Approaches to TB Drug Development
An Industry Perspective

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Conflict of Interest Disclosure

- The presenter, Charles D. Wells, M.D., works for Sanofi.

Approaches to TB Drug Development

- Approaches taken from industry-based development programs:
  - 2005-2014, onward to future
- Regimens studied and why
- Trial design, endpoints and outcome definitions used
- Nuances of combination drug development, given background therapy (ex. MDR-TB)
- Challenges/barriers in development programs
- Moving through registration/application process
- Path forward

Industry Considerations - Background

- For industry, expediency – clock is ticking
  - Patent protection time-limited (development 10-12 yrs.)
  - Reason-to-believe – quick path to/through Proof of Concept (PoC)
- *M. tuberculosis* biology works against expediency
  - Previously with TB trials
    - 6 months (treatment) + 2 years follow-up; relapse as endpoint
    - Sensible from public health perspective; challenge for developers
  - Animal models and EBA (≤ 14 days) early tools, but with limitations
  - Sputum culture conversion (SCC) as surrogate marker
    - Earlier SCC clinically meaningful; important for public health
    - But when? 2 mo vs. later? – debate continues
    - Practical considerations – slow, contamination, capacity

Target Product Profile: New TB Drug/Regimen Development Pathway to Target Label

Description of the Mechanism of Action	• Novel mechanism of action active against current resistant strains • No cross resistance between drugs in the regimen • Active on resistant strains to all available treatment
Indications & Target population	• Patients with active tuberculosis irrespective of HIV status: o Minimum case ➔ 1st line treatment for active M(X)DR TB† o Base case ➔ 1st line treatment of DS-TB‡, M(X)DR TB
Dosage and administration	• Oral fixed dose combination tablet; once daily
Efficacy	• M(X)DR-TB: Superior to SoC / optimized background regimen (OBR) • DS-TB: Non-inferior to SoC with shortened treatment duration (<< 6 months)
Safety	• Safer than SoC/OBR • Limited QT prolongation

†M(X)DR-TB – Multidrug/Extensively Drug Resistant Tuberculosis
‡DS-TB – Drug Susceptible Tuberculosis

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Development Strategies for New TB Agents/Regimens Target Patient Population

- M(X)DR-TB
  - Unmet medical need - better efficacy & shorter/easier/safer regimens
  - Superiority design (Sacks LV, Behrman RE. Tuberculosis, 2008):
    - "..exploring efficacy…in setting of drug resistant disease may present certain opportunity"
    - "..possibility of accelerated approval based on a surrogate endpoint"
  - Confers efficiency, but field steadily changing….
- DS-TB
  - RIPE highly efficacious
  - Shortening treatment (profoundly) as essential goal
  - Non-inferiority design

Development of New Tuberculosis Agents
Setting Stage for M(X)DR-TB as Pathway, Pre-2005

- Green Light Committee (GLC)† /Global Fund launch and expansion, for M(X)DR-TB, 1999-2005:
  - Limited access to treatment
    - Cumulative total: ≤ 20,000 patients worldwide
  - Limited diagnostic/DST capacity
  - Large reservoir of "chronic" patients (previous 2nd-line treatment)
  - Weaker 2nd-line drugs – early gen. fluoroquinolones, etc.
  - 24 months for treatment with high toxicity
  - Lack of experience with clinical trials/GCP
- Best programs in early years‡:
  - 2-month SCC = 30%
  - Cure: ≤ 65%; mortality: 10%-20%

†Gupta R, et al. Trop Med Int Health. 2002
‡Leimane V, et al. Lancet 2005; Mitnick C, et al. N Engl J Med 2005.

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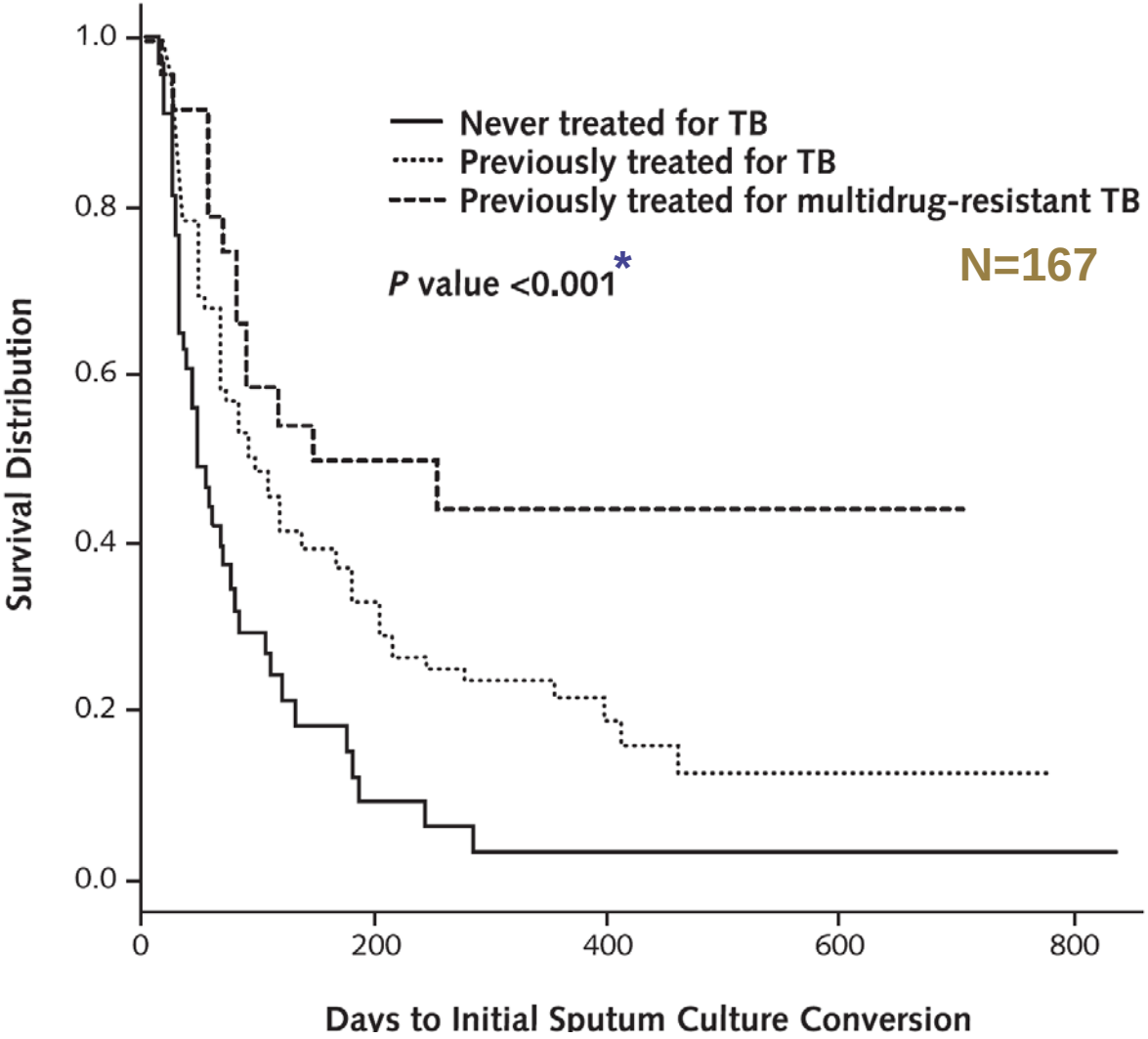
Time to SCC vs. Treatment History in MDR-TB Patients, Latvia, 2000† - Previous 2nd-line Treatment with Lower/Later SCC



* *log-rank test of the equality of the 3 survival curves*

†Holtz TH, et al. Ann Intern Med 2006

Developing New Agents for Tuberculosis, 2005-2014

- M(X)DR-TB as initial target for Bedaquiline and Delamanid
  - GLC sites as network and labs/liquid media;[1-3]
  - Stringent definitions for SCC/outcomes from WHO
  - SCC as endpoint from FDA & EMA (2009/2010); accelerated pathway
  - Design: optimized background regimen (OBR) + test agent vs. OBR
    - Bedaquiline (N=160): 6-mos. SCC: 79% vs. 58%[4]
    - Delamanid (N=481): 2-mos. SCC: 45% vs. 30%[5]
  - Limited datasets → restricted label/patient population
- Drug-drug interaction and treatment optimization trials of new agents have followed[6,7]
- However, field is steadily transforming…..

[1] Mitnick C, et al. PLoS Med. 2007;[2]Tupasi T, et al. Bull World Health Organ 2016
[3]Mycobacteriology Laboratory Manual:
http://www.stoptb.org/wg/gli/assets/documents/gli_mycobacteriology_lab_manual_web.pdf
[4] Gler MT, et al. N Engl J Med 2012; [5] Diacon AH, et al. N Engl J Med. 2014.
[6]https://clinicaltrials.gov/ct2/show/NCT02583048?term=Delamanid&draw=1&rank=3
[7]NCT02754765 Evaluating Newly Approved Drugs for Multidrug-resistant TB (endTB)

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Field for M(X)DR-TB – Progressive Improvements

- Expanding treatment capacity – GLC/Global Fund
  - >100,000 M(X)DR-TB patients treated annually
  - Decreased population of chronic patients
- Better diagnosis – from months to days - huge impact!
- Better drugs/access
  - Existing: Moxifloxacin, Linezolid, Clofazamine
  - New: Bedaquiline, Delamanid
- Shorter regimens among patients without previous 2nd-line treatment†
  - Bangladesh, 9-month regimen; N=206, Cure: 88%
- Greatly improved treatment success…
  - WHO reports overall‡: 52%
  - Mature MDR-TB treatment programs: ≥ 80%±; XDR-TB: ≥ 60%

†Van Deun A, et al. Am J Respir Crit Care Med 2010
‡ WHO Global Tuberculosis Report, 2016.
±JP Cegielski, et al. CID, 2016.

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M(X)DR-TB Outcomes from PETTS, 2005-2008†‡

- † PETTS – Preserving Effective TB Treatment Study
- Multinational prospective cohort study - N=1244 patients; 9 countries/26 sites
- Treatment: 5-drug intensive phase (6-8 mos.); total 20-24 mos.

Characteristic	Patients With Known Treatment Outcomes[a] (n = 973)			
	Successful Outcome, No. (%)	Poor Outcome, No. (%)	*P* Value	Risk Ratio (95% CI) for Treatment Success
GLC approval				
Yes	503 (82.9)	104 (17.1)	<.001	1.39 (1.27–1.52)
No[f]	219 (59.8)	147 (40.2)		
No. of SLDs tested in local laboratory				
0–2	288 (65.7)	150 (34.2)	<.001[c]	Reference
3	281 (79.1)	74 (20.8)	<.001	1.20 (1.10–1.31)
4–7	153 (85.0)	27 (15.0)	<.001	1.29 (1.18–1.42)
Previous treatment history				
None	111 (82.8)	23 (17.2)	.002[c]	Reference
First-line drugs	525 (74.1)	184 (26.0)	.03	0.89 (.82–.98)
SLDs	86 (66.2)	44 (33.9)	.002	0.80 (.69–.93)

‡ JP Cegielski, et al. CID, 2016.

Improvement in M(X)DR-TB Treatment Outcomes, Republic of Korea, 1996 - 2010†

	MDR-TB patients (1996–2000) (*n* = 86)	MDR-TB patients (2001–2005) (*n* = 125)	MDR-TB patients (2006–2010) (*n* = 123)	*P* value
Treatment success				
Total	46 (53.5)	86 (68.8)	103 (83.7)	<0.001
Cure	43 (50.0)	64 (51.2)	92 (74.8)	
Completed	3 (3.5)	22 (17.6)	11 (8.9)	
Unfavourable outcomes				
Total	40 (46.5)	39 (31.2)	20 (16.3)	<0.001
Failure	24 (27.9)	16 (12.8)	7 (5.8)	
Relapse	3 (3.5)	3 (2.4)	2 (1.6)	
Death	9 (10.5)	10 (8.0)	5 (4.1)	
Default	4 (4.6)	10 (8.0)	6 (4.8)	
Relapse rate (cases per 1000 person-years)	10.9	6.9	8.2	0.174

- Improved outcomes with more frequent use of later generation FQs and linezolid
- Linezolid for those refractory to 3-6 months Rx and/or XDR-TB (21%), 2006-2010

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†Kwak N, et al. Int J Tuberc Lung Dis. 2015; 19(5):525-530

Improving SCC/Outcomes for XDR-TB, 2005-2014

Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis[†]

	Immediate Start (n=19)	Delayed Start (n=20)	Overall Group
Sputum Culture Conversion			
4-month	15/19 (79%)	7/20 (35%)	
6-month			34/39 (87%)
Treatment Outcomes			
Cure			27/38 (71%)
Lost to f/u			3/38 (8%)
Failure			4/38 (11%)
Withdrew			4/38 (10%)

Management of Extensively Drug-Resistant Tuberculosis[‡] in Peru: Cure Is Possible

	N	Treatment Success (%)	Death (%)
XDR vs. MDR (Individualized treatment)			
XDR	37	18 (49)	8 (22)
MDR	494	372 (75)	39 (8)
XDR vs. MDR (Individualized treatment + 2nd-line DST)			
XDR	14	11 (78)	1 (7)
MDR	334	264 (79)	26 (8)

Delamanid for Extensively Drug-Resistant Tuberculosis [±]

2-month SCC
- DLM+OBR: 7/16 (44%)
- OBR: 1/10 (10%)

Mortality at 24 months
- ≥ 6 mos. DLM – 0/17 (0%)
- ≤ 2 mos. DLM – 2/9 (22%)

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[†]Lee M, et al. N Engl J Med 2012; Lee M, et al. N Engl J Med 2015

[‡]Bonilla CA, et al. PLoS ONE, 2008; [±]Gupta R., et al. *N Engl J Med*. 2015

Pathway Forward – New Agent/Regimen Development (1)

- Advances in non-clinical realm to improve translational accuracy for selection/development of new regimens†
  - Models – “Of Mice (Kramnik), Marmosets and Men” + hollow fiber infection
  - Better details on drug synergy/antagonism, cross resistance, differential and complementary PK, etc.
- Patient population – given better diagnosis, new agents and evolving standards
  - Pre-XDR/XDR-TB – superiority, but which comparator(s) – regimens with linezolid, bedaquiline, delamanid +/- clofazamine?
  - MDR-TB – shortened (9-month) regimen if no resistance to fluoroquinolones/injectables
  - DS-TB – non-inferiority trials with RIPE as comparator - treatment shortening

† Nuermberger E, et al. Antimicrob Agents Chemother 2016

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Pathway Forward – New Agent/Regimen Development (2)
Measuring Treatment Effect/Endpoints - Challenges

- Culture-based endpoints remain obstacle – limitations/inefficiencies
  - Slow results - solid medium, 4-6 weeks; MGIT, 42 days
  - Quanititative cultures
    - Most reliable method to determine bacillus number
    - High workload → serial dilutions, limited labs with capacity
  - Liquid medium – MGIT Time to Detection (TTD) – semi-quantitative
    - Correlation between agar CFU/TTD changes during treatment[†‡]
    - Likely reflecting recovery of TB bacilli from exposure to TB drugs during treatment
- EBA (14-day) – proof of activity; but with limitations
  - Some drugs, limited EBA (PZA, LZD) – but robust treatment effect
- Early SCC for M(X)DR-TB – easier to achieve with new agents…

[†]Bowness, et al.J Antimicrob Chemotherapy, 2015.
[‡]Liu Y. [†]http://www.resisttb.org/wp-content/uploads/2017/06/Otsuka-LAM-test_Resist-TB-Webinar_06-22-2017.pdf

Pathway Forward – New Agent/Regimen Development (3) Measuring Treatment Effect/Endpoints – Potential New Tools

- Combination rules for TB regimen development[1]
  - Demonstrating contribution of each drug in combination to extent possible (not sufficiently from existing data)
  - Requires regimen EBA +/- regimen SCC studies – factorial design
  - Time and resource intensive – more limited # of regimens evaluated
- Better tools for measuring treatment effect/endpoints
  - PET/CT imaging: early quantitative measure of anti-TB drug efficacy[2]
  - Sputum Lipoarabinomannan (LAM)
    - Quantitative (vs. MGIT/TTD)
    - Potential pharmacodynamic biomarker
    - Immunoassay to measure concentration with “real time” read going through qualification process for drug development tool[2]
      - Completed trial[3]; NextGen Trial (NCT02371681)[4]

[1]Guidance for Industry – Codevelopment of Two or More investigational Drugs for use in Combination; US DHSS FDA CDER 2013;
[2]Coleman MT, et al. Science Translational Medicine, 2017;[4]ClinicalTrials.gov: NCT02371681; NextGen EBA;
[3]Liu Y. †http://www.resisttb.org/wp-content/uploads/2017/06/Otsuka-LAM-test_Resist-TB-Webinar_06-22-2017.pdf

Pathway Forward – New Agent/Regimen Development (3) Trial Design Options

- Conventional design (up to 10 years)
  - SAD/MAD + PoC (EBA of combinations + 2-month combinations)
  - Phase 3 with fixed/balanced randomization
- Adaptive trial designs → greater efficiency
  - Bayesian (vs. balanced) adaptive design (i.e. endTB).
  - Multi-arm multi-stage (MAMS) design (i.e. PANACEA)
  - Both use information (i.e. SCC) to 'adapt' trial
    - Bayesian adaptive more efficient if >1 effective regimen
    - MAMS more efficient if only 1 effective regimen
- Key choice for strategy, thresholds, reliance on markers (LAM, EBA):
  - Relaxing standards → high % of candidates go through; false +'s
  - Calibrate screening → no false +'s; exclude viable treatments

Bayesian Response-Adaptive Trial in MDR-TB: endTB Trial†

- Phase 3 non-inferiority trial of MDR-TB treatment using Bayesian adaptive randomization to examine 5 new shorter experimental regimens:‡

Table 1. Six regimens proposed for testing in *endTB* trial.

#	Bdq	Dlm	Cfz	Lzd	FQ	Z
1	Bdq			Lzd	Mfx	Z
2	Bdq		Cfz	Lzd	Lfx	Z
3	Bdq	Dlm		Lzd	Lfx	Z
4		Dlm	Cfz	Lzd	Lfx	Z
5		Dlm	Cfz		Lfx	Z
6	Conventional control, composed according to WHO Guidelines, including the possible use of delamanid or bedaquiline					

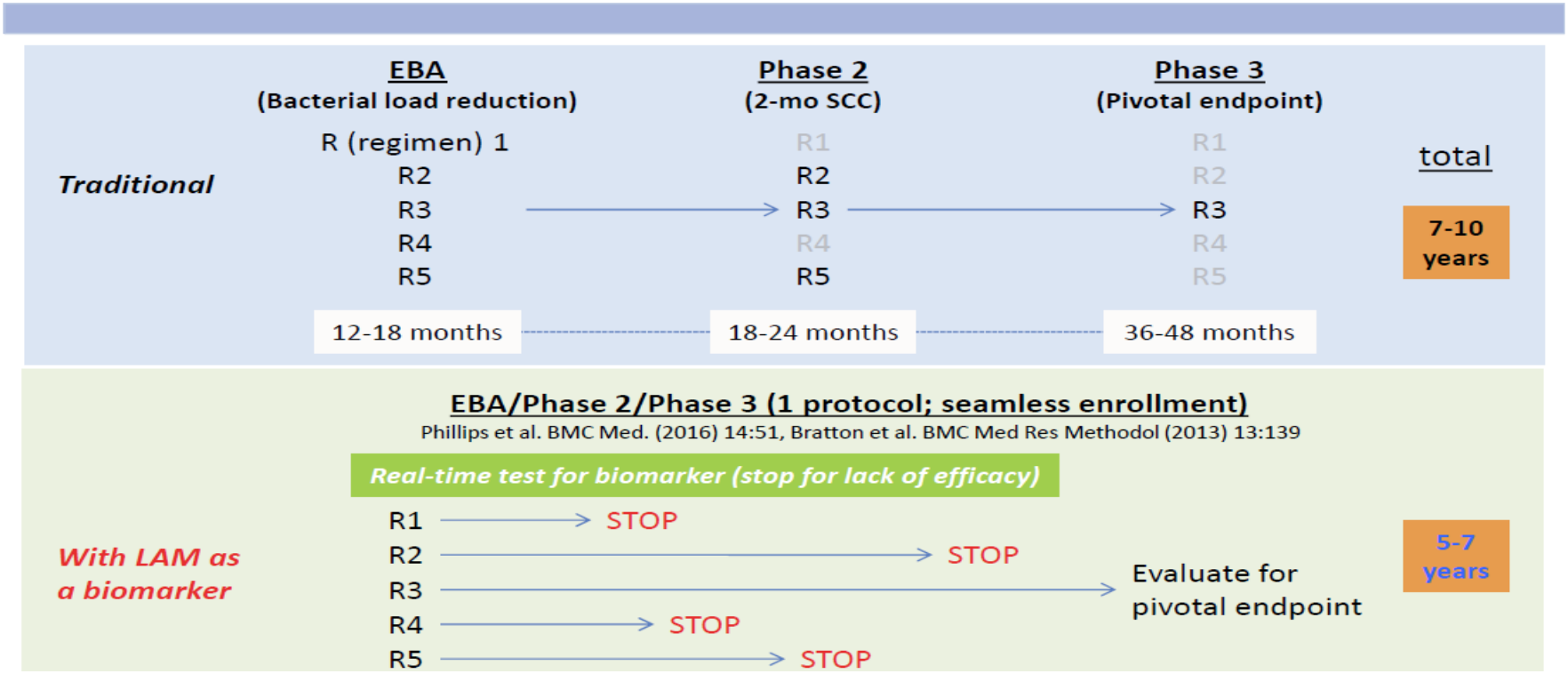
Bdq: bedaquiline; Dlm: delamanid; Cfz: clofazimine; Lzd: linezolid; FQ: fluoroquinolone; Mfx: moxifloxacin; Lfx: levofloxacin; Z: pyrazinamide.

- Reduced trial size (< 1,000 pts.) and duration with multiple superior regimens potentially identified; from simulation:
  - 27% fewer than balanced randomization
  - 80% power to detect up to 2 novel regimens non-inferior (margin 12%) to control (70% efficacy) at 73 weeks post randomization.
  - Up to 25% more participants would receive non-inferior regimens.

†ClinicalTrials.gov Identifier: NCT02754765 Evaluating Newly Approved Drugs for Multidrug-resistant TB.
‡Cellamare M, et al. Clinical Trials, 2017.

Envisioned Impact of Adaptive Trial Design + "Real Time" LAM: Potentially Shortens Development Time by 2-3 Years†

- Phase 1: SAD/DDI; MAD to include target population (EBA)
- Seamless Phase 2/3 trial with adaptive design of combinations



†http://www.resisttb.org/wp-content/uploads/2017/06/Otsuka-LAM-test_Resist-TB-Webinar_06-22-2017.pdf

Broader Considerations in Moving Forward To Registration

- Early engagement of authorities – seek critical feedback on design of programs/trials in face of steadily evolving field and pay attention!
  - Patient population, comparator arm, endpoints, follow-up
  - Trial design - special protocol assessments
  - Combination rules† – in vivo models + EBA for individual agents sufficient?
- Regulatory Harmonization across authorities – essential to making new treatments available to broader swath of patients, sooner
  - EMA, PMDA, and FDA met in Vienna in April 2017; agreement to align certain data requirements to stimulate development to fight antimicrobial resistance (AMR) and protect global public health.
- TB is “priority pathogen” in fight against AMR
  - Push/pull mechanisms to encourage and support new TB drug/regimen development are crucial

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†Guidance for Industry – Codevelopment of Two or More investigational Drugs for use in Combination; US DHSS FDA CDER 2013

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