Developing Antibacterial Drugs for Patients with Unmet Need: Experience and Recommendations

Ian Friedland, M.D.

Chief Medical Officer, Achaogen

FDA Workshop

July 2016

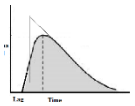
Disclosure: Full time employee of Achaogen

Achaogen's Position

- Infeasible to conduct fully powered trials given low number of enrollable patients
- Studies conducted in patients with unmet need provide critical data for clinicians
- Smaller datasets provide highly descriptive information for prescribers and can support exposure/response analyses
- Imperative that data in the unmet need population, including outcomes, is integrated into the product label

Standard Indications Do Not Address Unmet Need

Differences in Patient Populations are Profound

	Standard Study cUTI/AP	Unmet Need Study BSI, HABP/VABP due to CRE
 Unmet Need	No	Yes
 Patient Population	Few co-morbidities Low mortality No need for organ support	Significant co-morbidities High mortality Need for organ support
 Duration of Therapy	≤ 7 days	7 to 14 days
 Pathogens	Usual resistance ~20% ESBLs, Few CRE Polymicrobial infections rare	All MDR Some XDR or PDR Polymicrobial infections common
 PK	Similar to healthy volunteers Mildly increased V_d	Less predictable More variable Significantly increased V_d
 Combination Rx	Single agent data only	Adequate coverage may require use of combination therapy

Plazomicin is a New Aminoglycoside with Broad Enterobacteriaceae Activity Including CRE

In vitro Activity vs. Clinical Isolates of CRE

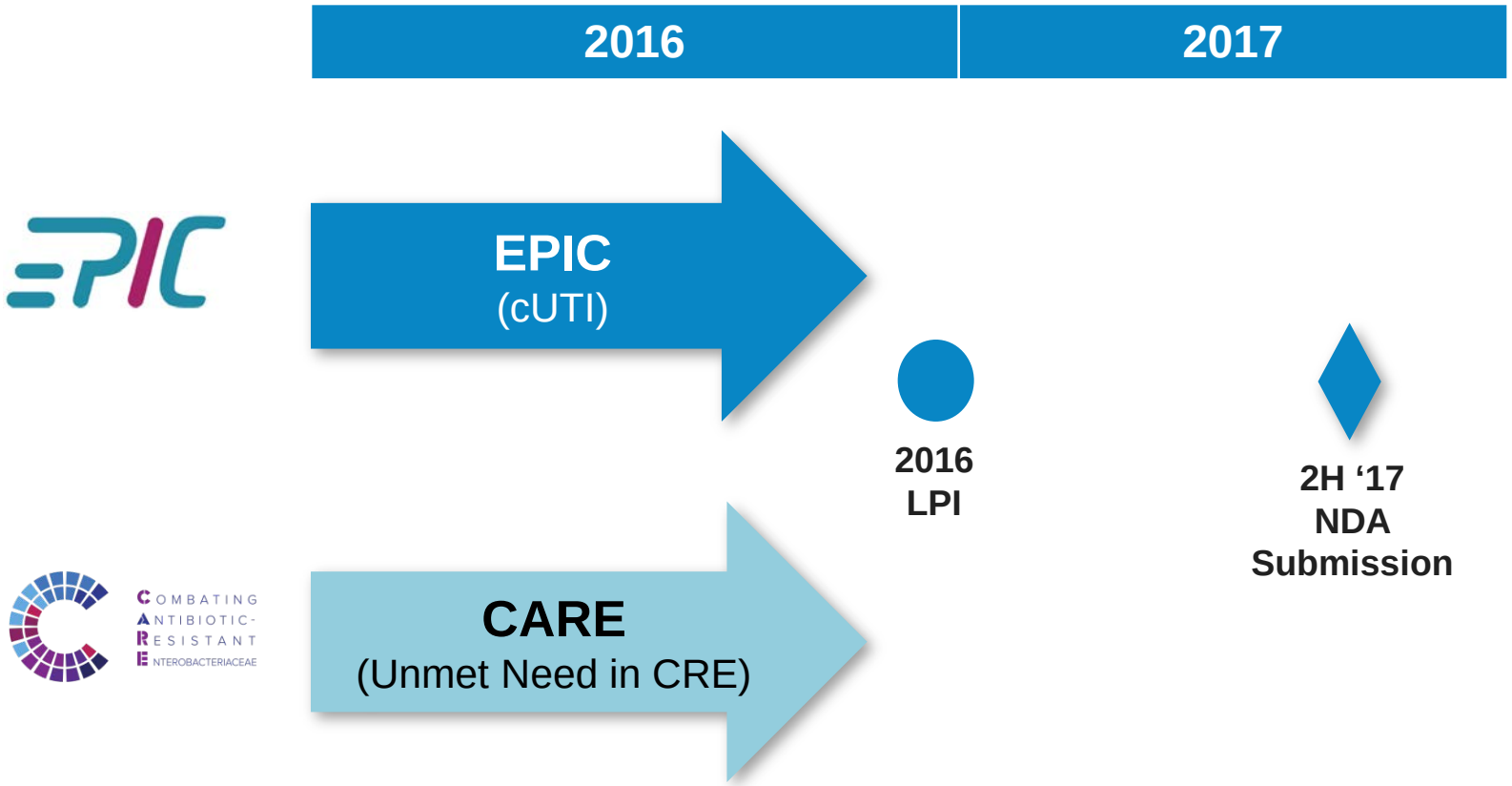
Compound	Class	N	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
Plazomicin	**Aminoglycoside**	**983**	**0.5**	**2**
Gentamicin	Aminoglycoside	978	4	>64
Amikacin	Aminoglycoside	983	32	64
Ciprofloxacin	Fluoroquinolone	822	8	8
Ceftazidime	Cephalosporin	498	64	64
Piperacillin/tazobactam	Penicillin/Beta-lactamase inhibitor	756	>64	>64
Tigecycline	Glycylcycline	804	1	4
Colistin/polymyxin B	Polymyxin	877	1	8

Susceptible

Non-Susceptible

Data from 1) *J Chemother* 2012;**24**:191-4, 2) *J Antimicrob Chemother* 2011;**66**:48-53, 3) *J Antimicrob Chemother* 2010;**65**:2123-7, 4), *Antimicrob Agents Chemother* 2009;**53**:4504-7, 5) *IDSA* 2014:E-1168B, 6) I *ECCMID* 2014:P1682

EPIC (cUTI) Provides Basis for Registration, CARE Provides Critical Data in an Unmet Need Population

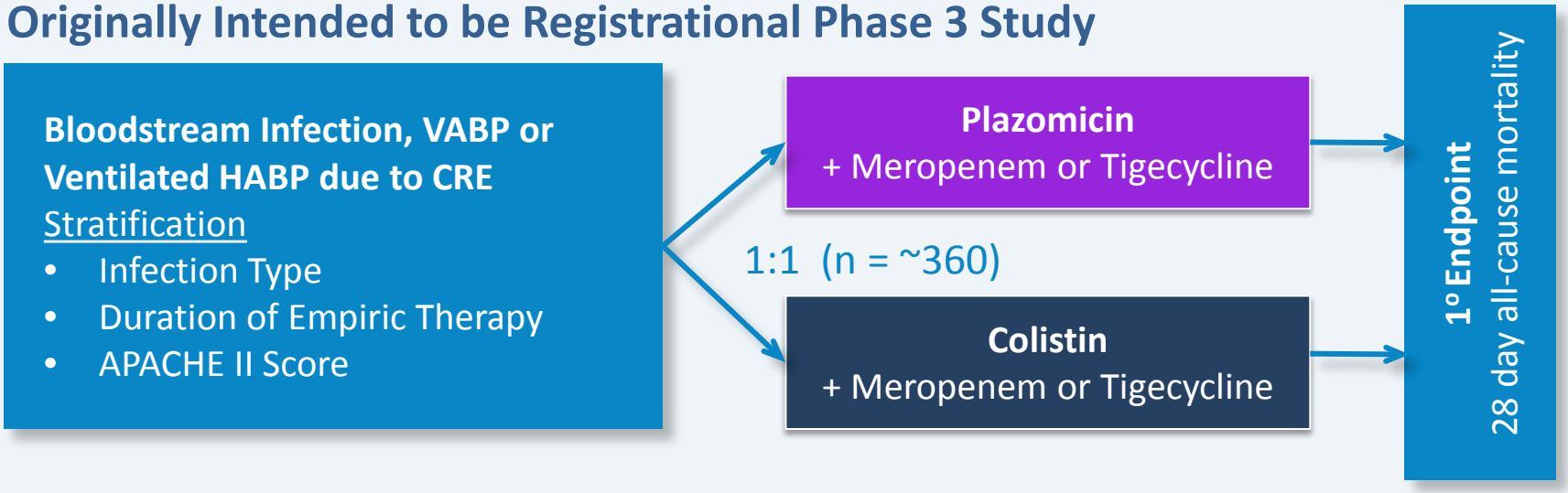


Achaogen's plazomicin program is funded in part with Federal funds from the **Biomedical Advanced Research and Development Authority**, Office of the Assistant Secretary for Preparedness and Response, Office of the Secretary, Department of Health and Human Services, under Contract No. HHSO100201000046C.

Original CARE Study Design
Pathogen-specific, Randomized, Open-label, Superiority

COMBATING ANTIBIOTIC-RESISTANT ENTEROBACTERIACEAE

Originally Intended to be Registrational Phase 3 Study



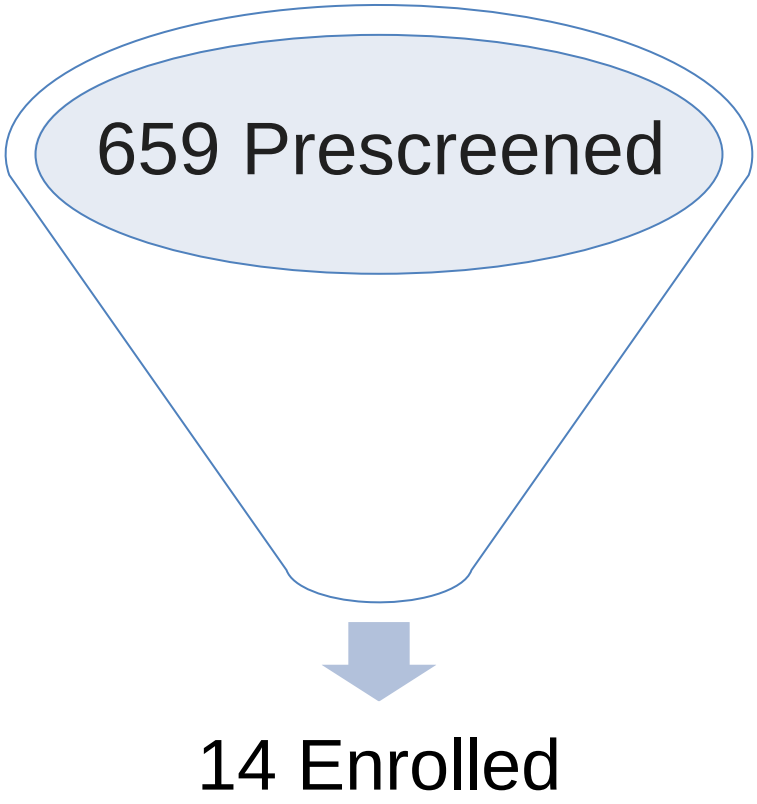
- Superiority in 28d ACM
- Assumed 35% mortality in the Control Arm (Meta-Analysis) with 12% absolute reduction with plazomicin
- 70% Power
- One-sided alpha of 0.05
- 286 pts with proven CRE → Total N of 360 (evaluability of 80%)

Feasibility Assessment Suggested 3 Years of Enrollment to Reach 360 Patients

Country	No. sites recommended	CRO Projected Enrollment (pts/site/yr)	No. Pts per year
Germany	5	1.2	6.0
Greece	10	1.4	14.4
Israel	5	2.4	12.0
Poland	7	1.3	10.9
Russia	11	1.8	19.8
Spain	7	1.8	12.6
Ukraine	6	0.9	5.8
Brazil	12	2.4	28.8
USA	5	0.9	4.8
TOTAL	**68**	**Avg: 1.32**	**115**

Enrollment Significantly Lower Than Projections

Early Metrics in CARE



Major Reasons for Prescreen Failure (~50%)

- Pathogen is not CRE
- >72 hrs empiric therapy

Additional Reasons

- Lack of consent
- Polymicrobial infection
- APACHE II Score <15
- Emerging colistin resistance

Enrollment Challenges
Experience from One Hospital in Greece

- 17 patients with CR-*Klebsiella* in 4 month period
- None from ICU
- 2 patients were enrolled
- Reasons for exclusion
  - 7 patients had APACHE II score < 15
  - 4 isolates were resistant to colistin
  - 2 refused consent
  - 1 patient terminal
  - 1 concomitant BSI with *A. baumannii*

Two Amendments Designed to Boost Enrollment While Maintaining Potential for Superiority

Cohort 1: BSI, HABP or VABP

Presumed or Documented CRE
Restricted Eligibility
- APACHE II < 15 ✗
- Known colistin resistance ✗
- Polymicrobial infection ✗
- Need prohibited antibiotics ✗

1:1 N~360

Plazomicin
+ Meropenem or Tigecycline

Colistin
+ Meropenem or Tigecycline

Primary Endpoint: Mortality at D28 or Significant Disease-Related Complications

Secondary Endpoints

Cohort 2: BSI, HABP, VABP, cUTI or AP

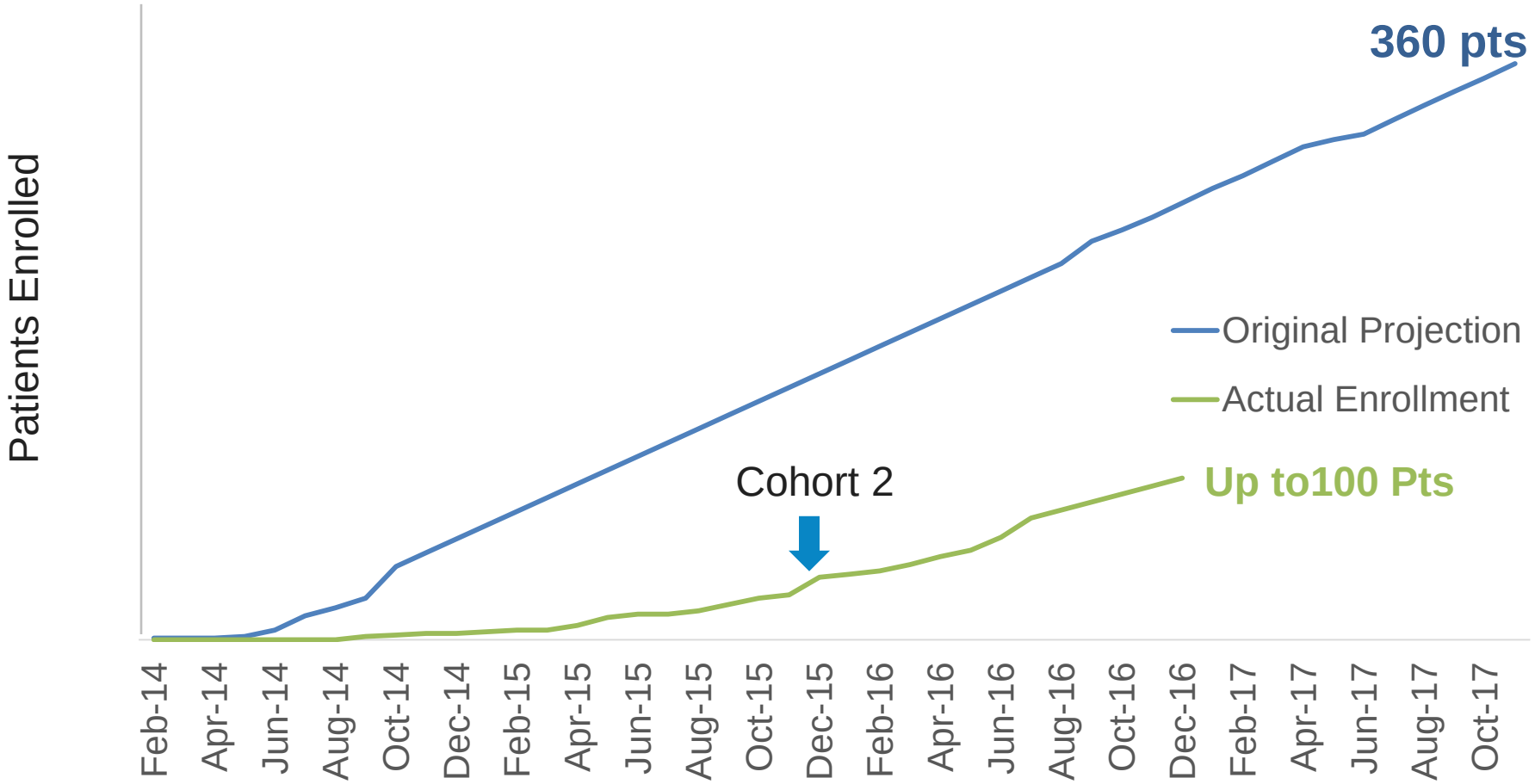
Presumed or Documented CRE
Broader Eligibility
- cUTI or AP ✓
- APACHE II ≤ 30 ✓
- Known colistin resistance ✓
- Polymicrobial infection ✓

BSI/HABP/VABP: Plazomicin + any suppl. antibiotic (N~50)

cUTI/AP: Plazomicin monoRx. +/- oral switch (N~50)

Patients can only enroll in cohort 2 if they are not eligible for cohort 1

Despite Significant Site Engagement and Broadening Eligibility, Enrollment Potential Limited



Lessons Learned from CARE Real World Experience

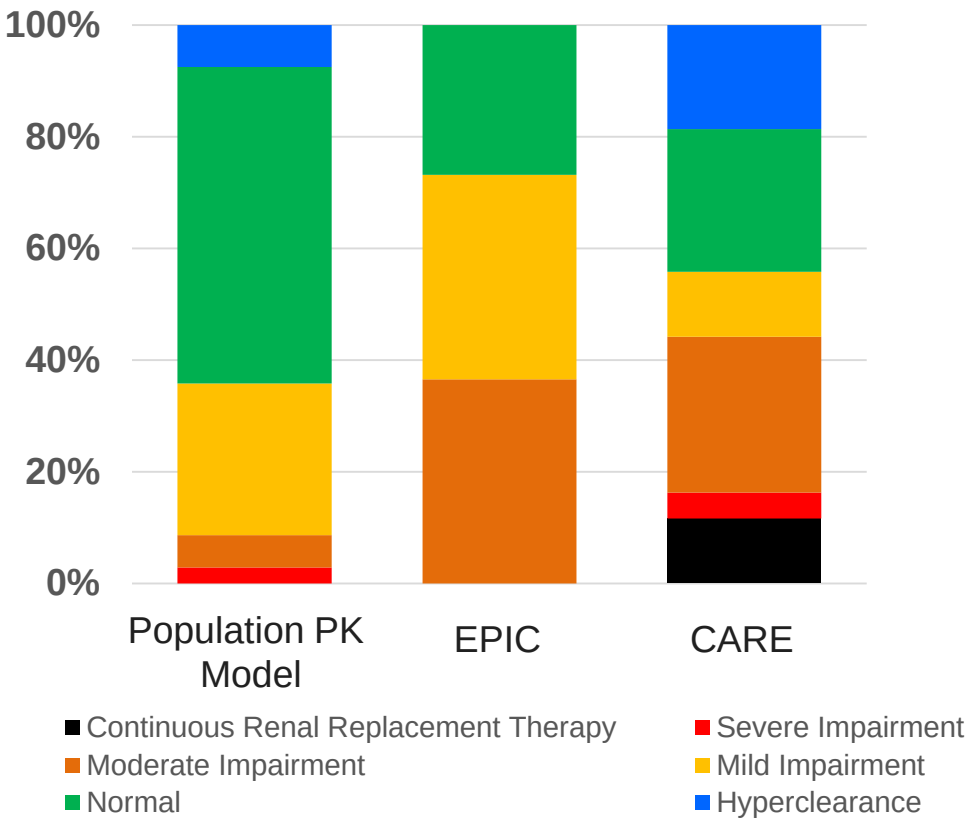
- Site surveys overestimated potential enrollment
- Only a small subset of sites enrolled patients
- Superiority study only feasible if many countries have CRE incidence similar to Greece
- Barriers to enrollment evolve: resistance to comparator, study competition, etc
- Intensive site engagement critical to support enrollment
- Studies are expensive; BARDA support essential to the program

Critical to Include Data in the Label to Ensure Information is Available to Prescribers

- Efficacy data in unmet need population, including clinical outcomes of highly resistant infections
  - Provided in context of proven efficacy in “usual” population
  - Nature of dataset, including uncertainty, can be highlighted
- PK in different populations
- Unique microbiological data
- Safety information in different populations
- Combination therapy

Critical Data Generated in CARE to Guide Plazomicin Use in Unmet Need Population

Baseline renal function in CARE is distinct from EPIC and Population PK Model



Broad Range of Renal Function

Difficult to Study in Phase 1 or cUTI Population

More Variable Drug Exposure

Allows Exposure/Response Analyses

Implications for Dosing, Including Guidance for Dose Adjustment

ACHAOGEN

CARE Provides Unique Microbiology to Inform Label and Support Breakpoint Assessment

Organism	Study	
	CARE	EPIC
Enterobacteriaceae	✔	✔
Multi-drug resistant Enterobacteriaceae	✔	✔
Aminoglycoside resistant Enterobacteriaceae	✔	✔
CRE	✔	X
Colistin-resistant CRE	✔	X
Tigecycline-resistant CRE	✔	X

- Pathogens from CARE provide data on higher MIC organisms, supporting clinically relevant breakpoint assessment
- Different bacterial species in CARE vs. EPIC

Conclusions

- Infeasible to conduct rigorous inferential trials given low number of enrollable patients
- Studies conducted in patients with unmet need provide critical data for clinicians
- Smaller datasets provide critical information for prescribers
- Imperative that data in the unmet need population, including outcomes, is integrated into the product label
- **If the regulatory path is clear, studies in unmet need population are more likely to be undertaken and funded**

Recommendations for Viable Study Designs

Small, Efficient Studies with Enrollment at Time of Empiric Therapy

Start with what's feasible: 40-80 patient studies

More sensitive endpoints (e.g. clinical response in BSI, HABP/VABP)

Aim for nearly all or all patients to receive study drug

Consider external or shared controls (trial network)

Designs that allow empiric therapy (rapid diagnostics can help)

Combination regimens: polymicrobial infections, empiric therapy

Harmonization between FDA and EMA