Biorepositories for Development of In Vitro Diagnostics: A Longer-term Perspective

Steven Gitterman, M.D., Ph.D.
Division of Microbiology Devices
Office of In Vitro Device Evaluation and Safety
CDRH, FDA

U.S. Department of Health and Human Services
Food and Drug Administration

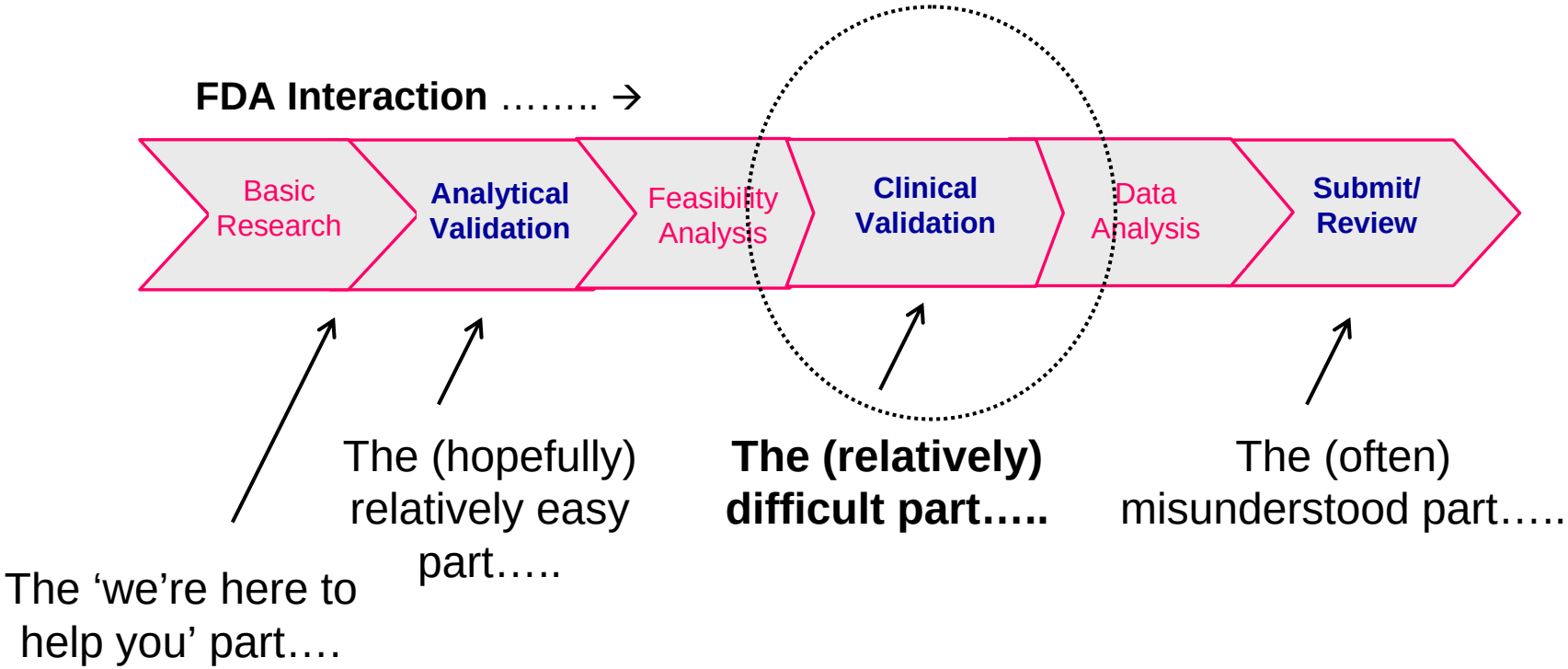
Summary (BLUF)

- Prospective clinical validation trials are ideal but not most efficient for clinical validation.
- Retrospectively archived ‘open’ biorepositories may aid in ‘expeditious’ clinical validation.
- This is an area of active discussion.
- Partnering with other interested groups (e.g., IDSA) may be valuable.
- This is not unique to infectious diseases but ID is somewhat unique for the need (in certain cases) to monitor effectiveness on an ongoing basis

Reasonable Examples

- Tuberculosis biomarkers
- ‘Uncommon’ pathogens
  - aspergillosis
- Resistant Pathogens
- Differential diagnosis for diseases with multiple etiologies, e.g., pneumonia, UTI, bacteremia….

The (Annotated) Prototype Development Pathway….



Clinical Validation of New Diagnostic Assays – Current Status

- Prospective studies
  - Clinical sites
- Purchase archived specimens from vendor/other source
  - Commercial vendor
  - Pharmaceutical company trial
  - Clinical investigator
- CDC/‘Public Health’ source
- Company specimen bank

Why Is The Need for Repositories Self-Evident…..

- Prospective clinical trials are difficult to begin with….
- A prospective clinical trial for a low-incidence disease is particularly difficult….
- A prospective clinical trial for a low-incidence disease when the incentives are low could be a perfect storm….

One Potential Way Out of This Box.....

- Prospectively Archived Repositories:
  - Prospectively collected archived specimens could serve as an essential component of clinical validation for new diagnostics
  - Specimens are entered into repository by predefined protocols
  - Repositories ‘available’ to assay developers

Prospectively Archived Repositories

- Neither a traditional “bank” or “repository,” ‘perhaps’ serving needs of both
- Limited to specimens obtained according to rigorous study protocol that itself may be implemented in other studies
- Each specimen linked to protocol specified clinical data collected with established (e.g., CDISC) data standards
- The number and nature of specimens in each “collection” will be predetermined by study protocol
- **‘Ongoing’ collection**

What Specimens Could be Added

- Any (defined by protocol/needs)
  - ‘genotypic’ isolates
  - ‘phenotypic’ isolates
  - ‘rare’ isolates
- Different matrices
  - Some matrices more difficult than others (e.g., sputum)
  - Some may be difficult to aliquot

Potential Repository Uses

- ‘Traditional use’: ‘classic’ specimen bank for diverse samples
  - May be particularly useful for multiplex assays
- ‘Training’ sets: less ‘controlled’ samples for preliminary test development/evaluation.
- ‘Validation sets’: rigorously collected sample sets for clinical validation, e.g., sequential specimens collected from a pre-defined protocol study (such as a clinical drug study or diagnostic protocol)
- ‘Unique studies’: protocols defined across repository collections, sampling for a new diagnostic test for assessing durable cure/relapse

Is This Possible - Yes

- Aspergillus Technology Consortium (AsTeC)
- Tuberculosis
  - Global Alliance for Tuberculosis (ReMox Trial/others)
  - Clinical Diagnostics Research Consortium (CDRC)
  - FDA TB RFA (?)
- ‘Influenza’
- Others (?)

Caveats

- Added complexity, i.e., specimens captured as part of another study, e.g., a drug trial
- Specimens ‘unaffected’ by storage
- Limited sample volume, especially if aliquoted
- Concomitant standardized clinical data captured
- Statistical input regarding repository design, sampling, data collection: work to be done
- **Not the whole nine yards, other regulatory requirements remain**
  - **Some prospective samples will be necessary, including specificity**
  - **fresh/frozen bridging study (essential to show equivalence for all specimen types)**

Advantages

- ‘Well characterized’ reference samples
  - Particularly valuable for multiplex instruments
- Reduction in clinical validation time
- Rigorous, scientifically valid results
- ‘Potential’ for direct comparison between assays
- Permit studies of targeted populations by separate ‘sampling’ protocols from within the repository

Thank-you