Managing Biometrics Tasks for an eCTD Submission

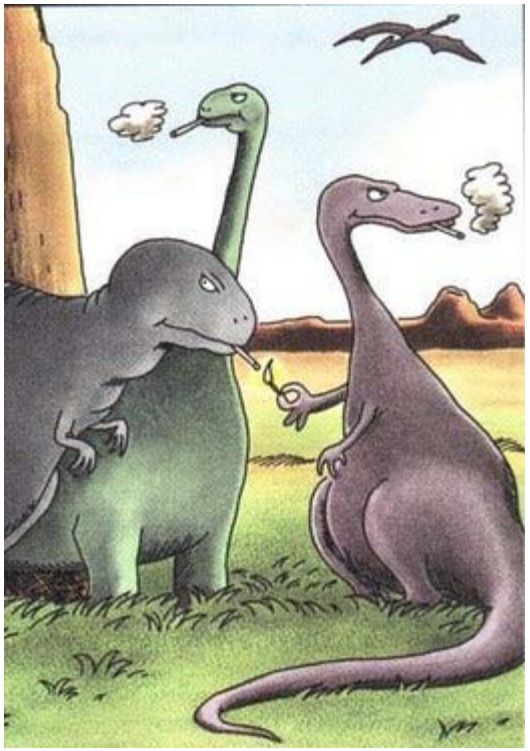
Disclaimers

- The views expressed are those of the presenter and *not necessarily of the FDA*
- With the FDA, as with the stock market, past performance is no guarantee of future direction…

Major Biometrics tasks for a Submission

- Strategy and planning
- Specify project deliverables
- Produce/QC analysis datasets and TFLs
- Evaluate project deliverables
- Assemble and audit the data submission
- Field FDA requests
- 120 Day Safety Update
- Prepare for the Advisory Committee meeting

A Brave New Regulatory World



- Regulatory environment is changing, risks have shifted
- It's important to understand FDA's issues and be honest with yourself about the statistical support for your labeling claims
- Ask FDA to vet your data strategy, get a formal response from your Review Division
- Make no assumptions!

Strategies for the submission

- Identify each study-level component of the submission, specify its treatment in the eCTD
  - Full CSR or abbreviated report, data or no data?
  - SDTM or 1999 Guidance "Item 11"?
  - Analysis data? ADaM or otherwise?
  - Analysis programs?
- Which studies are *required* in the ISS?
  - Often fewer than you think
- Get FDA to agree in writing
- How do you mitigate remaining risks?

Handling of Legacy Studies

- Do you need to submit data? Maybe not…
- Is the study in the ISS? Gotta be SDTM.
- Clinical Study Report (CSR) already done?
  - If CSR analysis is not based on SDTM, some level of re-analysis is called for
- Is there still a role for "Item 11" data based on the withdrawn 1999 Guidance?
  - An increasingly risky strategy…
- Whatever you decide, *make sure FDA agrees!*

Quality, Integrity, Traceability of Analysis

- Require your analysis data to be derived from the source datasets you will submit
- Require your TFLs to be produced from the analysis datasets you will submit
- Never submit data that has not been analyzed
- For key studies and analyses, build in independent assessments with reconciliation

Every Submission has a Trajectory…

- Flight time is determined by quality of planning, team's experience, submission complexity
- Adopt a fast-moving timeline, but do not try to compress it by making tasks parallel if they have dependencies. That's a recipe for a do-over.

Every Submission has a Trajectory…

- Pushing the timeline inappropriately increases project effort by 40% – 60% and rarely ends well…
- Track progress at the level of deliverables – any deliverable can stand on your air hose
- On the timeline Final should mean Final, not the start of evaluation

Need for Specifications

- It is essential to specify eCTD-ready deliverables *in detail,* preferably in RFPs and Work Orders
- If you don't, *you will not get submittable work products* regardless of what your contract says!
- Nothing useful actually starts until there are specifications
- If you think things are happening and there are no specifications, *the wrong things are happening*.

Getting Submittable Work Products

- Do your vendors have real experience producing eCTD-ready deliverables? Maybe not…
  - Vendors often drive with their rear-view mirror
  - Vendor experience is mostly with the 1999 Guidance
  - Clients "improve" their deliverables and the vendor never sees the final submission package
- No vendor has produced *your* package of deliverables before
- If you don't specify what your submission will contain, they cannot produce it

Evaluating Deliverables

- Something important is wrong in EVERY draft you do not evaluate!
  - This is a fact, not an assumption
  - It is true regardless of vendor or overall quality
- You need specs to do a meaningful evaluation
  - SDTM structure and content
  - Define documentation
- Plan to audit your eCTD deliverables
- No compromise until all other options are exhausted!

Auditing eCTD Deliverables

- Identify programs that produced the analysis datasets and CSR tables and figures. Do you have all of them?
- Read the programs to identify their data sources. Do you have all of them? (Hint: probably not.)
  - Often missing spreadsheets defining TMEs or meds of interest, or data not in the CDMS database, such as PK concentrations and parameters
  - Some of these can result in an RTF

Auditing eCTD Deliverables

- Are all datasets and variables adequately documented?
  - Good data badly documented is the same as bad data. It leads to wrong conclusions.
- If programs are submitted, are they adequately documented? Include a Program Guide.
- Get agreement with your e-publisher about who will produce pdfs, do hyperlinks, bookmarks.
- All document links work correctly?

Final Points

- Start planning with adequate lead time – 18 months to 2 years.
- Take time to develop a careful data strategy. It reduces the time, effort and cost of your submission.
- Verify your strategy with FDA. It's OK if they say it is…
- Adopt a fast-moving timeline, but do not try to compress it by making tasks parallel if they have dependencies.

Final Points (cont.)

- Make a list of every eCTD deliverable for every study, ISS and ISE; assign dates and responsibilities.
- Provide specifications for all major deliverables
- Get first draft deliverables at least by first subject off study, second draft before data lock. Evaluate every deliverable you ask for, while it can still be fixed.
- Derive analysis datasets from submission source data; Subject all submitted data to some analysis.

Final Points (cont.)

- Secure an independent assessment of key analyses.
- Set a high quality bar for data and documentation.
- Audit your eCTD deliverables.
- Do not compromise until you must or submission quality will degrade rapidly as it nears completion.
- Your vendors are your partners. They're on your team. Help them succeed!

Thank you!

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