Current and Emerging Therapies for Infectious Diseases

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Learning Objectives

1. Describe drivers for antibiotic development
2. List anti-infectives that were approved in 2017 for the treatment multi-drug resistant organisms
3. Discuss the antibiotics that should be approved for human use in 2018/early 2019

Key Drivers

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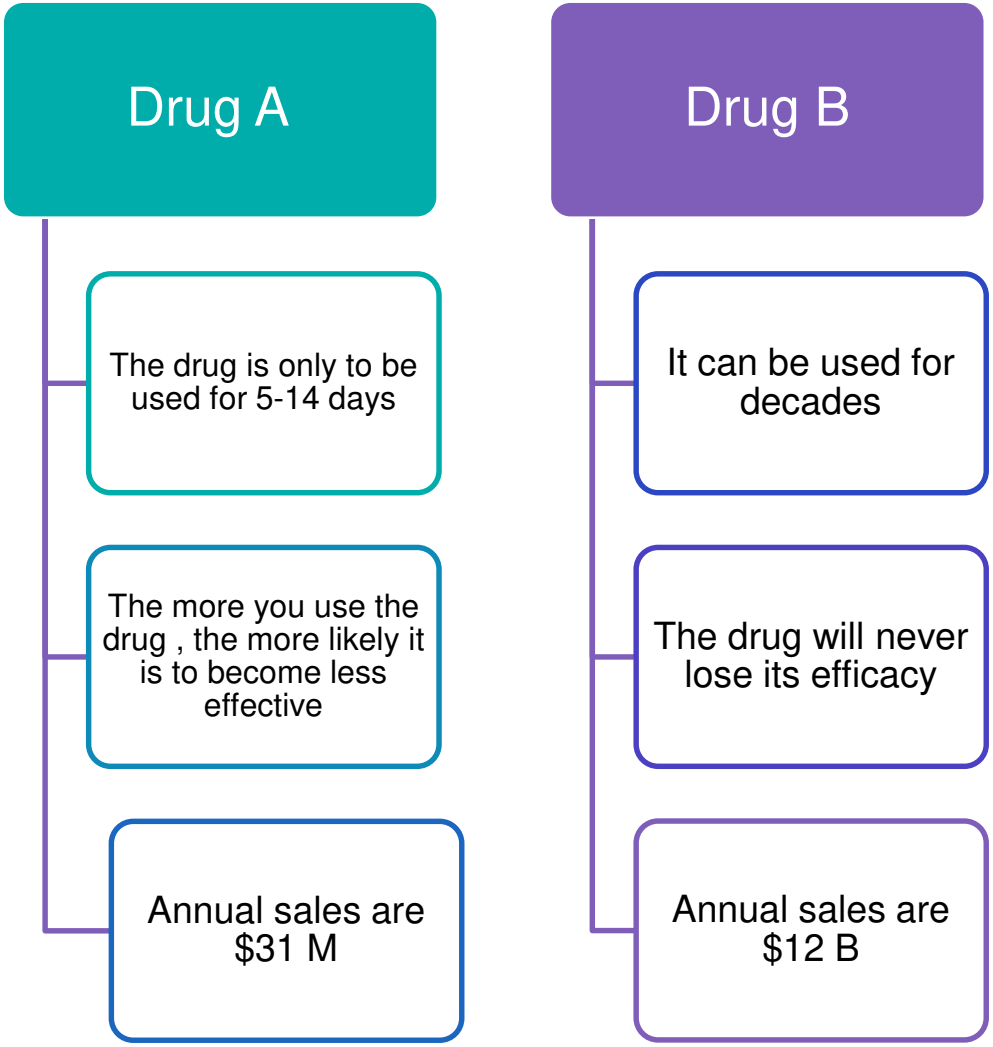
As a pharmaceutical executive, which drug would you recommend that your company bring to market?



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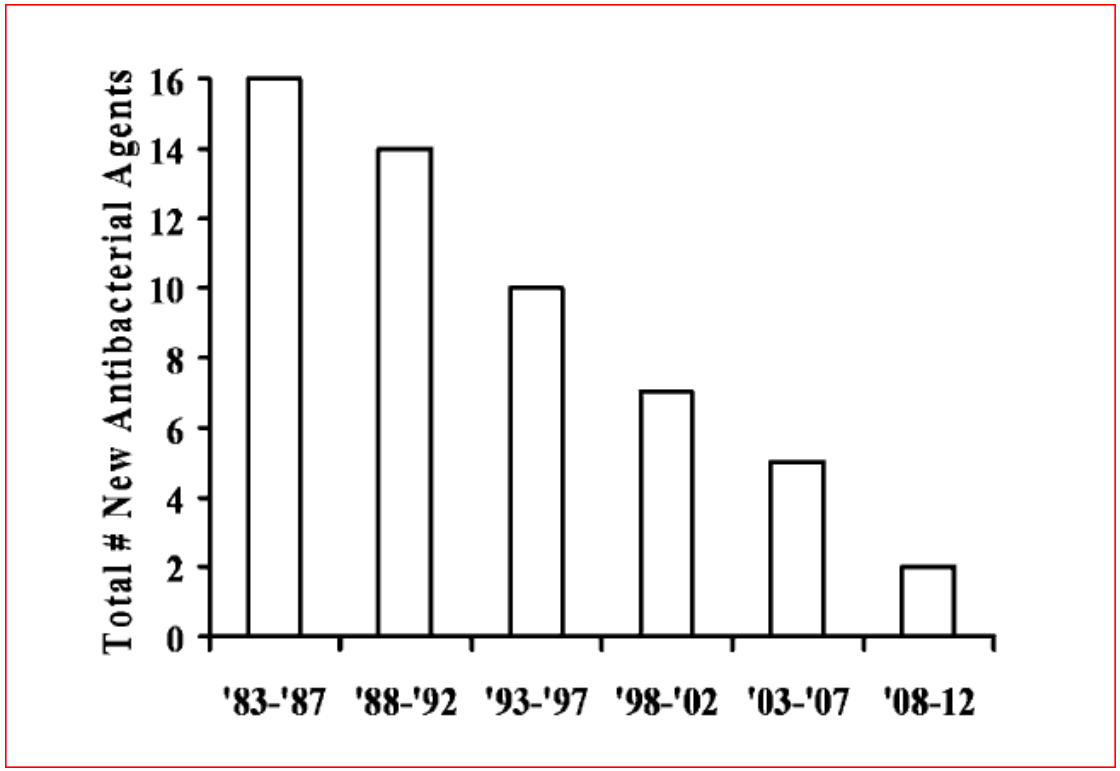
As a pharmaceutical executive, which drug would you recommend that your company bring to market?

Drug A:
Ceftazidime/Avibactam

Drug B:
Atorvastatin

What is influencing the development of drugs for resistant organisms?

- **No brainer first bullet point….resistance**
- **Here is where I show you the graph that everyone always shows**



Clin Infect Dis 2011;52(suppl 5):S397-S428.

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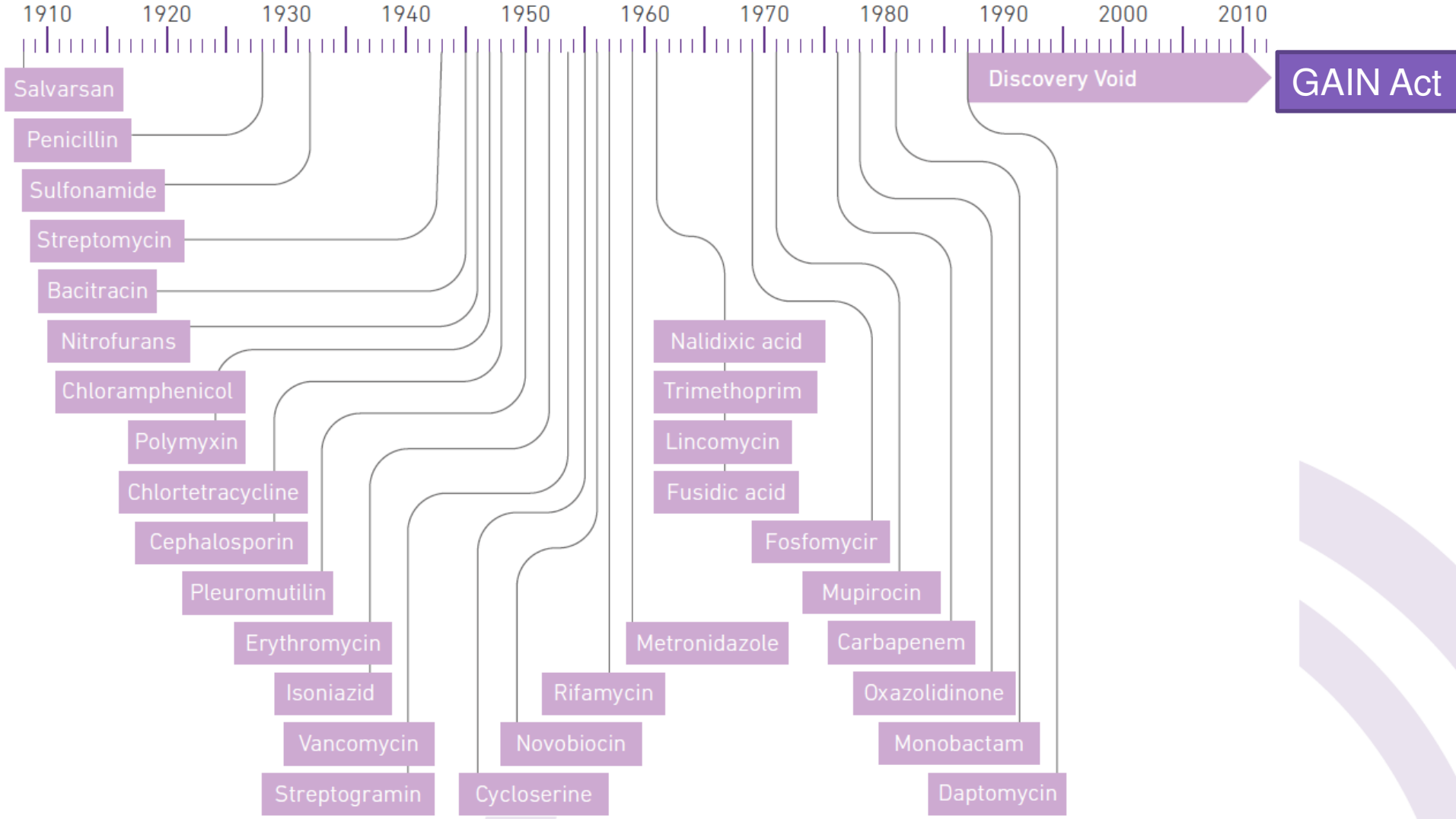
Figure 1 **Dates of discovery of distinct classes of antibacterial drugs**

Illustration of the "discovery void." Dates indicated are those of reported initial discovery or patent.



Adapted from Silver 2011 (1) with permission of the American Society of Microbiology Journals Department.

[a] Antibacterial drugs act against bacteria and include antibiotics (natural substances produced by microorganisms), and antibacterial medicines, produced by chemical synthesis.

Legislative Drivers

Generating Antibiotics Incentives Now (GAIN Act)

- **Signed into law on July 9, 2012**
- **Established definition of a Qualified Infectious Disease Product (QIDP)**
  - Extends exclusivity for new antibiotics an additional 5 years in addition to any existing patent extensions created by other regulations
  - NDA accelerated at FDA and "fast track status"
  - Requires FDA to issue new guidance on the development of pathogen-focused antibiotics

National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB)

- **March 2015**

GOAL 4: Accelerate Research to Develop New Antibiotics, Other Therapeutics, Vaccines, and Diagnostics	
Objectives	
4.1	Conduct research to enhance understanding of environmental factors that facilitate the development of antibiotic-resistance and the spread of resistance genes that are common to animals and humans.
4.2	Increase research focused on understanding the nature of microbial communities, how antibiotics affect them, and how they can be harnessed to prevent disease.
4.3	Intensify research and development of new therapeutics and vaccines, first-in-class drugs, and new combination therapies for treatment of bacterial infections.
4.4	Develop non-traditional therapeutics and innovative strategies to minimize outbreaks caused by resistant bacteria in human and animal populations.
4.5	Expand ongoing efforts to provide key data and materials to support the development of promising antibacterial drug candidates.

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https://blogs.fda.gov/fdavoice/index.php/tag/qualified-infectious-disease-product-qidp/

On the Horizon

Company/ Research Team	Project	Novelty*			Project description	Urgency/ Priority**	Bacteria Targeted / Stage of Early Development
		New Class	Non-traditional	New Target			Hit to Lead / Lead Optimization / Pre-Clinical / Phase 1
Achaogen	AKAO-LpxC	✓		✓	LpxC Inhibitor	✓	*Pseudomonas aeruginosa*
Antabio	PEI		✓	✓	Pseudomonas Elastase inhibitor	✓	*Pseudomonas aeruginosa*
Bugworks Research	Gyrox	✓			Gyrase-topoisomerase inhibitor	✓	Gram-negative activity
Cidara Therapeutics	CD201		✓	✓	Bifunctional immunotherapy	✓	Acinetobacter + *P. aeruginosa* + Enterobacteriaceae
ContraFect	Gram-negative lysins		✓	✓	Recombinant lysin protein	✓	*P. aeruginosa*
Debiopharm	Debio 1453	✓		✓	Narrow-spectrum inhibitors of FabI	✓	*Neisseria Gonorrhoeae*
Eligochem	Helical AMP	✓			Helical Antimicrobial Peptide	✓	Gram-negative activity
Entasis Therapeutics	ETX0282 CPDP				Oral Gram-negative combination	✓	Gram-negative activity
Forge Therapeutics	FG-LpxC	✓		✓	LpxC Inhibitor	✓	Gram-negative activity
Iterum	Sulopenem				Oral and IV penem	✓	Gram-negative activity
Microbiotix	T3SS Inhibitor		✓	✓	Virulence modifier	✓	*Pseudomonas aeruginosa*
Oppilotech	LPS	✓		✓	Targets synthesis of LPS	✓	Gram-negative activity
Redx Pharma	NBTI	✓			Dual-acting topoisomerase inhibitor	✓	Acin. + *P. aerug* + Enterobacteriaceae
Spero Therapeutics	SPR741			✓	Potentiator	✓	Gram-negative activity
Tetraphase Pharm	TP-6076				Next-generation tetracycline	✓	Acinetobacter + Enterobacteriaceae
VenatoRx	VNRX-PBP	✓			ß-lactamase Resistant PBP Inhibitor	✓	Entero-bacteriaceae
Visterra	VIS705		✓	✓	Antibody-drug conjugate	✓	*Pseudomonas aeruginosa*

CARB-X report. Available at http://www.carb-x.org/files/2016_CARB-X-Annual_Report.pdf

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2017 FDA Highlights [Antibacterials]

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QIDP

Approvals

- **June 19, 2017 - delafloxacin [Melinta Pharmaceuticals] approved under the trade name Baxdela**
- Indications
  - Treatment of acute bacterial skin and skin structure infections x 5-14 days
  - Spectrum of activity includes MRSA but gaps in coverage for gram negatives exist
  - Dosing
    - 300mg IV Q12 hours
    - 450mg PO Q12 hours
    - Renal dosing required for IV at CrCl 15-29 ml/min
  - Phase 3 ongoing for community acquired bacterial pneumonia and Phase 1 for complicated UTI

Breakpoint Comparisons for Selected Organisms

Species	Delafloxacin MIC (mcg/mL)			Ciprofloxacin MIC (mcg/mL)			Levofloxacin MIC (mcg/mL)			Moxifloxacin MIC (mcg/mL)		
	S	I	R	S	I	R	S	I	R	S	I	R
Methicillin susceptible *S. aureus*	≤0.25	0.5	≥1	≤1	2	≥4	--	--	--	≤2	4	≥8
Methicillin resistant *S. aureus*	≤0.25	0.5	≥1	--	--	--	--	--	--	--	--	--
Enterococcus faecalis	≤0.12	0.25	≥0.5	≤1	2	≥4	≤2	4	≥8	≤1	2	≥4
Streptococcus pneumoniae	--	--	--	≤1	2	≥4	≤2	4	≥8	≤1	2	≥4
Streptococcus pyogenes	≤0.06	--	--	≤1	2	≥4	≤2	4	≥8	--	--	--
Enterobacteriacae *	≤0.25	0.5	≥1	≤1	2	≥4	≤2	4	≥8	≤2	4	≥8
Pseudomonas aeruginosa	≤0.5	1	≥2	≤1	2	≥4	≤2	4	≥8	--	--	--

* *E. coli*, *K. pneumoniae*, and *E. cloacae*

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QIDP

Approvals

August 30, 2017 – meropenem/vaborbactam [The Medicines Company/Melinta] approved under the trade name Vabomere

Approved indication

- Complicated UTI (including pyelonephritis)

Phase 3 Trial Name	Population studied	Dosing	Results
TANGO 1 (n=550)	cUTI, AP	M-V (2g/2g) via a 3 hr infusion) or P-T (4g/0.5g via a 30 min infusion) every 8 hrs. Conversion to LV allowed after 15 doses of IV	Primary endpoint [overall success at end of IV] 98.4% (M-V) and (94.0%) in P/T group (95% CI of difference: 0.7, 9.1). M-V statistically superior to P/T.
TANGO 2 (n=72)	cUTI, AP, hospital acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, bacteremia, intraabdominal	M-V (2gm/2gm) vs. best available therapy	Trial stopped early after interim analysis revealed statistically significant differences favored M-V over best available therapy at test of cure in patients with CRE. Lower mortality rates were also reported in M-V patients.

cUTI = complicated UTI, AP = Acute pyelonephritis, M-V = meropenem/vaborbactam, P/T = piperacillin/tazobactam, LV = levofloxacin. Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209776Orig1s000SumR.pdf, www.clinicaltrials.gov

Antimicrobial Spectrum of Activity (In-Vivo)

Inhibitory Activity against β-Lactamases

Class of β-Lactamases	Enzymes	Ceftolozane-tazobactam	Ceftazidime-avibactam	Meropenem-vaborbactam
Class A (Serine)	TEM	√	√	√
	SHV	√	√	√
	CTX-M	√	√	√
	KPC (CRE)	None	√	√
Class B (MBLs)	IMP/VIM	None	None	None
	NDM	None	None	None
Class C (Serine)	amp C	Variable	√	√
Class D (Serine)	OXA	Variable	Variable	None

Zerbaxa® (Ceftolozane-Tazobactam) Prescribing Information, Merck Pharmaceuticals, Inc. 2016.
FDA Briefing Package for Ceftazidime-Avibactam. Food and Drug Administration Website. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM425458.pdf.

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Additional 2017/early 2018 FDA Activity

- October 2017 QIDP
  - Ceftazidime/avibactam [C/A] granted priority review for supplemental New Drug Application filed to expand indication to hospital and ventilator associated pneumonia in adults
  - Supporting study : Phase 3 REPROVE study
    - C/A 2.5gm over 2 hours every 8 hours vs meropenem (M) 1gm over 30 minutes every 8 hours x 7-14 days
  - Clinically modified intention-to-treat (n=726)
    - C/A cure rate =68.8% vs 73% in M group (-4.2%[95% CI -10.8 to 2.5])
  - Clinically evaluable (n=527)
    - C/A cure rate = 77.4% vs 78.1% in M group (-0.7% [95%CI -7.9 to 6.4])
- January 11, 2018 QIDP
  - Reviewed inhaled ciprofloxacin for the treatment of non-cystic fibrosis bronchiectasis in patients with chronic pulmonary infections caused by *Pseudomonas aeruginosa*
  - 12 No's ; 3 Yes'

Torres A, et al. Lancet ID Dec. 15, 2017;in press.
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm587657.htm

Projected approvals
2018 through early 2019

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QIDP

Lefamulin (Nabriva)

- **New compound that is a semisynthetic derivative of pleuromutilin that is isolated from a mushroom**
- **Veterinary compounds in this class include tiamulin and valnemulin used in swine and poultry**
- **This would be the second agent for human use in this class (after retapamulin)**
- **Spectrum of activity**
- *S. pneumoniae, M.catarrhalis, H.influenzae. L. pneumophila, C. pneumoniae, M. pneumoniae*
- *S. aureus* – Including MRSA
- STDs – *N. gonorrhoeae, C. trachomatis , M. genitalium* including multidrug resistant strains
- Minimal effects on GI flora including *B. fragilis*, *E.coli*, and *E. faecalis*

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Lefamulin (Nabriva) – BC3781

QIDP

- **Pursing indication for community acquired bacterial pneumonia**
  - 150gm IV q 12 hours over 60 minutes
  - 600mg PO q 12 hours
- **Phase 2 for acute bacterial skin and skin structure infections (ABSSSI)**
- **Two phase 3 studies for community acquired bacterial pneumonia**

LEAP 1 (IV to Oral) Trial	LEAP 2 (Oral) Trial
• 550 pts. with mod/severe pneumonia • Lefamulin vs. moxifloxacin +/- linezolid • Duration of treatment 7 days (10 if MRSA) • Preliminary analysis shows non inferiority	• 740 pts. with moderate pneumonia • Lefamulin (5 days) vs. moxifloxacin (7 days) • Trial in progress - expect topline data in Spring 2018

Prince WT, AAC 2013;57:208-94., ID Week 2017

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Eravacycline (Tetraphase)

QIDP

- Novel, fully synthetic fluorocycline with activity against multiple MDROs including CRE, *A. baumannii*, and colistin resistant bacteria
- IV and PO (Phase 1)
- IGNITE studies
  - Ignite 1 – non inferiority vs IV ertapenem
  - Ignite 4 – non inferiority vs IV meropenem
  - Ignite 2 - didn't meet endpoints for cUTI (inferior to levofloxacin) so company has to complete 1 more Phase 3 study. [Blamed it on PO].
  - Ignite 3- ongoing phase 3 trial comparing eravacycline IV vs ertapenem in cUTI. Enrollment completed.
  - Expect NDA to be filed in Q1 18 with QIDP/fast track within 8 months

Horn P , ID Week 2017

Plazomicin (Achaogen)

QIDP

Spectrum of Activity

- Enterobacteriaceae including CRE and ESBLs (*Klebsiella pneumoniae* and *E. coli)*
- *S. aureus* (in vitro)
- "greater potency that current aminoglycosides including

Phase 3 studies

EPIC – cUTI vs meropenem with conversion to PO levofloxacin

Plazomicin 15mg/kg q 24 hr

CARE – serious infections caused by CRE

- Cohort 1: plazomicin 15mg/kg q24h or colistin (plus mero or tigecycline)
- Cohort 2: plazomicin monotherapy
- Talking points: lower nephroxicity than colistin, must dose based on AUIC, lower relapse rates in cUTI
- NDA submitted – PDUFA date June 25, 2018

Friedland, ID Week 2017

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QIDP

Fosfomycin (Zavante)

- **Intravenous fosfomycin (Zolyd, ZTI-01)**
- **Fosfomycin has broad spectrum activity for both G+ and G -**
  - ZUES (ZTI-01) Phase 2/3 trial compared fosfomycin 6gm as a one hour infusion given q8h vs piperacillin/tazobactam 4.5gms IV q8 hrs for treatment of cUTI, including acute pyelonephritis
  - Zavante intends to submit filing in early 2018 [fast track]

Table 2. Clinical Cure and Microbiologic Eradication Rates for Patients from ZEUS Trial with Antimicrobial Resistant Phenotypes (TOC, m-MITT), % (n/N)

	ESBL		Amino-R		CR		MDR	
	Cure	Erad.	Cure	Erad.	Cure	Erad.	Cure	Erad.
ZTI-01	92% (49/53)	57% (32/56)	97% (29/30)	67% (20/30)	100% (7/7)	57% (4/7)	92% (36/39)	59% (23/39)
P-T	93% (51/55)	47% (27/57)	88% (30/34)	40 (14/35)	89% (8/9)	33% (3/9)	86% (31/36)	37% (14/38)

CR: Carbapenem-resistant; ESBL: extended spectrum beta-lactamase; MDR: multidrug-resistant; m-MITT: microbiologic modified intent-to-treat

Ellis-Grosse E, et al. ID week # 1830

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Omadacycline (Paratek)

QIDP

Class: Aminomethylcycline

Spectrum of activity against CDC Top Pathogen Threats

Category	Organisms
Gram positive	VRE, MRSA, VRSA, MDR *S. pneumoniae,* Erythomycin resistant Grp A *Streptococcus,* Clindamycin resistant Grp B *Streptococcus*
Gram negative	Carb R *E. coli* (but limited activity against Carb R *K. pneumoniae*), ESBLs, drug resistant *Salmonella*
Anaerobes	*C. difficile* [but not developing for this indication]

http://paratekpharma.com/science/omadacycline/

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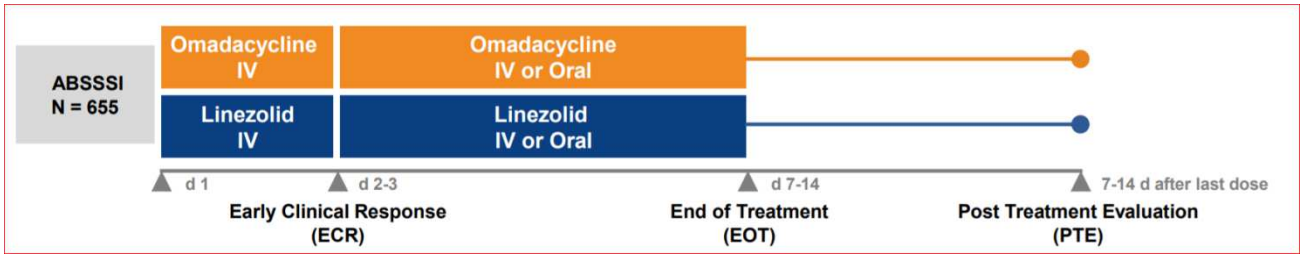
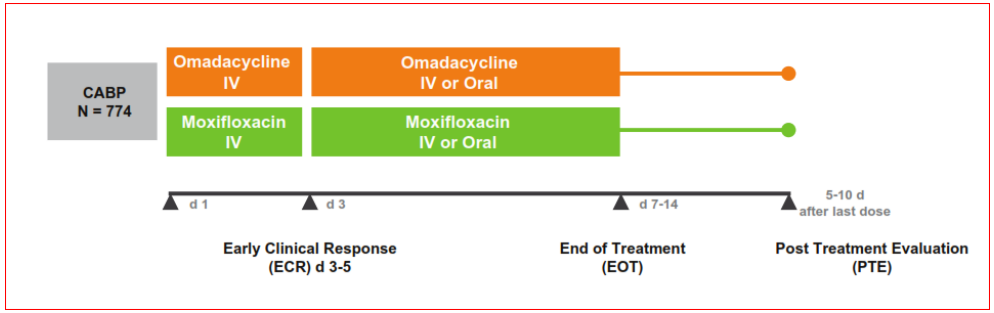
Omadacycline (Paratek)

QIDP

- **Phase 3 OASIS trial – ABSSSI**
- Omadacycline [100mg IV q12h x 2 doses, then 100mg IV q24hr with option to convert to 300mg PO q24h after 3 doses] vs linezolid 600mg IV/PO Q12hr



- **Phase 3 OPTIC trial – CABP**
- Omadacycline as above vs moxifloxacin



- **Phase 2 complicated UTI - planned**
- **Anticipate NDA submission in quarter 1 2018 for ABSSI and CABP**

https://paratekpharma.com/media/1410/eccmid-oasis-oral-final-22apr2017-vff.pdf, Stets ID Week 2017 #1883

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Iclaprim (Motif Biosciences)

QIDP

- Dihydrofolate reductase inhibitor
- Originally designed by Hoffman LaRoche to be more potent than trimethoprim. Can be given as monotherapy
- Rapidly bactericidal activity against MDR gram positive including MRSA that non susceptible vancomycin, linezolid, and daptomycin

Summary Minutes of the
Anti-Infective Drugs Advisory Committee
November 18-20, 2008
Location: Holiday Inn, The Ballrooms, 10000 Baltimore Avenue, College Park, MD

Questions to the committee:

1. Do the data presented demonstrate the safety and effectiveness of iclaprim for the treatment of cSSSI? Please vote Yes/No.

Vote: ***Yes= 2*** ***No = 16*** ***Abstain = 0***

Due to problems with the electronic voting system, this vote was later found to be 2 Yes and 17 No votes. Please see the transcript for details regarding individual committee member's votes.

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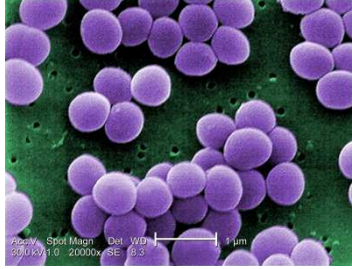
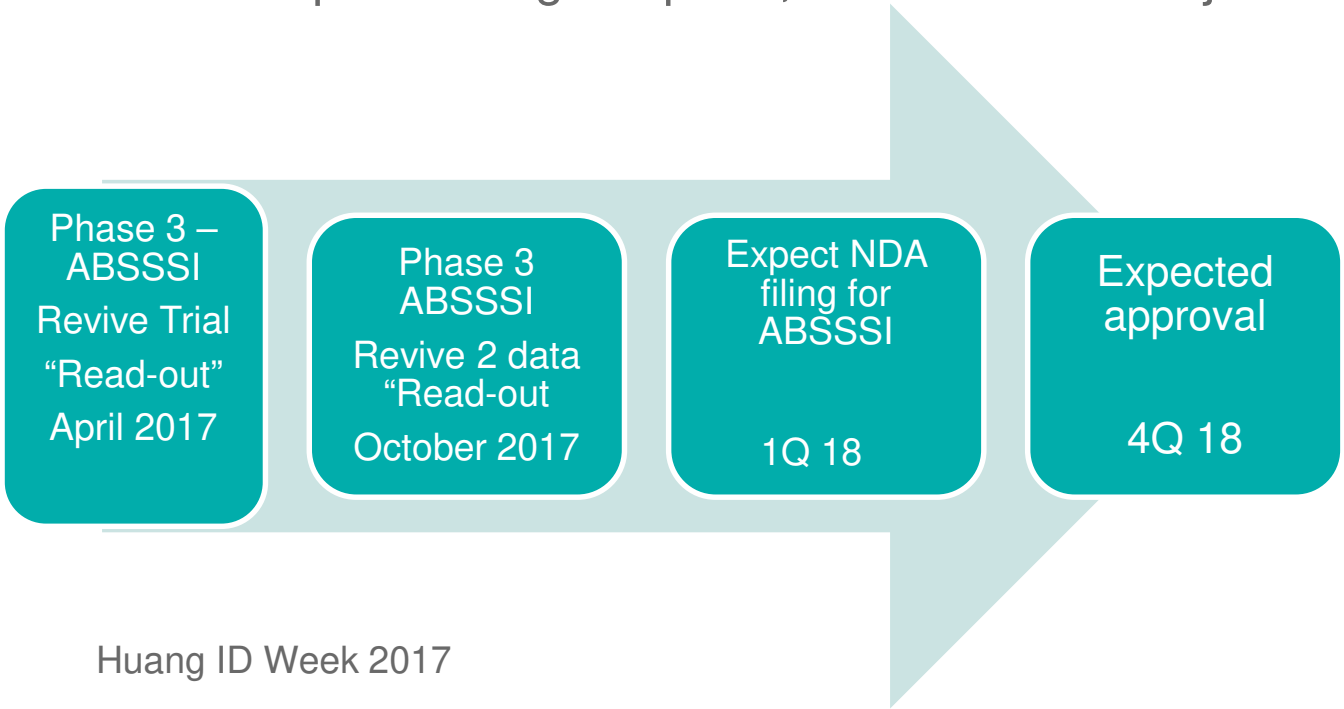
Iclaprim (Motif Biosciences)



- Key trials
  - Phase 2 study (n=70) with HABP/VAP vs vancomycin for 7-14 days.
  - Two Phase 3 studies (REVIVE 1 and 2)
    - Non inferior to vancomycin in both studies
    - Dose = iclaprim 80mg IV q12h ; no renal dose adjustment



Huang ID Week 2017

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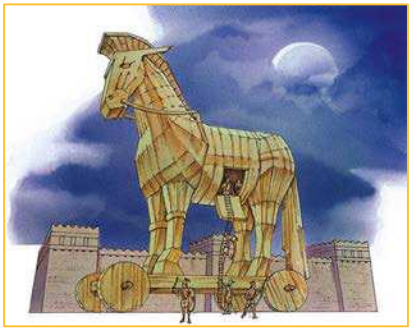
Cefiderocol (Shinogi)

QIDP

- Mimics natural siderophore iron complexes required by bacteria to survive. Actively transported into the periplasmic space
- Cephalosporin that has molecular backbone from cefepime and ceftazidime and binds ferric iron
- Broad spectrum activity against MDR gram negatives but no gram positive or anaerobes
- Completed studies for cUTI and ongoing trial for HAP/VAP/HCAP vs carbapenem. Also have an ongoing study vs. CRE.

  2gms IV every 8 hours
- Anticipate approval in 2019

Echols R ID Week 2017



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QIDP

Relebactam + imipenem/cilastatin (MD-7655) – Merck

- Similar in activity to meropenem/vaborbactam
- Clinical efficacy in Phase 2 cUTI and cIAI studies
- Phase 3 ongoing in HABP/VABP

Study	Patient Population	Study Design	Total Sample Size
RESTORE-IMI 1 (PN 013)	cUTI, CIAI, or HABP/VABP caused by IMI-R, but IMI/REL and colistin susceptible isolates	IMI/REL 500/250mg Q 6 hrs Colistin (as CMS) given 150mg colistin base every 12 hours after 300mg loading dose) + IMI 500mg every 6 hours Primary endpoint: overall response based on pre-determined criteria	54
RESTORE – IMI 2 (PN014)	HAB/VABP	IMI/REL 500mg/250mg every 6 hours Pip/Tazo 4.5 gms every 6 hours Can add Linezolid IV empirically for MRSA Primary endpoint is all cause mortality at day 28	536 (268 per group)

Oral drugs to Watch

- **Sulopenem**
  - Former Pfizer product purchased by Iterum pharmaceuticals in development for uncomplicated UTI but will activity against multidrug resistant gram negative organisms.
  - Moving into phase 3 in 2018 with anticipated filing in 2019
- **Ceftibuten/Clavulanate – Phase 3 cUTI trial begins in 2018**

Organism	ESBL Enzyme	Amoxicillin-Clavulanate MIC (µg/mL)	Ciprofloxacin MIC (µg/mL)	C-Scape MIC (µg/mL)
E. coli	CTX-M-15,TEM-1	16	≤0.03	0.5
E. coli	CTX-M-15,TEM-1	8	>4	0.5
E. coli	CTX-M-14	8	≤0.03	0.5
K. pneumoniae	SHV-5,TEM-1	8	0.25	0.12
K. pneumoniae	SHV WT,CTX-M-15, OXA-1/30-like	16	1	0.5
K. pneumoniae	SHV-11,SHV-12,TEM-1	8	>4	0.25
K. pneumoniae	SHV-30	8	0.12	0.25
P. mirabilis	CTX-M-15-like,TEM WT	2	≤0.03	0.03
P. mirabilis	CTX-M-14-like,TEM WT	8	4	0.03
P. mirabilis	None	0.5	>4	<0.015
P. mirabilis	None	1	≤0.03	<0.015
E. coli	None	8	>4	0.25
K. pneumoniae	None	2	>4	0.06

http://www.achaogen.com/cscape

Helpful Resource

Pew Charitable Trust

http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development

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