Economic Challenges and Considerations in Antibacterial Drug Development

Prof. Kevin Outterson
Boston University
@koutterson

Enhancing the Clinical Trial Enterprise for Antibacterial Drug Development in the United States

FDA, NOVEMBER 18-19, 2019

Disclaimer

My views are personal and do not necessarily reflect the views of CARB-X or any CARB-X funder.

How do you know a system is broken?

- Wrong outputs (rate, number, type, quality)
  - Approvals down prior to 2002 (CID 2004;38:1279-86)
  - 26/61 NME antibiotics approved 1980-2009 were subsequently withdrawn or discontinued (J Law Med Ethics Fall 2013;688-96)
- Smoke / Fever / Check engine light

The antibiotic R&D check engine light is on

Inputs

- ✓ Clear signals sent by CDC 2014, GAIN, CARB
- ✓ Basic research funding by taxpayers & charitable foundations
- ✓ Billions of combined private & public capital deployed in product development

Outputs

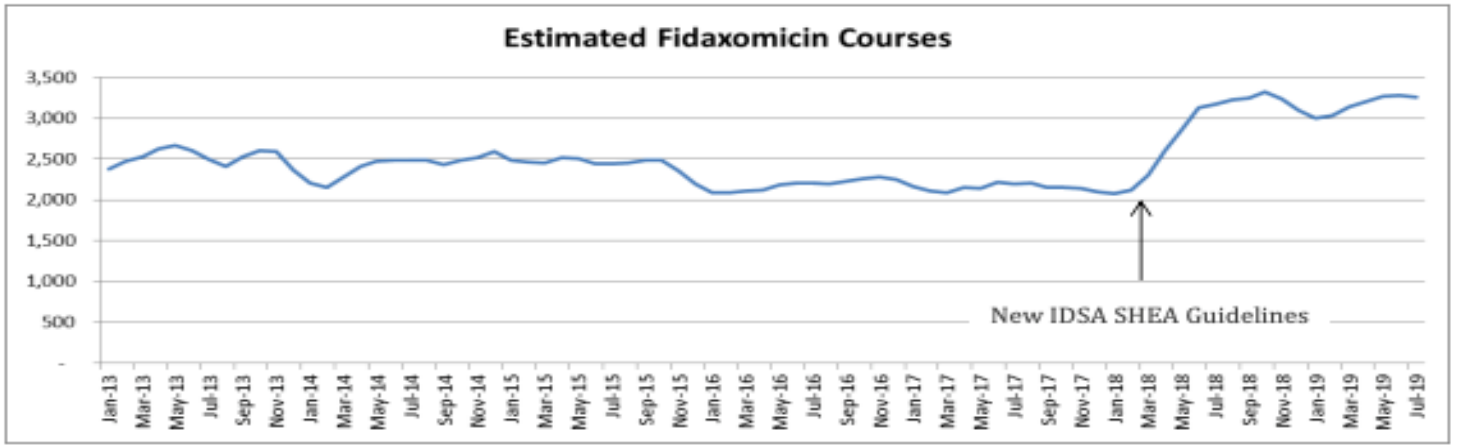
- ✓ Clinical pipeline ”fragile”- see Pew
- ✓ Preclinical pipeline (actually working)
  - ✓ Theuretzbacher U et al., NatRevMicrob 2019 (pending) (next slide)
- ✓ Which new antibiotic do physicians value most?
  - ✓ See guidelines discussion below
- ✓ Which new antibiotic does the market value most?
  - ✓ Inhaled amikacin
  - ✓ Most market caps are low
  - ✓ Inability to raise $ for commercialization; 50% of recent approvals threatened with insolvency

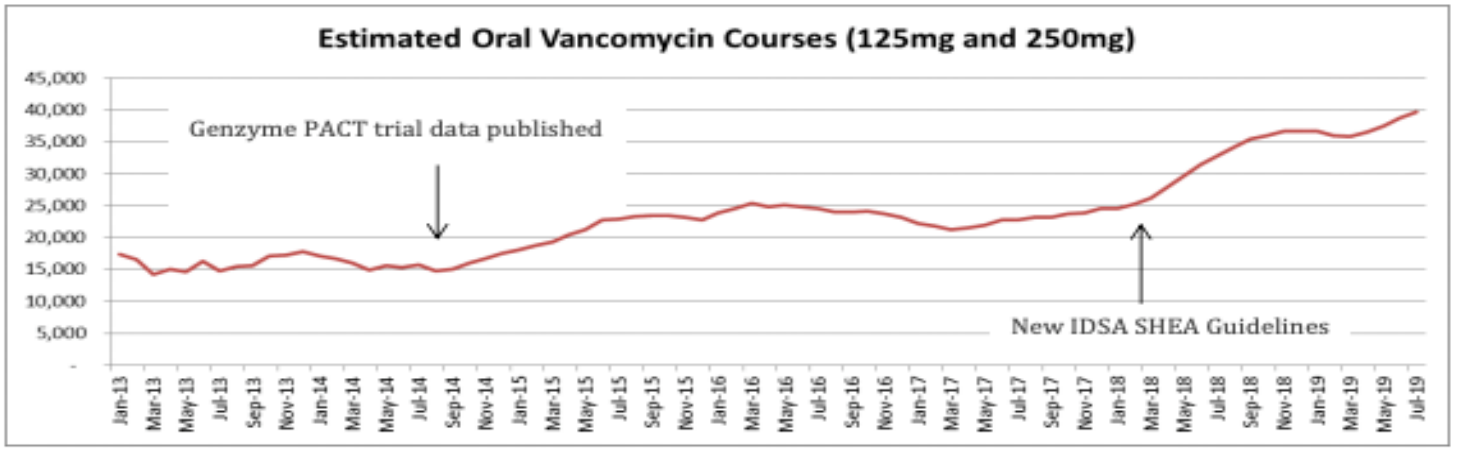
Preclinical pipeline is more encouraging

- Highly novel
- Focused on Gram-negative priority bacteria[1]
- But:
  - Most in very small companies
  - Many non-traditional products lack a clear regulatory path[2]
  - Shortage of funding after Phase I
  - Private funding tight

1 Theuretzbacher U, et al., NatRevMicrob 2019 (pending)
2 Rex JH, et al. Nat Commun *2019;*10(1):3416.

Guidelines may be more impactful than publication





- Guidelines cut through the signal to noise ratio in peer reviewed publication
- Physicians follow peer expert guidelines

Source: Alan Carr, Needham, Sept 2019 Antibiotics Update

~~18~~ 17 public antimicrobial companies

TICKER	PRICE	52 HI	52 LO	YTD RETURN	2018 RETURN	MKT CAP	EV	CASH	L12M OPEX	DEBT	2020 REV EST	2020 EV/Sales	Development Status
BSLN-SWX	45.24	62.70	33.46	13.2%	(47.4%)	537.5	561.5	178.4	152.8	202.4	146.6	3.8	Market
CDTX	1.68	4.95	1.22	(28.5%)	(65.4%)	45.0	1.8	44.6	60.9	1.4	-	N/A	Phase 3 Underway
CFRX	0.35	2.63	0.27	(77.1%)	51.5%	27.8	17.0	14.2	31.6	3.4	-	N/A	Phase 2 Completed
ETTX	7.40	13.70	3.97	81.8%		97.2	39.3	59.5	47.7	1.6	5.0	7.9	Phase 3 Underway
INSM	16.44	33.13	11.31	25.3%	(57.9%)	1,466.6	1,225.0	601.3	365.1	359.7	217.4	5.6	Market
ITRM	6.25	10.30	4.70	24.8%		90.2	56.7	51.3	97.5	17.8	1.0	57.9	Phase 3 Underway
MCRB	4.03	9.26	2.02	(10.8%)	(55.4%)	281.8	197.5	102.2	117.4	18.0	33.8	5.8	Phase 2/3 Underway
MLNT	2.25	24.90	1.62	(43.2%)	(95.0%)	30.9	101.2	90.3	187.4	160.6	100.9	1.0	Market
MTFB	0.63	11.50	0.50	(90.4%)	(39.0%)	10.8	8.6	12.3	18.6	10.1	-	N/A	FDA Review
NBRV	2.02	3.27	1.12	38.4%	(75.6%)	148.2	98.6	73.9	95.8	24.3	31.1	3.2	FDA Approval
POLN-SWX	6.57	34.75	4.19	(63.2%)		72.6	(80.5)	155.6	N/A	2.5	16.6	(4.8)	Phase 3 Suspended
PRTK	3.74	12.20	2.87	(27.1%)	(71.3%)	121.7	130.9	253.5	133.8	262.7	55.9	2.3	Market
SCYX	1.10	1.90	0.35	128.4%	(79.2%)	61.3	44.0	35.3	38.4	18.0	0.3	159.3	Phase 3 Underway
SMMT	1.34	2.46	1.10	16.2%	(89.6%)	42.9	6.0	36.9	61.4	-	18.8	0.3	Phase 3 Underway
SPRO	9.95	14.48	5.52	61.8%	(47.7%)	185.6	86.5	103.4	53.6	4.3	11.8	7.4	Phase 3 Underway
SYN	0.47	8.00	0.37	(16.0%)	(96.9%)	7.9	(13.2)	21.7	14.8	0.6	-	N/A	Phase 2
TTPH	0.26	3.66	0.23	(77.0%)	(82.1%)	14.1	(27.7)	71.0	88.4	29.1	34.0	(0.8)	Market
NBI	3234.62	3865.88	2801.14	6.3%	(9.3%)								
MAX				128.4%	51.5%	1,466.6	1,225.0	601.3	365.1				
MEAN				(2.6%)	(60.8%)	190.7	144.3	112.1	97.8				
MIN				(90.4%)	(96.9%)	7.9	(80.5)	12.3	14.8				

- Most valuable: INSM (inhaled amikacin)
- AKAO bankrupt
- MLNT 2019 10-K
- NBRV, PRTK, &TTPH stock prices below $4

Chart: Alan Carr, Needham, Sept 2019 Antibiotics Update

Running the engine diagnostic – what could be wrong?

- **Bad signal** (companies encouraged to bring wrong product to market)
  - Classic critique of top-down planning
  - But: functional markets send accurate signals back to product development
- **Signal distortion** (signal was correct, but companies misinterpreted(or epi circumstances changed) and brought wrong products to market)
  - You might question plazomicin/Achaogen, but if everyone is in the same boat, perhaps it is a systematic issue and not a one off
- **Market distortion** (market not valuing needed products appropriately)

Possible lines of action

1. Inadequate signals to physicians (**labels**, guidelines, clinical studies)
2. Friction (delay in formulary adoption, delay in dx integration, breakpoints)
3. Inappropriate market valuations (**DRGs, unpriced positive externalities or unpriced inability to exclude free riders**)

*Given the focus of today's workshop, I will only cover the items in **bold***

1. Labels

- Plazomicin
- Ceftazidime/avibactam
- Lefamulin

Could we account for additional clinical information in a LPAD environment?

Plazomicin

WARNING: NEPHROTOXICITY, OTOTOXICITY, NEUROMUSCULAR BLOCKADE and FETAL HARM

See full prescribing information for complete boxed warning.

- **Nephrotoxicity has been reported with ZEMDRI. The risk of nephrotoxicity is greater in patients with impaired renal function, the elderly, and in those receiving concomitant nephrotoxic medications. (5.1)**
- **Ototoxicity, manifested as hearing loss, tinnitus, and/or vertigo, has been reported with ZEMDRI. Symptoms of aminoglycoside associated ototoxicity may be irreversible and may not become evident until after completion of therapy. (5.2)**
- **Aminoglycosides have been associated with neuromuscular blockade. During therapy with ZEMDRI, monitor for adverse reactions associated with neuromuscular blockade particularly in high-risk patients. (5.3)**
- **Aminoglycosides, including ZEMDRI can cause fetal harm when administered to a pregnant woman. (5.6, 8.1)**

Plazomicin

---------- INDICATIONS AND USAGE ----------

ZEMDRI is an aminoglycoside antibacterial indicated for the treatment of patients 18 years of age or older with Complicated Urinary Tract Infections (cUTI) including Pyelonephritis. (1.1)

As only limited clinical safety and efficacy data are available, reserve ZEMDRI for use in patients who have limited or no alternative treatment options. (1.1)

To reduce the development of drug-resistant bacteria and maintain effectiveness of ZEMDRI and other antibacterial drugs, ZEMDRI should be used only to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms. (1.2)

Ceftazidime / avibactam

AVYCAZ (ceftazidime and avibactam) for injection, for intravenous use
Initial U.S. Approval: 2015

----------RECENT MAJOR CHANGES----------

Indications and Usage, Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)	(*1.3*)	01/2018
Dosage and Administration	(*2*)	01/2018

----------INDICATIONS AND USAGE----------

AVYCAZ is a combination of ceftazidime, a cephalosporin, and avibactam, a beta-lactamase inhibitor, indicated for the treatment of patients 18 years or older with the following infections caused by designated susceptible Gram-negative microorganisms:

- Complicated Intra-abdominal Infections (cIAI), used in combination with metronidazole (*1.1*)
- Complicated Urinary Tract Infections (cUTI), including Pyelonephritis (*1.2*)
- Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP) (*1.3*)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of AVYCAZ and other antibacterial drugs, AVYCAZ should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. (*1.4*)

Lefamulin

INDICATIONS AND USAGE

XENLETA is a pleuromutilin antibacterial indicated for the treatment of adults with community-acquired bacterial pneumonia (CABP) caused by susceptible microorganisms. (1.1)

To reduce the development of drug resistant bacteria and maintain the effectiveness of XENLETA and other antibacterial drugs, XENLETA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.2)

A thought experiment…

- ESKAPEapenem “Greybox” statement:

> When used in LIMITED POPULATIONS, with limited or no treatment options, the following clinical information should also be considered: [Indication X, note to small clinical study A]

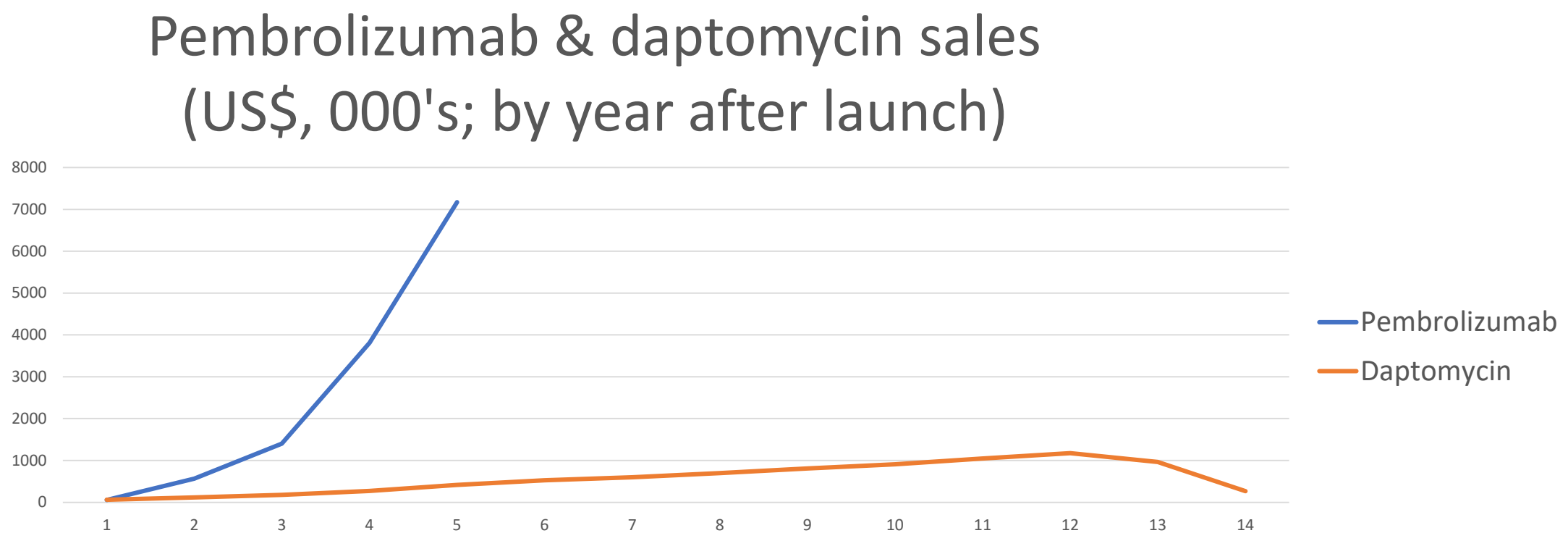
- Sunset the Greybox in [five] years, to encourage SNDAs

2. DRGs

- Cost-saving tool from Reagan Administration 1983
- Physicians are billed separately, but all other hospital expenses are in the bundled payment
- Drove down ALOS (discharge to subacute)
  - But: Drive-by deliveries, readmission penalties
- Retrospective cost structure discourages innovative products
  - NTAP gives 2-3 year partial carve-out (additional payment) until the new costs are included in the DRG recalculation
  - Never happens for new antibiotics (stewardship, et al)
- Companies are asking for a carve-out from Congress (DISARM) or CMS (FY2021 IPPS Rule)

Outterson K. A shot in the arm for new antibiotics? Nat Biotech 2019;37:1110-12.

Even in Part B, antibiotic sales curves are not like immune-oncology, but daptomycin was a success



3. Social value: **STEDI** as she goes

- ERG 2014: social value of antibiotics greatly exceeds the value the market is placing on these products
- UK Netflix pilot
  - Spectrum: broad / narrow
  - Transmission: treatment as prevention
  - Enablement: modern medicine (entire industry should step up)
  - Diversity: choices are good
  - Insurance: fire protection (but, free riders here)

Can FDA help with quantifying these values for particular drugs?

Sources: Outterson K, Rex JH. (pending 2019); York / NICE Papers; Sertkaya ERG 2014

Conclusions

- Many of these economic issues are beyond FDA's remit, but are in the wheelhouse of other agencies at HHS
- It might be worth exploring whether additional clinical information under LPAD authority (the "Greybox") could help inform clinicians and reduce frictional delays
- Support CMS if it chooses to carve-out QIDPs from the DRG
- Advance the conversation on broader social value of antibiotics (STEDI)