21st Century Cures: Implications for Susceptibility Test Interpretive Criteria

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Background

- There have been significant challenges faced by clinicians, clinical microbiology laboratories, drug and device manufacturers in providing appropriate antimicrobial susceptibility information for patient care
- Important that the most appropriate and relevant information be available for care of patients
- Often considerable delays between drug labeling updates and device updates
- Process of updating breakpoints in labeling is an iterative process
- Clinically there might be need for interpretive criteria for organisms not listed in the Indication section of drug labeling

Current Labeling

- Subsection 12.4 of labeling (Microbiology) describes the relevant microbiology data for the drug (mechanism of action, resistance, interaction with other antimicrobials)
- Two lists are included to describe the antimicrobial spectrum of activity (first and second lists)
- Microorganisms included in the first list are associated with a labeled indication
- For microorganisms included in the second list, efficacy of the drug in treating clinical infections caused by the microorganisms has not been established; the microorganisms should be relevant to a labeled indication

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm182288.pdf

New Legislation

- 21st Century Cures Act was signed into law on December 13, 2016
- Title III, Subtitle E – Antimicrobial Innovation and Stewardship
  - Section 3044. Susceptibility test interpretive criteria for microorganisms; antimicrobial susceptibility testing devices
  - Section 3041. Antimicrobial Resistance Monitoring
  - Section 3042. Limited Population Pathway for antibacterial and antifungal drugs (LPAD)

https://www.congress.gov/114/bills/hr34/BILLS-114hr34enr.pdf

Section 511: Requirements

- FDA to establish interpretive criteria website within 1 year of enactment
- Website will include:
  1. FDA-recognized breakpoints established by standard development organizations (SDOs)
  2. Other breakpoints, where:
     - FDA does not recognize, in whole or in part, a standard
     - FDA withdraws, in whole or in part, recognition of a standard
     - FDA approves an application for a drug for which breakpoints are not included in a standard
     - FDA determines a product that contains the same active ingredients requires different breakpoints due to the characteristics of the product, and such different breakpoints are not reflected in a standard

Section 511: Requirements (contd.)

3. Following disclaimers:
   - That the website provides information about the in vitro susceptibility of bacteria, fungi, or other microorganisms, as applicable to a certain drug (or drugs)
   - That the safety and efficacy of such drugs in treating clinical infections due to such bacteria, fungi, or other microorganisms, as applicable, may or may not have been established in adequate and well-controlled clinical trials in order for the breakpoints to be included on the website
   - The clinical significance of the breakpoints in such cases is unknown
   - That the approved product labeling for each drug provides the uses for which FDA approved the product

Section 511: Requirements (contd.)

- Federal Register notice to be published not later than the date on which the interpretive criteria website is established
- FDA will review certain breakpoints every 6 months and update the website as appropriate
  - When updates occur, FDA will publish a notice on the website
- When a drug is approved based on breakpoints not included in or different from those recognized or otherwise listed on the website, FDA will update the website to include the breakpoints on which the approval was based
- FDA will compile all website updates and publish an annual notice in the Federal Register for public comment
  - FDA must review comments and, if appropriate, update the website in response

Standard Development Organizations

- For FDA to recognize standards established by an SDO, the SDO must meet the following criteria:
  1. Establishes and maintains procedures to address potential conflicts of interest and ensure transparent decision-making
  2. Holds open public meetings to ensure an opportunity for public input, and establishes and maintains processes to ensure input is considered in decision-making
  3. Permits standards to be made publicly available (e.g., through National Library of Medicine)
- CDER is currently considering how to apply the criteria to evaluate eligibility of relevant SDOs

Drug Labeling

- Labeling for drugs approved after establishment of website will contain reference to website in lieu of breakpoints
- Application holders will have 1 year following establishment of website to remove breakpoints from approved drug labeling
  - replace with a reference to the website
  - can be submitted as annual reportable change
- An applicant can seek breakpoints that differ from those listed on the website
  - Will need to provide data to support the proposed breakpoints

Q and A

- What information should be submitted in an NDA?
  - *An NDA should continue to contain the usual types of information needed to support establishing breakpoints such as surveillance data, activity in vitro and in animal models of infection, and clinical data*
- Will FDA still be setting breakpoints for new drugs?
  - *Yes, if there are no breakpoints established by an SDO that the FDA can recognize at the time of approval, breakpoints should be identified by FDA and these will be listed on the website*
  - *If an SDO has established breakpoints that the FDA recognizes, they will be listed on the FDA website*

Q and A

- Can SDO's set breakpoints prior to the FDA?
  - *Yes, an SDO can set breakpoints prior to the FDA. It is up to the Sponsor if they choose to submit the data to an SDO prior to FDA identifying or recognizing breakpoints.*

Section 506(h): LPAD

- The drug is intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs
- Standards for approval under 505(c) and (d) or standards for licensure under 351 of Public Health Service Act are met
- Written request from the Sponsor that the drug be approved as a limited population drug

LPAD: Additional Requirements

- Labeling: To indicate that safety and effectiveness has only been demonstrated with respect to a limited population
  - All advertising and labeling will include “Limited Population” in a prominent manner and
  - The prescribing information will contain the statement “This drug is indicated for use in a limited and specific population of patients”
- Promotional Materials:
  - Pre-submission of promotional materials at least 30 days prior to dissemination of such materials

Section 3041: Antimicrobial Resistance Monitoring

- Monitoring at federal healthcare facilities
- Report on antimicrobial resistance in humans and use of antimicrobial drugs
- Antimicrobial stewardship activities

Summary

- There are often significant delays between updates to drug labeling and updates to AST devices
- Provisions of 21st Century Cures Act allow for some options regarding susceptibility test interpretive criteria
- FDA website for interpretive criteria will be established later this year
- Labeling for drugs approved after establishment of website will contain reference to website in lieu of breakpoints

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