The Power of Statistics to Improve Science: Examples from CMC Statistics

Jennifer L. Kirk

November 13, 2024

IABS CMC Statistics Workshop 2024

DISCLAIMER

This presentation is an informal communication and represents my own best judgement. My comments do not bind or obligate FDA.

STATISTICS & SCIENCE

- Statisticians have a lot of power to improve science
- Contribution goes beyond analysis of the data, but often overlooked
  - Especially true for CMC statistics; clinical stats better appreciated
- Examples from my team's review work
  - 2 opportunities for improvement
  - 2 successes
- I hope the examples I present show how statistics can be valuable and maybe (?) cost-effective

OPPORTUNITIES FOR IMPROVEMENT

- Not typically clear when a statistician is involved in most CMC submissions, but…
- Often see submissions where there is sub-optimal:
  - Experimental study design and/or analyses
  - Analysis of historical/observational data
- Many of the issues are ones that a statistician would immediate identify:
  - Lack of control of /accounting for critical sources of error or confounding
  - Use of statistical methods poorly aligned with scientific goal
- Unfortunately, not always something that can be fixed after the fact

OPPORTUNITY #1: ANALYSES

- Applicant submitted a bridging study to qualify a new working reference standard
  - Study design: Paired testing of assay control on multiple days by multiple analysts
  - Analyses: TOST with pre-defined acceptance criteria
- Data looked great: highly similar means, highly correlated results…but the TOST *failed to demonstrate equivalence* (!)
  - Applicant excluded some “outliers” based on statistical tests and recalculated TOST results which passed; CBER concerned that the “outliers” were normal assay variability
- What went wrong?
  - Assay had high run-to-run variability, which was accounted for in the paired study design, but applicant failed to use a paired TOST
  - Use of appropriate analysis fixed the problem: paired TOST passed & consistent with data

OPPORTUNITY #2: DESIGN/ANALYSES

- Applicant previously implemented a change in potency assay method
  - Demonstrated new method adequately validated
  - Demonstrated equivalence over a narrow portion of the assay range
- Subsequently observe a small shift upwards in release potencies that applicant attributed to the change in assay method
  - Proposed a correction factor (CF) estimated from release data from the two assays; data was unpaired as collected several years apart (before and after change)
- CBER had several concerns
  - Shift did not appear large compared to prior manufacturing variability
  - No discussion of other potential changes in manufacturing, etc. that could explain
  - Analysis of historical data had several problems: confounding by time, extremely unbalanced design, stability data; unclear if data could provide an accurate estimate of CF if needed

OPPORTUNITY #2: DESIGN/ANALYSES

- In response to CBER's concerns, applicant submitted
  - Information about any changes made to manufacturing or assay after the assay method change
  - Subset of historical data that was paired
- Paired data showed a similar effect, but had a much smaller sample size
  - Small, relatively consistent shift
  - Magnitude of correction factor estimated from paired data similar to previous estimate from messy data

OPPORTUNITIES FOR IMPROVEMENT

Summary:

- Statisticians can add value in even very “simple” settings
- Appropriate study designs significantly strengthen the evidence from CMC analyses, especially for messy data
- Justify choices when there is scientific or statistical discretion

SUCCESSFUL EXAMPLES

- Not typically clear when a statistician is involved in most CMC submissions, but…
- Submissions that do well appear to have meaningful and early statistical involvement with detailed statistical information that addresses limitations

SUCCESS #1: BAYESIAN SHELF LIFE

- Post-licensure shelf life extension
- Proposed data & analyses:
  - Data from ~200 batches with data through 24 months at multiple different temperatures (no extrapolation beyond data)
  - Bayesian mixed effects model with
    - Fixed effects: temperature, time
    - Random effects: intercept, slope
  - Priors:
    - Fixed effects: uniform
    - Random effects: half-Cauchy
  - Predicted time point at which the 95th percentile of the posterior exceeds the end of shelf life specification for the worst-case release lot

SUCCESS #1: BAYESIAN SHELF LIFE

- Applicant provided detailed statistical information:
  - Explanation of Bayesian stats (not strictly necessary for us)
  - Rationales for their prior choices
  - Detailed model description including mathematical formula
  - Model fit diagnostics like trace plots, autocorrelation plots, and posterior predictive plots

- Facilitated a detailed and timely statistical review

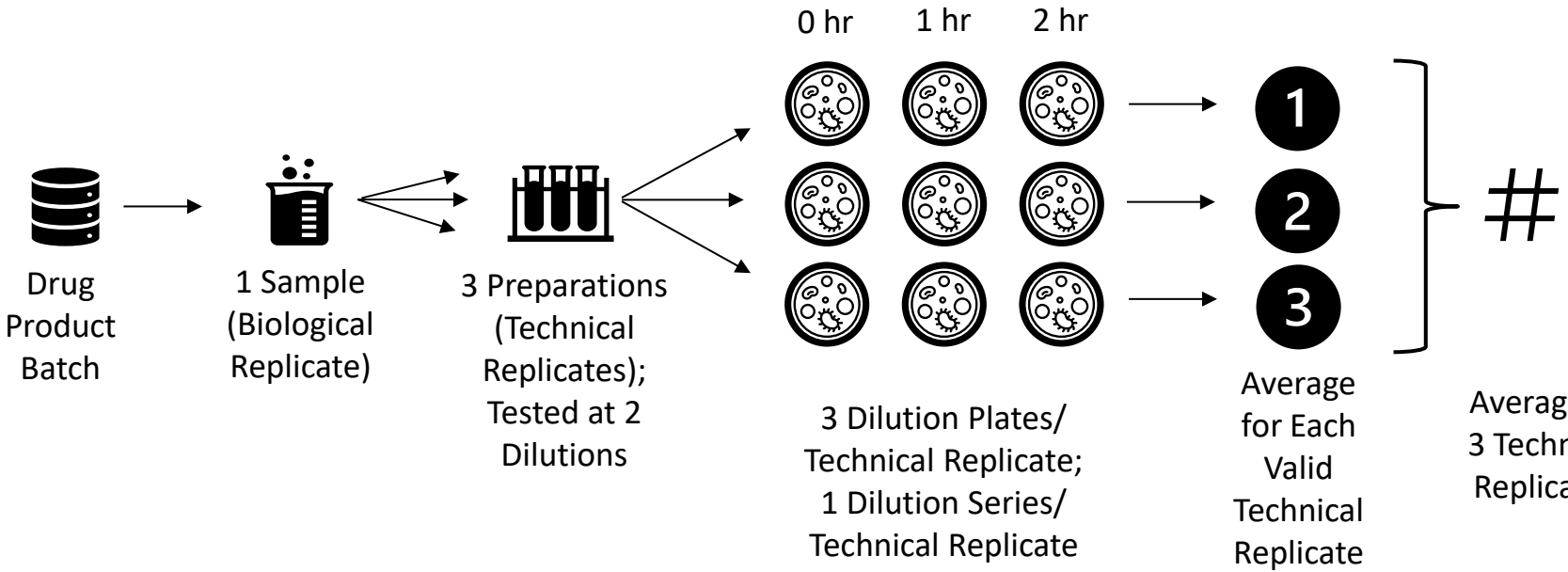
SUCCESS #2: ORIGINAL BLA

- Original BLA for therapeutic product
  - Product packaged as individual doses taken by patient
  - Novel product to treat a disease with an unmet need

- Several CMC related issues with the submission:
  - Potency assay method was overly complicated, not optimized
  - Potency assay validation had inappropriate study design & analyses
  - Content uniformity procedure was not appropriate

SUCCESS #2: POTENCY ASSAY

Original Assay Procedure

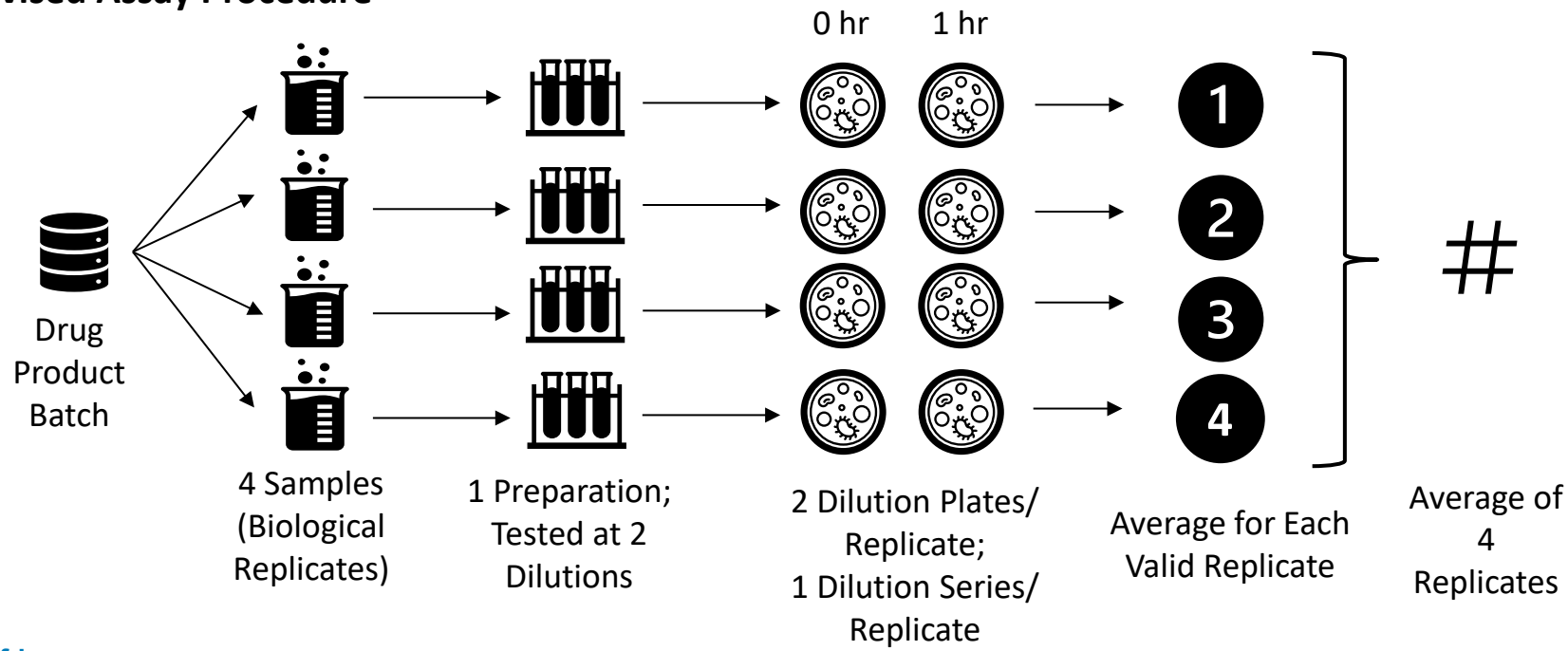


SUCCESS #2: POTENCY ASSAY

- Potency assay statistical concerns:
  - Assay is overly complicated: opportunity for error/problems
  - Replication strategy was not strategic to reduce variability
  - Replication over time assumes constant effect; if not may introduce bias
- Comments sent to sponsor recommending they use development/qualification data to redesign assay procedure prior to redoing validation

SUCCESS #2: POTENCY ASSAY

Revised Assay Procedure



SUCCESS #2: POTENCY ASSAY

Potency assay validation statistical concerns:

- Study Design
  - Did not follow assay procedure, test all sample types, or cover an appropriate range
  - Intermediate precision included data from a second site
  - Did not include appropriate replication for repeatability
  - Acceptance criteria were not justified/not appropriate
  - Patchwork of studies was difficult to interpret
- Analyses
  - Lacked statistical method details
  - Exclusion of data based on hypothesis testing when acceptance criteria not met

SUCCESS #2: POTENCY ASSAY

- Comments sent to sponsor describing these concerns and making recommendations:
  - Use a study design that will demonstrate that the assay as conducted during routine testing is fit-for-purpose by following the SOP, testing multiple concentrations, and testing all sample types
  - Use a single study with a factorial design that can provide estimates of accuracy, precision, and linearity over the range
  - Propose acceptance criteria appropriate for your product quality needs with adequate scientific justification
  - Describe your appropriately-chosen statistical methods in detail
- Because of the substantially simplified assay, applicant was able to address these concerns

SUCCESS #2: CONTENT UNIFORMITY

- Content uniformity proposal was originally based on
  - An assay that CBER considered unable to measure potency and was not properly validated
  - Used USP <905> which has substantial statistical issues
    - Does not account for uncertainty
    - Cannot ensure that batches that pass are likely to be acceptable
    - Procedure is specific to small-molecule drugs setting
- CBER concerned that the content uniformity procedure proposed would not adequately ensure product quality

SUCCESS #2: CONTENT UNIFORMITY

- CBER requested and reviewed development data and concluded that the revised potency assay could be feasible for content uniformity
- CBER provided comments to the applicant recommending:
  - Use of revised potency assay for content uniformity
  - Applicant propose an alternative (decision) procedure to monitor content uniformity, with justification of choices, that includes
    - A plan for sampling an adequate number of dose units
    - An assay that has been validated for testing individual dose units
    - A statistical summary of the content uniformity
    - Acceptance criteria that the statistical measure will be compared to during routine testing

SUCCESS #2: CONTENT UNIFORMITY

Applicant was able to

- Implement a significantly simplified potency assay
- Eliminate the need for second assay to test content uniformity
- Combine testing for content uniformity and potency in a single run
- Implement a content uniformity procedure that provided better statistical assurance
- Validate for potency and content uniformity in a single, simpler study
- In a priority review BLA timeline (!)

SUCCESSES

Summary:

- Talk early and often with a statistician (and CBER)
- Justify choices when there is scientific or statistical discretion
- Provide detailed statistical information

ACKNOWLEDGEMENTS

Thanks to my team members:

- Chunrong Cheng, Branch Chief
- Fang Chen
- Ngoc Ty Nguyen
- Hairong Shi
- Linye Song
- Ho-Hsiang Wu

And our CMC scientist colleagues:

- Leslie Wagner
- Siobhan Cowley


FDA
U.S. FOOD & DRUG
ADMINISTRATION