FDA Workshop
Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Tests

Pharmaceutical Company Experience and Perspective

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About me

- Prior to coming to Merck in 2000, I was the Director of a large Medical Microbiology Lab in New York City
  - I am thus acutely aware of the issues under discussion today: breakpoints (new and updated), RUO vs approved tests, the fact that there is a multitude of susceptibility testing devices and the problem with the time lag between when a new antibiotic is available and when it is first available on a device.
- When INVANZ was first approved in 2001, it was almost 3 years before it could be tested on a susceptibility device; little has changed since then

Zerbaxa was approved in December 2014

- … but there is no automated commercial device available to test for susceptibility to this antibiotic
- Manual tests (disk, manual MIC, a gradient diffusion) were approved approximately 1.5 years after Zerbaxa approval

We need to close the gap between antibacterial drug approval and the availability of susceptibility tests

Why approved AST are so important

- For clinicians to make decisions for patients with limited options- especially for MDR GN organisms where susceptibility can't be reliably predicted by surrogate testing
  - FDA-cleared tests required by hospitals for patient reporting purposes
  - MDs reluctant to use an antibiotic that hospitals can't test and reluctant to use Research Use Only devices
    - For hospitals to receive RUO devices, customers required to agree to Terms and Conditions stipulating RUO will not be used in determining therapeutic options for patients or for other diagnostic purpose.
  - RUO devices thus have a limited utility and are not a bridging solution.

Why approved AST are so important-cont'd

- To understand the local ecology so that institutions (formulary and antimicrobial stewardship committees) can make informed decisions about access to a new antibiotic
- To be able to detect the emergence of resistance, an important potential risk of any new antibiotic

Drug sponsor goal

Ensure providers have access to manual and automated susceptibility tests for new antibiotics as quickly as possible

- Manual tests (disks and gradient diffusion strips including manual MIC tests) are especially important to be made available as soon as possible after approval
- End users prefer automated tests so speeding commercial Antimicrobial Susceptibility Testing (cAST) availability should be the long term goal
- In tandem we should strive to reduce the lag between drug approval and cAST availability

Reasons for delayed cAST availability

- Internal delays (drug and device side) can slow co-development
- Complexity of device development processes
  - Development queues
  - Device may be approved but software update may come later
  - Commercial availability of device may come some time later
- Drug approval vs device approval timing
  - Require approved FDA breakpoints
  - Device approval submission only some time after drug approval
- Delay in updating of “new breakpoints for old drugs”

How we work with device manufacturers

Selection of partners and working agreements

- There are many technologies/many device manufacturers
  - Microbiology laboratories decide which device to use for their susceptibility testing so a new antibiotic must be on all/most of the devices
  - The drug sponsor must also take into account the susceptibility testing ex-US: different breakpoints, different device(s) and different panels/cards
- Detailed confidential collaboration agreements must be signed with each manufacturer; internally these can take months

Working with the manufacturers

Resource and data sharing

- The cAST development expense for a new antibiotic is costly, in the range of tens of thousands of dollars for a manual test and upwards to a million or more for automated tests. Such expense must be absorbed between the drug sponsor and device manufacturer

Working with the manufacturers

Resource and data sharing-cont'd

- The drug sponsor provides relevant information to the manufacturers, including the scope of clinical development (indication[s] and organisms sought), nonclinical data (*in vitro* and *in vivo*, AST methods, QC and provisional breakpoints) and estimated New Drug Application (NDA) submission timelines.
  - Recently deposited a panel of bacterial isolates with the CDC including MICs and characterized molecular mechanisms of resistance
- Formal presentation of basic information and data on the new antibiotic is made in face-to-face meetings with device manufacturers (on request) and with the STMA (Susceptibility Testing Manufacturers Association)

Improvements to the working relationship

Merck has significantly simplified the processing of collaborations with device manufacturers

- We established a Zerbaxa Susceptibility Testing Development Team which includes licensing, legal, manufacturing and microbiology; team meets regularly with each device manufacturer to follow progress and expedite any delays
- In addition, for any future antibiotic in development, plan to review the basic information about the new drug with all of the device manufacturers at the same time

Learnings with MK-7655A (imipenem/relebactam)

- MK-7655A (imipenem/relebactam, I/R) is in phase 3 development
- Set an aspirational goal of I/R being on automated devices no later than 6 months after approval
- Initiated all contracts concurrently with the Zerbaxa agreements
- Simplified the process for imipenem and relebactam powder availability
- The I/R Susceptibility Testing Development Team meets regularly with each of the device manufacturers and any issues and delays are addressed quickly
- A panel of I/R susceptible and resistant isolates, with mechanisms of resistance fully characterized, will be deposited with the CDC
- We are looking forward to meetings with CDER and CDRH, initiated by device manufacturer(s) to discuss development plan and seek early guidance

Potential Challenges to co-development

Risks to the device manufacturers

- Some uncertainty that a new antibiotic will be approved
- Manufacturers have development queues and a queue may be "booked up" for a given year
  - New antibiotics and "old" antibiotics with new breakpoints compete for time and resources
- Adoption of a new automated AST panel may be slow
  - Panel/cards are expensive—labs may hesitate to change or discard "old" cards/panels
  - "Resistance" cards are expensive, not widely utilized
  - QC and validation to be performed
  - Integration with the Laboratory Information System may be required

Continued…

- The return on investment for new panels/cards/devices is low; device manufacturers are not incentivized to expedite development in part because there may be a low demand for cAST at antibacterial drug launch
- Although antibiotic resistance is a well recognized issue, medical societies, hospitals and quality assurance organizations have not prioritized the availability of AST devices
- No guideline recommendations for new drugs and availability of the new drugs on susceptibility testing devices

Drug sponsors & prescribers encouraged to address antibiotic resistance

- Sponsors are encouraged to innovate: GAIN Act, incentive discussions (DRIVE-AB, etc.), IDSA's "10 by 20" and guidance on antibacterial development to address unmet needs
- Hospitals & providers are encouraged or mandated to initiate Antimicrobial Stewardship Programs

Yet, similar incentives/mandates are lacking for AST manufacturers to develop new drugs (and old drugs with updated breakpoints)

What can be done to prioritize AST development?

Coordinated development of antibiotic and devices and prioritization of AST availability are key

- We welcome the FDA draft guidance on coordinated development including these recommendations:
  - Earlier collaboration and sharing of information between drug and device manufacturers & CDER and CDRH, beginning early in the antibiotic development process. (The logistics should be better defined in the guidance)
  - Joint meetings (where possible) with all device manufacturers to share basic information
  - The submission of co-development plans to CDER and CDRH
- We encourage professional and medical societies to become actively involved in this critical discussion to prioritize the availability of AST devices

Coordinated development of antibiotic and devices and prioritization of AST availability-suggestions

- We recognize that it may be difficult to achieve concurrent drug approval and device approval, therefore we look forward to clear guidance and proposed options from the FDA for providing susceptibility data to physicians during the “gap” period between drug approval and device availability, including the utilization of data from RUO tests
- More discussion is needed to address limiting risks and incentivizing device manufacturers to develop tests for new antibiotics; explore the possibility of funding cAST development through a “BARDA-like” mechanism, explore reimbursement, etc.