U.S. FOOD & DRUG ADMINISTRATION

Postcards from the Edge: Regulatory Reflections

"There is no point at which you can say, 'Well, I'm successful now. I might as well take a nap.'" Carrie Fischer

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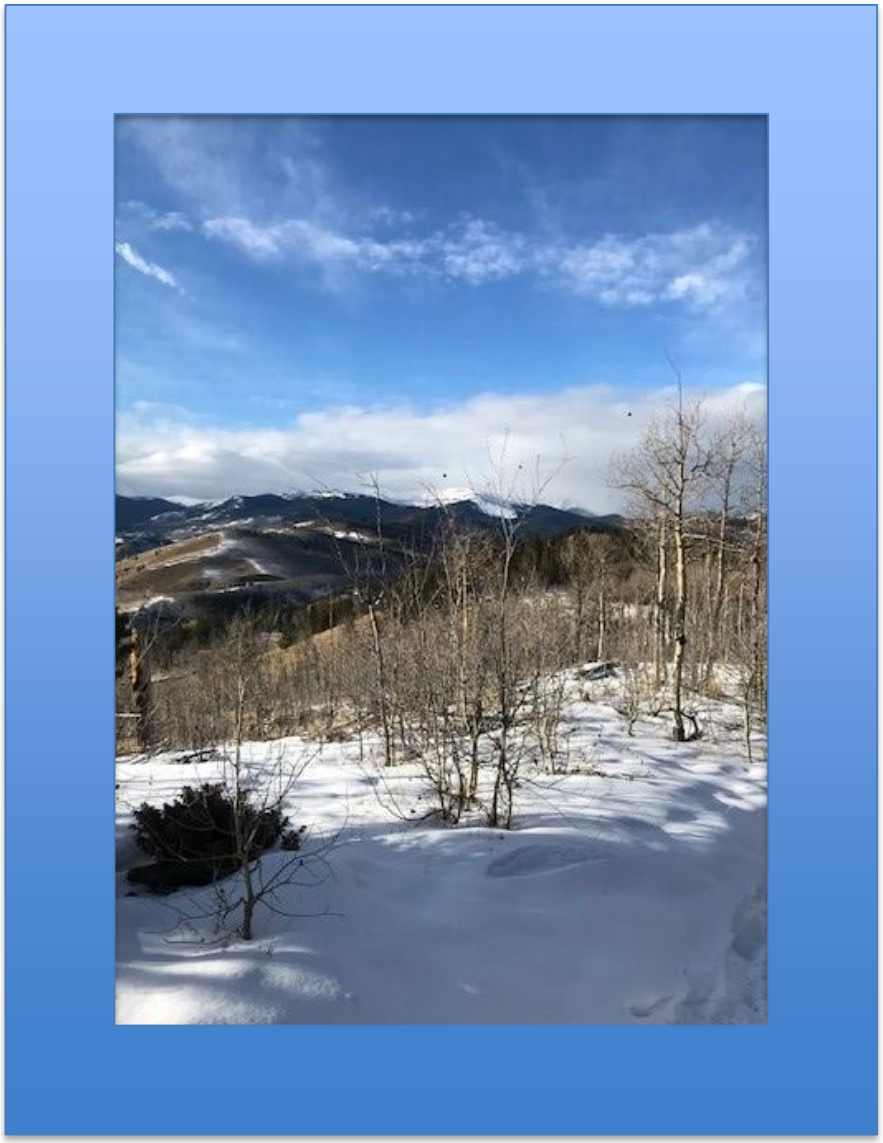
Outline

- Postcard 1: Potency reference material qualification
- Postcard 2: Measuring things that change
- Postcard 3: Do you know what you are measuring
- Postcard 4: Staying in control
- Postcard 5: PMCs



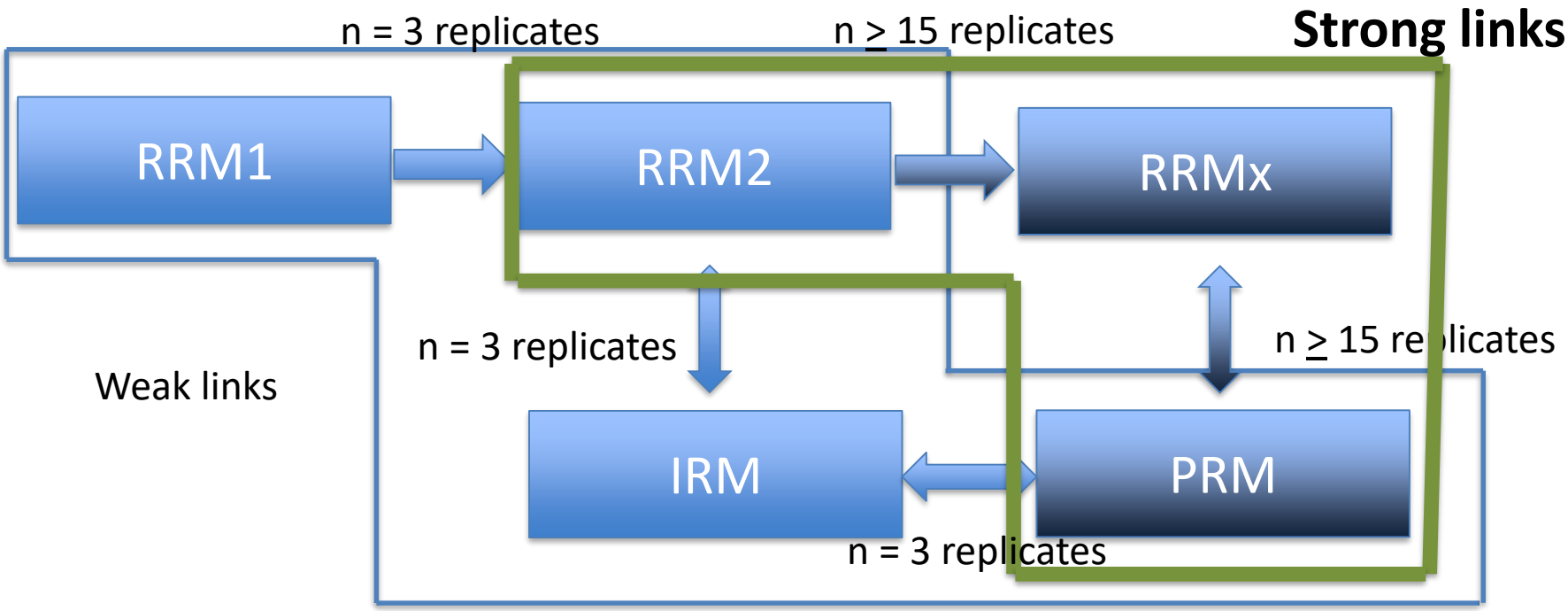
Colorado

Postcard 1:
In for the long haul – potency reference material qualification.

Reference Material Potency Qualification in Development: Example 1

- Reference material (RM) potency for multiple RMs initially established using 3 replicates
- FDA communicated that would not be sufficient to maintain a link between the potency of material used in clinical and analytical studies and the commercial RM
- Conclusion: The Sponsor shifted to qualifying RM using 15 replicates thereby maintaining a link between development data and commercial RM

Reference Material Potency Qualification in Development: Example 1



RRS – research reference material
IRM – interim reference material
PRM – primary reference material for commercial product

Reference Material Potency Qualification in Development: Example 2

- Potency qualified for 2 clinical RM and the proposed commercial RM using a single independent dilution of RM tested on 4 plates
- RM1=104% relative potency; RM2=112% relative potency; RM3=80% relative potency
- Is the potency of the 3 reference materials the same or different?

Reference Material Potency Qualification in Development: Example 2

- During the BLA review cycle the Sponsor was asked to requalify the reference materials and then recalculate the potency of the clinical lots
- RM1, RM2, and RM3 were each tested a minimum of 9 times.

Reference Material Potency Qualification in Development: Example 2

- RM1 activity was designated to be 100% because it was used in the clinical trials.
- RM3 (commercial) had a relative potency of 112% against RM1.
- RM2 (clinical not used) had a relative potency of 124% against RM1.
- Conclusion: The Sponsor updated their RM qualification program to include at least 9 independent assessments of potency and the potency of RM3 was established as 112%

Postcard 2: A trip down the river – measuring things that change

Great Falls National Park, MD

Change by Design

- Prodrug – protein chemically conjugated to 4 – 8 small molecule inhibitors
- Inhibitors are designed to be released non-enzymatically in the blood over time, T1/2 = 20 h
- Prodrug is inactive
- Complexity – the inhibitors are released over time during the potency assay. Therefore, product potency is constantly changing during the assay.

Change by Design

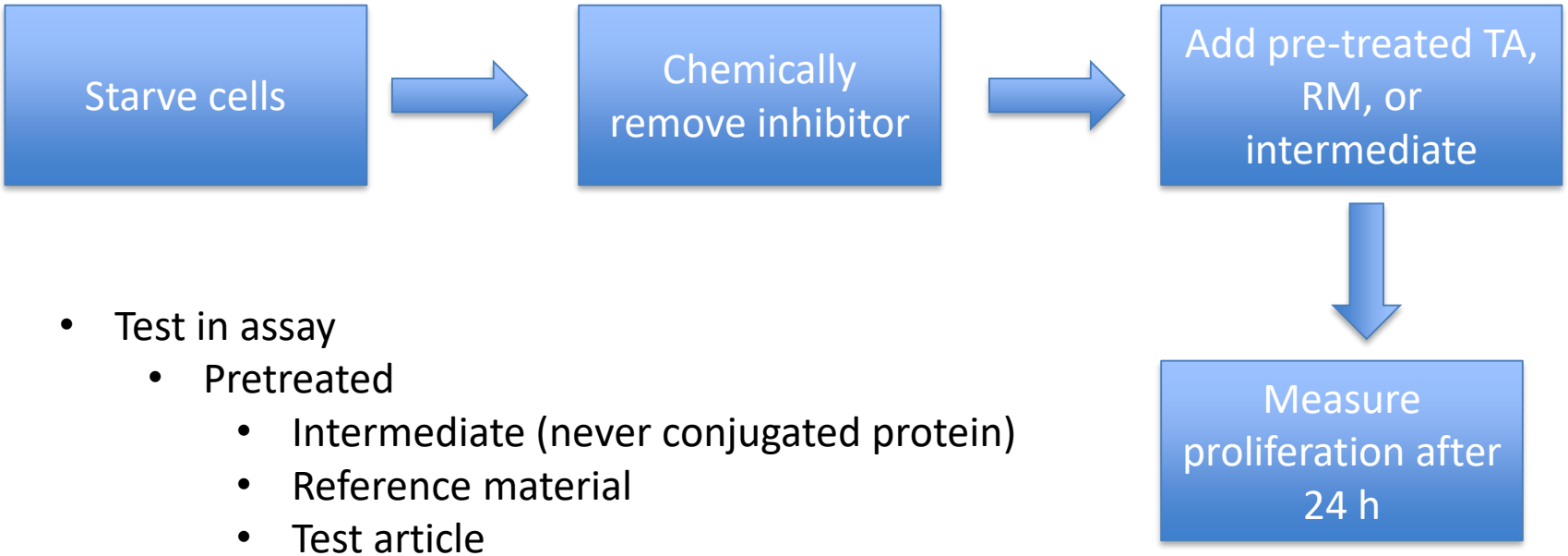
Phase 1 Assay

Prior to phase 3 the Sponsor proposed a new assay because they found the phase 1 assay lacked robustness and had high inter-assay variability

TA = Test article
RM = Reference material

Change by Design

Proposed Phase 3 Assay



- Test in assay
  - Pretreated
    - Intermediate (never conjugated protein)
    - Reference material
    - Test article

Change by Design

- Sponsor optimized the pretreatment process and characterized the extent of inhibitor removal by RP-HPLC, SDS-PAGE, peptide mapping, LC/MS, bioassay
- FDA questioned the relevance of this assay since the molecule was designed to lose the inhibitor over time and asked how the consistent release of inhibitor would be controlled

Change by Design

- Most recent communication from the Sponsor is that they further optimized the phase 1 assay and now have acceptable robustness and precision
- FDA hasn’t seen the data yet
- To be continued….

Postcard 3: Do you know what you are measuring?

Mount Rainier, Washington

Do You Know What You Are Measuring?

- Drug is a biologic that is chemically conjugated to a payload.
- The biologic binds to a marker expressed on cancer cells
- The drug is designed to release the payload non-enzymatically both in the serum and in the cell for both targeted and by-stander killing
- Potency assay is a cytotoxicity assay using a cell line that expresses the marker

Do You Know What You Are Measuring?

- Oxidation of the protein significantly reduced binding to the marker in a binding assay but potency was not reduced in the cytotoxicity assay
- FDA expressed concerns that the cytotoxicity assay does not distinguish between targeted and bystander killing
- The Sponsor is developing a multi-assay control strategy
- To be continued…

Postcard 4: Staying in control

Hoover Dam, Nevada

Staying In Control

- Reference material unexpectedly failed EC50 acceptance criteria of 15 – 35 ng/ml during requalification
- EC50 acceptance criteria were set using EC50 data from multiple batches rather than multiple replicates of a single batch
- EC50 acceptance criteria were recalculated to be 14 - 25 ng/ml using data from hundreds of runs with the RM
- Results from 9 independent runs are sufficient for reference material requalification.
- Conclusion 1: RM EC50 acceptance criteria were not set correctly. RM potency acceptance criteria should not include manufacturing variability.

Staying In Control

- Reference material EC50 was 13 ng/ml at next requalification time point
- During routine assay performance EC50 is calculated from a single run and acceptance criteria range is 5 – 35 ng/ml
- After extensive investigation the Sponsor determined that the assay had changed but the reference material was acceptable

Staying In Control

- The Sponsor introduced an independent quality control to help ensure assay suitability
- Conclusion 2: The assay initially lacked a critical control

Postcard 5: Post marketing commitments

Post Marketing Commitments

- Reviewed PMCs for 29 BLAs approved between January 1, 2018 and April 30 2019
- Potency assay related PMCs:
  - Develop a control strategy for effector function (2 applications)
    - Assays to monitor effector function should be included in the product control strategy when effector function cannot be eliminated as a mechanism of efficacy for the drug
  - Confirm the suitability of the assay or acceptance criteria (2 applications)

Post Marketing Commitments

- Potency assay related PMCs continued:
  - Implement an independent quality control (1 application)
  - Explore alternative assays (3 applications)
    - Develop a non-animal based assay
    - Further evaluate structure function relationships to ensure all MOA were identified
    - Add a potency assay to monitor a secondary MOA

Conclusions

- Reference material potency should be established using a sufficient number of independent replicates to ensure accurate potency assessment
- RM potency acceptance criteria should not include manufacturing variability
- Potency assays should evaluate the mechanism of action of the drug
- Multiple assays may be needed when there are multiple mechanisms of action
- System suitability controls are critical for identifying changes to assay performance

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