

AST Device Development: The Pharma Perspective

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Disclosures

- Kevin Krause is an employee of Achaogen, Inc.

Significant Progress has Been Made in Antibacterial Drug Development *But Fundamental Challenges in AST Development Remain*

- Antibiotics that address unmet medical needs are coming to market faster
 - Use of the 505b2 pathway
 - Streamlined development pathways
 - Expedited NDA reviews
- This has been driven by renewed attention to the space with focus on innovation
 - FDA/EMA collaboration
 - The GAIN Act
 - BARDA, NIAID (ARLG) and CDC initiatives
- However, AST development has not kept pace
 - New drugs still launch with few to no commercial AST tests available
 - Physicians reluctant to use new antibacterials without AST

We need simultaneous approval of drug with the AST device, which can only be accomplished with fundamental changes in how ASTs are developed

Three Fundamental Challenges Need to be Addressed

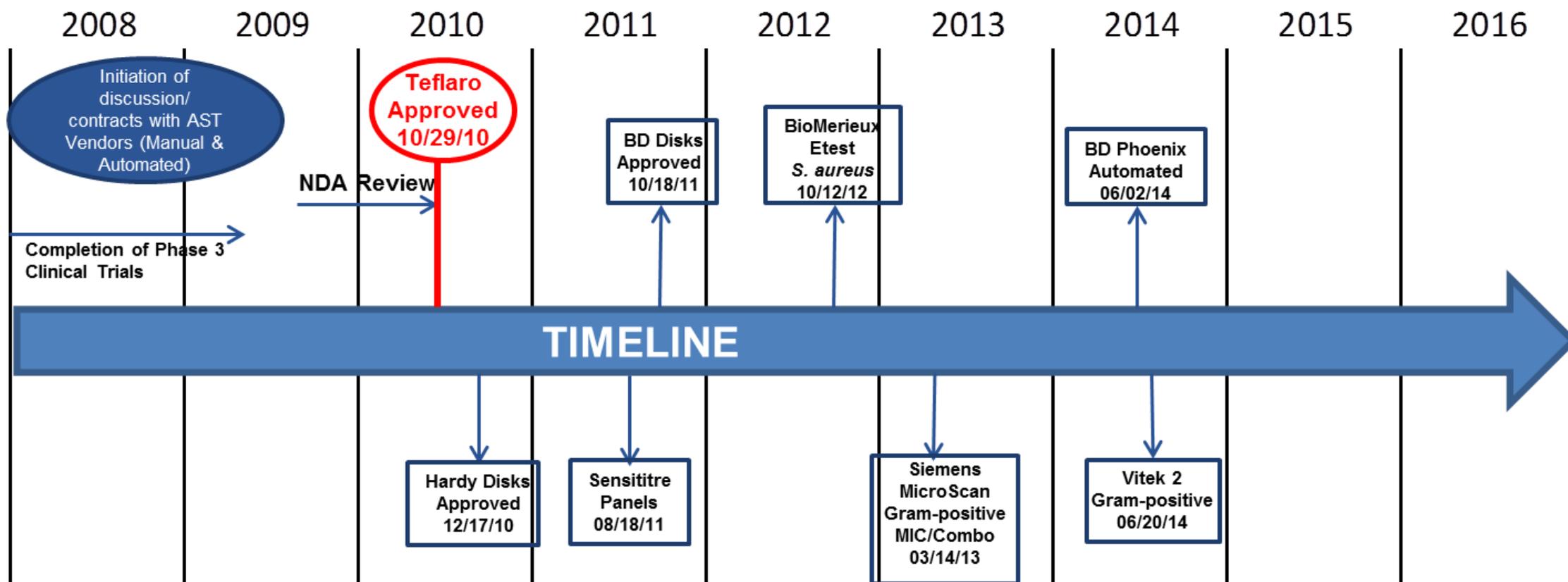
- Eliminate delay between drug and AST device approval
- Timely data updates for marketed drugs is slow (e.g. updating breakpoints, improving performance)
- Seamless integration of communications between Pharma, AST device developers, CDER and CDRH

Challenge #1 - The Lag Between Drug and AST Approval Creates a Significant and Unnecessary Obstacle to the Provision of High Quality Patient Care

- There is an urgent need for new antibacterials to treat MDR infections
- Identifying patients that would benefit from new antibiotics is challenging without AST
 - Drives potential for inappropriate antibiotic selection
 - Poor clinical outcomes for patients
- Negatively impacts timely susceptibility feedback post drug launch
 - Delayed input on what additional new clinical data would be most useful to clinicians
 - Delays knowledge of resistance patterns and real-world AST method reliability

The Regulatory innovation that has enabled streamlined antibiotic development urgently needs to be expanded to incorporate AST device development

A Recent Example - 510(k) Clearance Timeline for Ceftaroline (Teflaro™) AST



Automated Devices Were Not Cleared Until Almost 4 Years Post Drug Approval

The Lag in AST Approval Has Been Exacerbated by Accelerated Drug Approvals

- Historically, the registrational pathway for most drugs included 4+ Phase 3 studies
- Approval of new agents addressing an unmet medical need based on streamlined development pathways exacerbates lag between drug and device approval
 - Avycaz™ approved based on Phase 2 data, potential to address unmet medical need
 - BUT no accelerated regulatory pathway for AST exists
 - As of September 2016 (19 months post-approval), only disks and TREK Sensititre available

Current AST development timelines delay new antibiotics getting to patients

Desired State:

Enabling Simultaneous Review of an NDA and an AST 510(k)

Revise 510(k) Requirements for Organism Testing

- Use Phase 3 Central Lab generated data from Investigational devices as an alternative to the requirement for data from “Fresh Clinical Organisms” for the 510(k)
- Revise rules on only using data from species in the approved package insert when related organisms are available (e.g. Enterobacteriaceae)

Establish AST Centers of Excellence, as Part of a National Surveillance Program, that Test New Drugs Early in Development

- Identification of resistant organisms for use by AST companies during development
- Expand publically available “Clinical Stock” and “Challenge Set” organisms to address 510(k) requirements
- Added benefit – understand the true spectrum of activity for new antibiotics

Consider a “Limited Use” Approach to 510(k) Clearance

- Application of a limited use statement for new AST devices for drugs that address an unmet medical need when exact performance and usage information aren't available

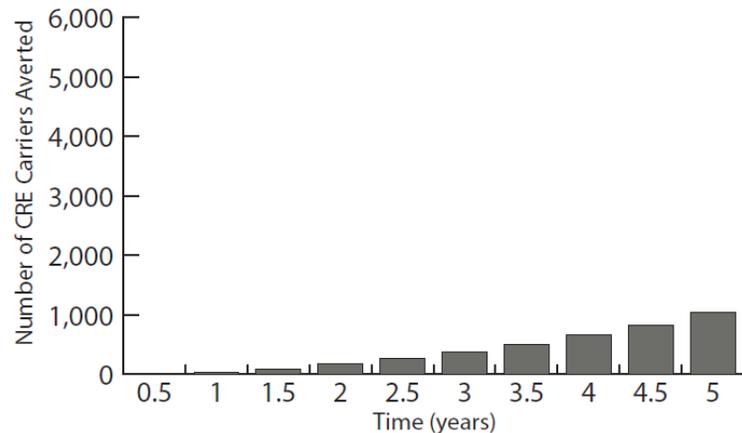
Challenge #2 – Making Changes to AST Devices is Slow and Hampers Development of AST for New Drugs

- Outdated breakpoints for approved drugs leads to poorly informed treatment decisions and the potential for worse clinical outcomes
- Implementation of Breakpoint Updates
 - Significant lag time between breakpoint change and implementation
 - Takes too long to collect required data
 - Strains limited resources at AST companies and limits their capacity to make AST available for new drugs
- Examples:
 - Telavancin AST development was stalled when automated devices were shown to have difficulty detecting VISA/VRSA
 - Ceftaroline AST development was stalled when automated devices had problems with piperacillin-tazobactam reporting

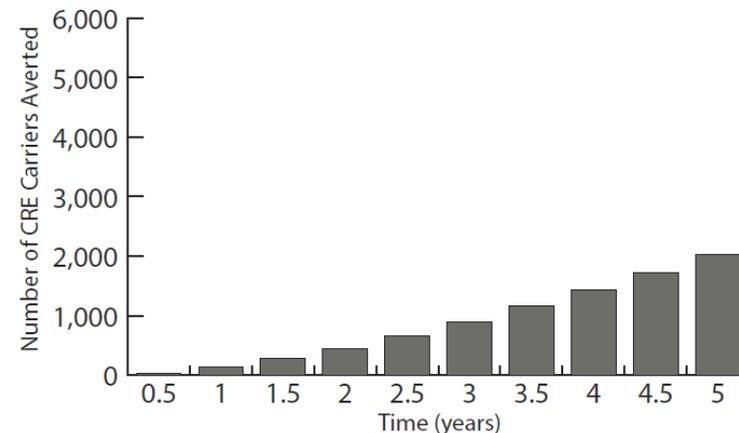
There Are Public Health Implications for Slow Implementation of New Breakpoints

- The FDA and CLSI lowered the carbapenem breakpoints for Enterobacteriaceae in 2010, but these changes have not yet been implemented on most AST systems
- Bartsch, et al JCM (2016) modeled the impact of this delay on CRE carriage rates in the U.S.
- Results - immediate use of new breakpoints in 2010 could have decreased incidence of CRE carriage by ~8,500 patients over 5 years

A. Acute care hospitals



B. Long-term acute care hospitals



C. Nursing homes

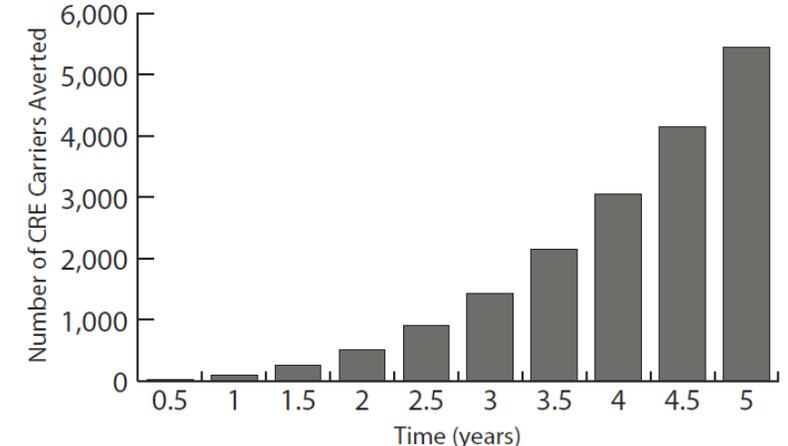


Figure 1 from Bartsch et al. Impact of Delays between the Clinical and Laboratory Standards Institute (CLSI) and the Food and Drug Administration (FDA) Revising Interpretive Criteria for Carbapenem-Resistant *Enterobacteriaceae* (CRE). J. Clin. Micro. Accepted manuscript posted online August 31, 2016.

Minimizing Effects of Breakpoint Changes for Approved Drugs: *Facilitating implementation*

Establish AST Centers of Excellence, as Part of a National Surveillance Program, that Test New Drugs Early in Development

- In addition to previously discussed role, these sites can also rapidly identify problems with AST performance and help implement breakpoint changes
- Program could also be used to monitor performance of AST devices and breakpoints once launched

Development of AST Products That Group New Antibacterials

- Segregates new drugs from changing breakpoints on legacy drugs
- Panels might primarily be used when a MDR pathogen is isolated and data on new drugs is needed
- This panel could be updated more regularly and would allow more flexibility in development cycles

Assess a Much Broader Range of Antibiotic Dilutions During Development

- The 510(k) process for updated breakpoints could be simplified if data from expanded drug ranges validated during initial AST development could be utilized
- This already happens in principle when we develop multiple calling ranges
- However, that approach is currently optional and many companies opt-out of this approach

Challenge #3 – Lack of Communication Between Pharma, AST Device Developers, CDRH and CDER

- Joint discussions between the FDA, Pharma and AST companies rarely if ever occur
 - Missed opportunity for information sharing and coordination of activities
 - Leads to setting of breakpoints before investigational devices are reviewed by CDRH (Dry-form panels and Kirby-Bauer disks)
- Alignment between Pharma and AST companies
 - Communication often begins early but initiation of development often lags
 - Challenges arise when Pharma changes plans or obtains new data or when AST companies run into technical challenges

AST development requires coordination between multiple stakeholders, but communication is typically compartmentalized

AST Development is a Complicated Project and Has Lots of Moving Parts

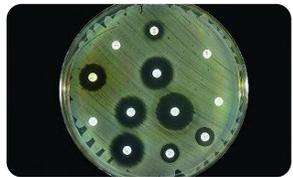
Seamless and timely communication is critical for success

AST Development Requires Significant Pharma Resources

- Need dedicated and experienced personnel from Pharma to manage multiple partners and device streams
- Significant financial investment from Pharma - >\$2.5M across all devices
- Need to match development timelines to cyclic development of AST devices
- Limited spots available for AST development for new drugs at each device company

Defined in Early Development

- Drug powder handling
- QC ranges
- Disk mass
- Target organisms
- MIC testing methods
- MIC – agar dilution correlation
- Preliminary Reference Testing Methods



Defined in Late Development

- Final Reference Testing Methods
- Tentative Breakpoints
- Timelines
- Launch plans
- Planned Markets
- MIC vs. dry-form panels

Facilitating dialogue and enabling partnerships: *Pharma, AST Companies and the FDA*

Earlier and Better Communication between Pharma and AST Companies

- Clear discussions of data and issues very early-on in the drug and AST development process
- Expediting the contracting process from both sides
- Schedule regular calls to discuss progress and issues
- Leverage the CLSI and STMA to facilitate broader communication between parties
- Allow broader understanding of each others perspective

Joint Meetings Between Pharma, AST, CDRH and CDER for Designated Products

- Update guidance to include such meetings as gating criteria for an IND, pre-Phase 2/3 and pre-NDA meetings
- Discuss potential pathogen lists, tentative breakpoints, timelines, AST queue and availability of isolates needed for development
- Allow for the FDA to tailor an AST development pathway that makes sense for each drug

Call to Action

- We need simultaneous approval of drugs and AST devices for new antibiotics
- We need to enable Pharma, AST companies and the FDA to work together on ways to bring drugs and AST devices to market faster
- Regulatory flexibility on data requirements would expedite this process
 - Streamlining of data requirements
 - Increased flexibility in the types of isolates used for 510(k) studies
 - Isolates from Phase 3 clinical studies
 - Establishment of a national surveillance program to increase availability of challenge organisms
 - New avenues for AST device labeling to allow for limited use statements
- Congress/HHS should be encouraged to create financial incentives for AST development
- Today is the first step – we have made great progress on streamlining antibiotic drug development, but we still need to fix the timelines for AST availability

Call to Action - Now is the time to enable simultaneous approval of drugs and AST devices to better serve patients who desperately need new therapeutic alternatives