical-vs-drugs-part-2-how-do-you-discriminate-more-on-halicin/
    - https://amr.solutions/2020/02/25/chemicals-vs-drugs-part-3-xkcd-has-the-final-word/



- Let's take a brief tour of key points
  - *Invisible from the outside, Pharma has a lot of important plumbing!*

Image reproduced with permission from https://xkcd.com/1217/.

Can you make it? CMC[1]



- How does a molecule become a physical medicine (tablet, injectable, etc.) to give to a human?
- You must plan for
  - Early materials for preclinical studies
  - GMP (Good Manufacturing Practice) materials for human studies
  - Sufficient quantity at scale & on stability for Ph3 and registration
- **This is a science unto itself**
  - In parallel with the NDA/MAA (you've heard of those), you also file a dossier on the manufacturing process that is of equal length
- Advice: Start early! Have a CMC guru on your team
  - Great CARB-X + GARDP workshop from 2017 on this:
  - Search for "amr.solutions 2017 bootcamp"

[1]Chemistry, Manufacturing, & Controls

What dose? PK, ADME, and PD



- PK: Where does it go? What happens to it?
  - ADME: Absorption, Distribution, Metabolism, and Excretion
  - Does it go to the right body compartments?
  - Will it be easy to use? How many doses/day? Is it (can it be) oral?
  - Does it have (is it likely to have) drug-drug interactions?
  - **You can't really know the answers in detail until P1**, but you can make guesses once you have some PK in some animal species
- PD (Pharmacodynamics): What concentration do you need?
  - Strong PK-PD is the reason a smaller trial program is acceptable proof of drug utility
  - Deciding on a target exposure is a subtle art. There are talks on this during the workshop; For other ideas see Hope 2016.[1] It's focused on antifungals, but the ideas do generalize

1. Hope W, Drusano GL, Rex JH. Pharmacodynamics for antifungal drug development: an approach for acceleration, risk minimization and demonstration of causality. JAC 71:3008-19, 2016

Is it safe? Toxicology (1 of 2)



- You need to study supratherapeutic exposures of new agent *and its metabolites* in 2 animal species
- Serious infections often require prolonged therapy: **your studies must span relevant periods**
  - 0-90 days of exposure: day-for-day coverage in man
  - 180-270 days: enough for indefinite exposure
- Metabolites can be tricky. You can try to predict human metabolites but you don't *know* until Ph1
  - Sometimes you have to do additional studies
  - Forewarned is forearmed. Be sure your investors know!

Is it safe? Toxicology (2 of 2)





- Don't panic! *Everything* has toxicity
  - But, take it seriously – toxicity is the main cause of failure in the clinical stages of development
  - **See Prasad AAC 2022 "Leaks in the Pipeline"** and this newsletter
    - https://amr.solutions/2022/06/14/leaky-pipelines-when-is-a-molecule-a-drug/
- Your job is to triangulate three things
  - Exposure that you think is required (PK-PD is your guide)
  - The nature of the toxicity (monitorable? reversible?)
  - The Unmet Need you are addressing
- This is your first look at benefit-risk (B-R)!
  - B-R needs be B >>>>>> R for uncomplicated UTI
  - B-R can (perhaps) be B ≥ R for cure of endocarditis
    - It depends on the nature of the Risk
- Advice: Have a PK-PD expert & a medic on your tox team

How will you develop it?



- Get help!
  - Clinical Operations: Making things happen at sites
  - Clinical: Medical advice on what's possible
  - Regulatory: Rules of the road
- It may seem like this things are a long way off…
  - But, early advice in these disciplines will pay off
  - FDA & EMA are willing to advise as well

Executive Summary (& Agenda)



- We really need new antibiotics! Glad you are here!
- Attend to the plumbing: Avoid leaks in the pipe(line)
- Anticipate Phase 3: Is your product developable?
  - Sadly, cool science is not enough!
  - The SSSS test
  - Narrow-spectrum and/or rare? *Proceed carefully*
  - Indirect effects? *Proceed **VERY** carefully*
- If you build it, will they come? Embed durable value
- Summary

The Bad News

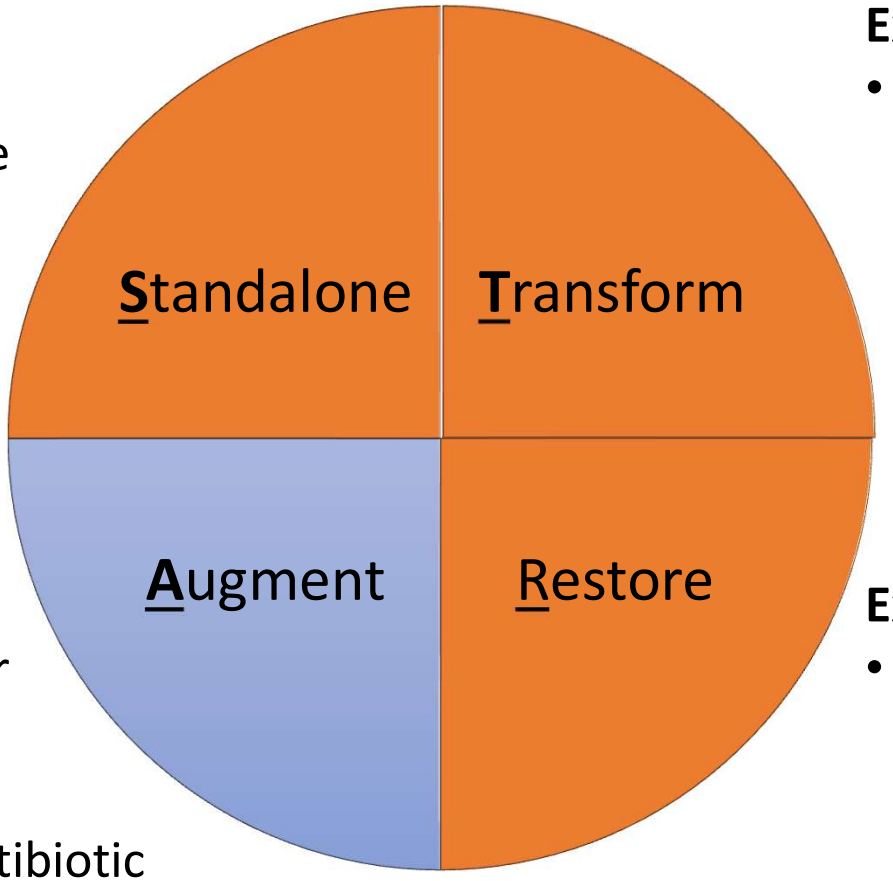


- Cool Science ≠ Developable Product
  - Necessary, but not sufficient
- Why? Don't we need New Drugs for Bad Bugs?
  - Yes, but it is very hard to study Bad Bugs on their own
- Generally easy: Product meets the SSSS test:
  - Has the **spectrum** for a defined **syndrome** and the **speed** required to be suitable as the **sole therapy**
  - Key idea: **Most therapy must treat an entire syndrome**
    - Unless the organism *is* the infection (e.g., TB), **it is not always obvious what bacteria is causative**
    - The initial treatment needs to cover all likely causes
- **Everything else: BIG challenges**

STAR: Four treatment archetypes[1]

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Examples
- Traditional small molecule
- Phage
- Antisense



Example
- Gram-negative activity from colistin + approved Gram-positive antibiotic

Example
- Virulence factor inhibitor or anti-toxin antibody + approved antibiotic

Example
- BL-BLI (Beta-lactam beta-lactamase inhibitor) combinations

1. Rex et al. Designing development programs for **non-traditional antibacterial agents**. Nature Communications. 2019;10(1):3416.

Standalone, Transform, and Restore: *Direct activity*



- Has the speed and spectrum to be the sole therapy
- Examples:
  - **Standalone (NEW on its own):**[1] Phage, lysins, antisense, and (of course) standard small molecules
  - **Transform:** NEW added to 2nd agent not otherwise active on the target (e.g., polymyxin + known Gram-positive agent where combo has Gram-negative activity)
  - **Restore:** BL-BLI
- In each case, an entity complete in itself
  - Even if it has more than one component
  - Usually has an MIC
- Key advantage: Standard NI trials[2] can be used

1. This would also describe ANY new mechanism standalone molecule, small or large.
2. NI = Non-inferiority trials. I just do not have time today to go into trial designs and the deep topic of non-inferiority vs. superiority!!
   Please see https://amr.solutions/2020/09/19/in-praise-of-non-inferiority/ and its related YouTube video: https://youtu.be/dx9mrQfSNT4

Narrow-spectrum problem (1 of 2)



- Narrow-spectrum antibiotics require a setting where activity for a specific pathogen **can be seen in isolation**. There are 3 possible patterns:
- Pattern A: Organism = Syndrome (*N. gonorrhoeae*)
  - Other examples: TB, Salmonella, etc. Never normal to carry these!
  - Diagnostic can select; Straightforward study design
- Pattern B: Organism appears within a syndrome **and** symmetrical gaps in the spectrum of existing agents make it possible to show activity of NEW:
  - Example: ertapenem[1] does not cover *P. aeruginosa*. So, NEW + ertapenem vs. imipenem shows activity of NEW.
  - Low rate of *P. aeruginosa* is the remaining problem
  - A diagnostic could support selective enrollment

Ertapenem is a carbapenem that lacks activity against Pseudomonas aeruginosa. Imipenem is a carbapenem that DOES cover P. aeruginosa. So, you could say that ertapenem has a Pseudomonas-sized hole in its spectrum relative to imipenem. See also link to a workshop on Drug X-1 on the "Read, Listen, and Learn" slide, a hypothetical narrow-spectrum agent for *P. aeruginosa*

Narrow-spectrum problem (2 of 2)



- Pattern C: Organism is one of several causes of a syndrome and **existing agents often cover it**
  - Ex: *Klebsiella* as a component of cIAI & pneumonia
  - Therapy in these conditions is **syndromic**
  - There is a strong desire for therapy that covers all likely pathogens
- **Danger, Danger, Will Robinson!**
  - **ALERT: This is a HARD problem ... Be careful!**
  - It will likely be hard to arrange things so that your product can be seen to be active
  - Perhaps you could do this for *E. coli* in UTI
  - **A diagnostic is NOT a reliable fix for this** … it is very hard to know which bug is doing what
  - This difficulty surfaces both during development (hard to run a trial) and in routine care (hard to know when to use the selective agent)
  - And a focus on just MDR *K. pneumoniae* will not fix it (next slide)…

Narrow (and/or Rare): Summary



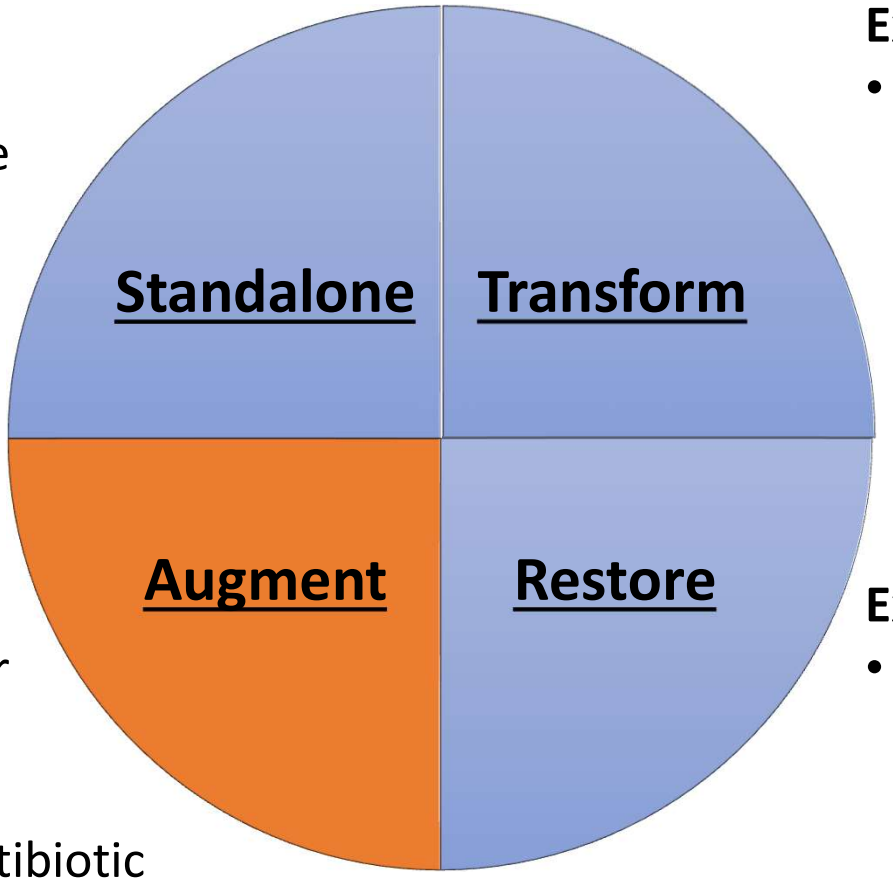
- Unless the pathogen is distinct to the infection, pursuit of individual pathogens or (just) rare pathogens (MDR or otherwise) is very hard
  - **A rapid diagnostic does not create the patients!**
  - If the target organism has a frequency of 1%, then you must screen 100 to find that 1 … or even more if the diagnostic is imperfect
- **Net of all this advice**: Products that meet the SSSS[1] test are *much* more easily developed
- Everything else is harder
  - Get help early – make plans to solve this problem!!

[1]SSSS: Has the **spectrum** for a defined **syndrome** and the **speed** required to be suitable as the **sole therapy.**

STAR: Four treatment archetypes[1]

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Examples
- Traditional small molecule
- Phage
- Antisense



Example
- Gram-negative activity from colistin + approved Gram-positive antibiotic

Example
- Virulence factor inhibitor or anti-toxin antibody + approved antibiotic

Example
- BL-BLI (Beta-lactam beta-lactamase inhibitor) combinations

1. Rex et al. Designing development programs for non-traditional antibacterial agents. Nature Communications. 2019;10(1):3416.

Augment an existing therapy



- Example: Virulence inhibitor or such
  - Usually lacks an MIC equivalent and has no discernible in vitro effect on the base therapy in the laboratory
  - Not sufficient alone: Must also give an active antibacterial (e.g., toxin inhibitor + an SSSS antibiotic)
- Distinctive hurdles
  - Base therapy needs to work
    - Might protect a base therapy from emergence of resistance but doesn't solve existing resistance problems
  - Dose: Lack of an MIC → harder to apply PK-PD
    - If the PK-PD rationale has gaps, it becomes harder to validate dose/exposure logic. You may need two studies
  - **Superiority problem**: Must show NEW + SOC[1] > SOC
    - This needs a slide of its own…

1. SOC = Standard of Care

Superiority[1] & Endpoints

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- Ultimately, these agents force a study of this form
  - NEW + SOC vs. SOC … *and with fully dosed, active SOC*
  - We will want to see that NEW + SOC **is superior to** SOC
- Are there settings where this might be possible?
  - Endocarditis is a good candidate: more rapid bloodstream clearance might have a measurable clinical effect
  - But, this is a hard study to enroll and there is so much noise in the data – clinical improvement may be tough
- **Endpoints:** Would different endpoints help?
  - A challenging question! Whatever is proposed must be compelling.
  - Are there population-level variations on "feels, functions, survives" that we should begin to recognize? *No good answers here, as yet.*[2]
- Finally, know that this is not a regulatory problem per se
  - The agencies are simply the first to point out the issue
  - Why should I use this? Why should I pay for this?



1. For more on this, see https://amr.solutions/2020/09/19/in-praise-of-non-inferiority/ and its video: https://youtu.be/dx9mrQfSNT4
2. See link to a workshop on Drug Z-3 on the "Read, Listen, and Learn" slide, a hypothetical agent for prevention of acquisition of resistance.

Executive Summary (& Agenda)



- We really need new antibiotics! Glad you are here!
- Attend to the plumbing: Avoid leaks in the pipe(line)
- Anticipate Phase 3: Is your product developable?
- If you build it, will they come? Embed durable value
  - Reimbursement is changing – you should plan for this!
- Summary

Pop Quiz: Have you used a fire extinguisher today?

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Pop Quiz: Have you used a fire extinguisher today?

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Let's be more concrete.
Are you using a fire extinguisher <u>right now?</u>

Fundamental starting point

- Antibiotics enable all of modern civilization!
  - Safety net for surgery, cancer therapy, and essentially everything else
  - Infrastructure for civilization: Healthy citizens make the economy go!

- Stated differently…

Antibiotics are the fire extinguishers of medicine!



Speaker personal opinion.

Current economic model is broken



- Current approach to antibiotics
  - Everyone is delighted to have a new antibiotic
  - But, use is delayed and deferred in effort to preserve new antibiotic
- Stewardship perspective: Entirely rational
- Economic perspective: A financial loss
  - Many analyses show same thing
  - It is not financially rational to do antibiotic R&D
  - Bankruptcies! Achaogen, Melinta
    - http://amr.solutions/blog/scary-scarier-scariest-achaogen-ft-editorial-cbs-60-minutes-on-amr
    - https://amr.solutions/2020/01/05/melinta-goes-bankrupt-never-let-a-good-crisis-go-to-waste/
- Issue: Pay-per-use model reimburses for only a piece of the value … **& we're working to fix this…**

STEDI: Antibiotic value beyond mere use

But, we don't (yet) have an agreed way to capture these values





Antibiotics are the fire extinguishers of medicine!

The "STEDI" values of antibiotics

Value	Description of benefit
Spectrum	Replacing broad spectrum agents with narrow spectrum agents and thereby reducing collateral damage to the microbiome
Transmission	Avoiding pathogen spread to the wider population by effectively treating patients
Enablement	Availability of effective treatment enables other types of medical interventions (eg, surgery, oncology)
Diversity	Having a range of treatment options reduces selection pressure
Insurance	Having an agent available in case of a sudden or significant increase in the prevalence of pathogens resistant to existing agents

Table from Outterson K, Rex JH. Evaluating for-profit public benefit corporations as an additional structure for antibiotic development and commercialization. *Translational Research*, 2020. The STEDI concept was adapted from Rothery et al. Framework for Value Assessment of New Antimicrobials. http://www.eepru.org.uk/wp-content/uploads/2017/11/eepru-report-amr-oct-2018-059.pdf, 2018.

It's expensive!



- Average all-in cost to approval[1] = $1.3b
- Running costs of a drug in its first 10 years: $350m[2]
  - $100m in post-approval commitments: pediatrics, etc.
  - $25m/year to run the plant that makes your drug, surveillance, pharmacovigilance
- All together: ~$1.7b per molecule
  - Usage-based income will not recover those costs[3,4]
  - New antibiotics often have ≤ $25m/year in sales
- Can it be done for substantially less?[5,6]
  - On average, no. There are no discounts or regulatory shortcuts for being small or large, for-profit or non-profit, degree of novelty, etc.
  - Small company models are already very, very lean[5]

[1]Wouters J, et al. *JAMA* 2020;323:844–53. AMR.Solutions: "Melinta, Part 2 / Bankruptcy Is Not The End / Post-Approval Costs For An Antibiotic", available at https://amr.solutions/2020/01/07/melinta-part-2-bankruptcy-is-not-the-end-post-approval-costs-for-an-antibiotic/. [3]AMR.Solutions: "Mandatory Reading: Alan Carr's Jan 2020 Antibacterial And Antifungal Market Review", available at: https://amr.solutions/2020/01/28/mandatory-reading-alan-carrs-jan-2020-antibacterial-and-antifungal-market-review/. [4]AMR.Solutions: "What Does An Antibiotic Cost To Develop? What Is It Worth? How To Afford It?", available at: https://amr.solutions/2020/03/06/what-does-an-antibiotic-cost-to-develop-what-is-it-worth-how-to-afford-it/. [5]Drakeman DL. Benchmarking biotech and pharmaceutical product development. Nat Biotechnol, 32(7): 621-5, 2014. [6]AMR.Solutions: "All-In Cost Of A New Antibiotic From Discovery To 10 Years On Market", available at https://amr.solutions/2021/01/09/all-in-cost-of-a-new-antibiotic-from-discovery-to-10-years-on-market/

Paying for it: Push and Pull

- Substantial public thinking over the past 10+ years
  - UK AMR Review; DRIVE-AB project; US legislative efforts; Swedish pilot project, EU Pharma strategy, and more
- Key insights: We need 2 different kinds of funding
  - Push incentives that encourage work to start: Grants
    - $750m for Discovery to Phase 1: CARB-X, Novo REPAIR, etc.
    - $1b for Phase 2-3: AMR Action Fund
    - Lots of (mostly small) companies have entered the fray
  - Pull incentives paid ***on successful approval***
- Many papers on this, see amr.solutions for more
  - In particular, the 1 Sep 2020 newsletter is a good start
  - https://amr.solutions/2020/09/01/reimbursing-for-innovative-antibiotics-encouraging-updates-from-the-amr-conference/



Video explainer: https://www.youtube.com/watch?v=6gd8iXLbZak

How does Pull work?



- Pull = Payments made without regard for use[1]
  - The UK pilot as a benchmark: The UK has identified two high-end new agents for Gram-negative bacterial infections
  - The UK is contracting to buy them for the UK at up to GBP 10m/yr
    - Scaled to 10 years and to full 10m/yr, this is GBP 100m
    - **The purchase is independent of actual use**
  - The UK is 3% of the G20: 100m x 33 = GBP 3.3b ≈ $4b
- This is right on target! *Strong work, Team UK!*
  - All estimates[2] converge on $2-4b as the needed reward size
  - This type of Pull incentive levels the economic playing field!
- So, how do we engage and extend?
  - Wealthy countries need to contribute their fair share
  - Targets must be fair and consistently available
  - So far, the only sizeable further effort is in the US (PASTEUR)

1. See https://amr.solutions/2021/09/14/outstanding-discussions-of-pull-the-nhs-pilot-and-antibiotic-value/. See also this excellent 5-minute video explainer: https://www.ft.com/video/adada10f-5747-4976-a3e0-958b0165e0ef
2. Multiple estimates have been made. The best current summary is found in Outterson K, Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines. Health Affairs. 2021;40(11):1758-65. Also see a recent report to the G7 Finance ministers discussed in this newsletter: https://amr.solutions/2022/06/04/notable-reports-incentives-who-amr-hub-strategy-barda-capacity-building-fleming-fund/

Pull awards can/will guide R&D



- Think of R&D as a big ship … *a 10- to 15-year-long ship*
  - Big ships turn slowly, but they do turn
- Pull awards tied to desired features will turn the ship
  - Novelty, Indications, and Spectrum can all be measured[1]
  - The UK Pilot has published a point scoring system[2]

Example on next slide

- Key: Targets must be held constant
  - Products coming to approval at any given time are the result of decisions made a decade or more previously
- Some additional detail on next slide. *For an extended discussion…*
  - AMR.Solutions:[3] "Assessing Antibiotic Value: DTR, Fire Extinguishers, And A View From Australia" -- the idea of Difficult-to-Treat-Resistance (DTR) is a noteworthy build on features such as novelty and spectrum

- **Hint, hint: What does this tell you about choosing a project?**
  - **Big Pull rewards will only go to projects that make you say "Wow! I need that!"**

[1]Rex JH, Outterson K. Antibiotic Reimbursement in a Sales-Delinked Model: Context and a Benchmark-Based Global Approach. The Lancet Infectious Disease, 16: 500-5, 2016. [2]Search for "slide 25" on https://amr.solutions/2020/03/29/uk-antibiotic-subscription-pilot-implies-pull-incentive-of-up-to-4b-across-the-g20/. [3]https://amr.solutions/2020/06/07/assessing-antibiotic-value-dtr-fire-extinguishers-and-a-view-from-australia/

UK Pilot: Point Score Scheme



- Up to 11,250 points for **priority pathogen coverage**
- Unmet need: Up to 6000 points across High, Medium, and Low unmet need
- Coverage of **key resistance determinants**: Up to 6000 points based on extent of coverage of pathogens expressing various resistance determinants.
- **Utility in various disease settings**: Up to 6000 points for the spectrum of primary care (lowest) to ICU (highest)
- Novelty: **New class (2000 points), New target (1500 points), New Mechanism of Action (1500 points)**, low rate of development of resistance (1500 points), lack of cross-resistance (1000 points), and Other benefits (up to 500 points)
- Certainty of supply, Stewardship, and arrangements for Surveillance are each worth up to 5000 points

The PASTEUR Act in the US is likely to have a similar feel!

Executive Summary (& Agenda)



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- Attend to the plumbing: Avoid leaks in the pipe(line)
- Anticipate Phase 3: Is your product developable?
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- Summary

Key points

- Get help with the parts where you are not expert
  - CMC, toxicology, PK, PK-PD, Clinical, Regulatory … these are very special domains.
  - This workshop will introduce you to sources of help!
- Plan for Phase 3
  - How will you study it? In whom will you study it?
  - **Is that study feasible in non-geologic time?**
- Will anyone care?
  - What is the “Wow, I need that!” story for your drug?
  - Places to start? Novelty, oral, lack of cross-resistance

Thanks for listening!



Strategies for Early R&D: Plumbing, Phase 3, and Durable Value

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22 June 2022

NIAID - Early R&D Strategies for Novel Antibacterial and Antifungal Drugs

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Please note these details!

Slides happily shared … just drop me a note