Impact Assessment of FDA's Data Integrity Notifications to Sponsors

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Outline

- Background leading up to the notification actions
- Analysis of the impact on public health and sponsors
- Lessons learned
- Next steps

Background

FDA inspections (2019) and investigative analysis

- Anomalous and unreliable study data from two CRO facilities, Panexcell and Synchron

Instances of significant misconduct

- Spanned multiple studies in ANDA submissions, over number of years, and across several drug products and multiple applicants

General letters to the CROs

- Explain the observed anomalies
  - no scientifically valid reason provided to rule out the evidence of data falsification

CRO = Contract Research Organization

FDA Actions

Notifications to Stakeholders (Sept. 2021)

Informed sponsors to repeat studies from these CRO facilities, at alternate sites

- approved, tentatively approved, and pending applications (ANDAs, NDAs)

Changed the therapeutic equivalence (TE) rating for the affected generic products to "BX"

Advised patients to continue with their treatment or consult their health care professional

Notifications to CROs

Rectify the system-wide failures to ensure sustained compliance with FDA regulations

BX = Drug products that FDA at this time, considers not to be therapeutically equivalent i.e., for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence

A Precedence for Data Integrity

Regulatory action by FDA is precedent setting and a pivot from past cases

- Driver of action was extensive investigative analysis by assessors
- Not solely based on observations during inspections (no Form FDA 483 issued for one of the sites)
- All study data ever submitted from the two CRO facilities were rejected, in contrast to only study data from a specific time period, in earlier cases

Common Themes from Applicants' Responses and FDA's Assessment

1. **Plan to submit repeat studies**

2. **Re-analyze study samples** at an another CRO
   - Subject samples were available at the CRO facility for reanalysis

FDA's Assessment

- The CROs are responsible for creating false data in the studies, therefore, the integrity of the stored samples cannot be assured

Common Themes from Applicants' Responses and FDA's Assessment, continued

3. Disagree with the need to repeat the study

- no concerns were raised during FDA inspection for the site or study
- applicants' investigations and/or third-party audits did not uncover issues

FDA's assessment

- Past inspections do not provide sufficient reassurance when data are intentionally manipulated
  - data falsification may become apparent when assessors evaluate the totality of the information and all evidence before them
- No confidence in the conclusions of applicant investigations and audits:
  - for the same applications, Agency's analyses had identified data anomalies

Common Themes from Applicants' Responses and FDA's Assessment, continued

4. Revert the TE Code from "BX" to "AB"

- agree to re-conduct bioequivalence (BE) studies
- without supplementing the ANDA with a repeat study

5. "BX" rating will trigger a drug shortage

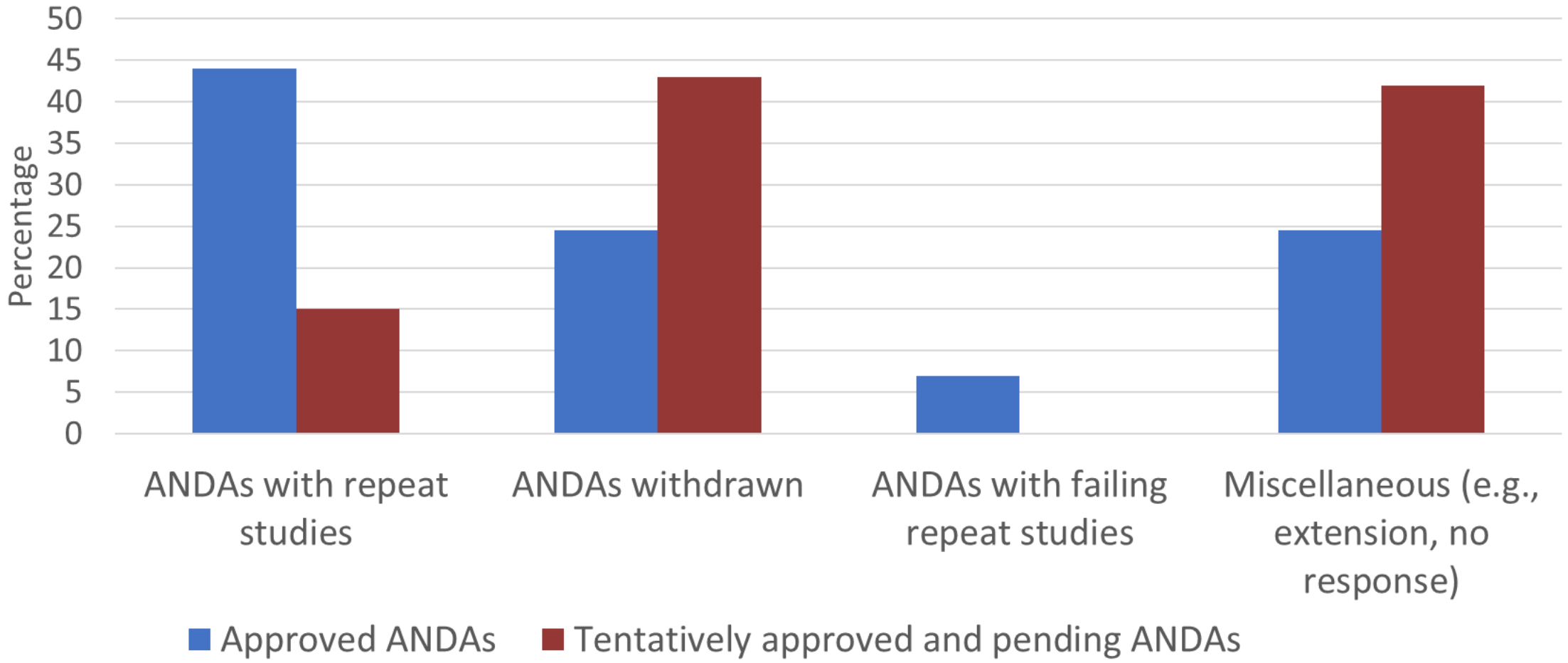
- product has a major market share
- grant an extension of AB rating to avoid a shortage

AB = Therapeutic equivalent products for which actual or potential bioequivalence problems have been resolved with adequate evidence supporting bioequivalence

<u>FDA's assessment</u>

- Agency needs to treat all approved applications similarly, irrespective of the market share

Status* of Impacted ANDAs



* as of Feb 2023

Impact on Key Stakeholders

Patients

No additional burden for the patients

- No drug shortages identified
- No significant safety signals or lack of effect signals identified

Applicants

- Decreased market share
  - market share impact analysis showed a decrease for many generic drugs
- Withdrawal of ANDAs
  - substantial numbers withdrawn, either for business reasons or a non-bioequivalent product

Key Lessons

1. No place for falsified data in FDA regulated product
   - FDA will take action once it becomes aware of falsified data and/or information in the submissions

2. Sponsors should provide greater oversight for the outsourced portions of the applications
   - cost at the back end can be costlier than cost at the front end

3. Agency and applicants need to stay vigilant to the observed patterns of data manipulation, e.g.,
   - preferential chromatographic reintegration and sample reanalysis
   - falsification of laboratory records
   - sample substitutions
   - slipping in fabricated values for a couple of samples in statistical analyses

Next Steps

Additional measures for oversight by the Office of Generic Drugs, to ensure compliance

- Enhanced analytics to identify data integrity issues
  - leveraging the functionalities of software tools' to automate detection of data discrepancies and/or atypical data in the submission
  - adopting these tools as integral part of the assessment of the submission

- Working collaboratively and in partnership
  - early exchange of information and/or data evaluation when concerns are raised during assessment or inspection
    - cross-office, multi-disciplinary team approach
    - global regulatory partners

Next Steps; continued

Recommendations to sponsors, CROs, and site personnel

- Sponsors should be diligent in site selection, monitoring the study conduct, and confirming the reliability of study data for the outsourced portions

- CROs should establish a robust QMS and site's leadership should promote a culture of quality

- Sponsors and site personnel should report fraud in study conduct
  - sponsors should inform us of any fraud they may identify or suspect during the study monitoring

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QMS = Quality Management System

Question 1

Market shares of generic drugs were not impacted by FDA's actions

True

False

Question 2

Sponsors are expected to verify the accuracy of reports submitted by a CRO in support of a marketing application

True

False


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