

Pet Peeves and Roadblocks in CMC: Improving your Quality Submissions through the Product Lifecycle

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Disclaimer

- This presentation does not represent official FDA policy.
- However, it represents the opinions of most of the reviewers in OBP.
- So, it may be more important than official FDA policy!
 - (Just kidding!)

Objectives

- Take Home Messages and Pet Peeves
- Roadblocks
 - Basics
 - Phase 1
 - Phase 2/3
- Comparability
- Breakthrough Therapy Designation
- Contract Manufacturing and Testing

Take Home Message #1

A grumpy
reviewer is
not your best
friend!!!!!!



Overarching Pet Peeves

- Inefficient use of reviewer time
 - While you might like to believe that a reviewer is assigned to only one IND or BLA – yours, this is pure fantasy!
- Poor communication



"It cost \$1299. But when you factor in the time wasted sitting in front of it, well, the real cost is enormous."

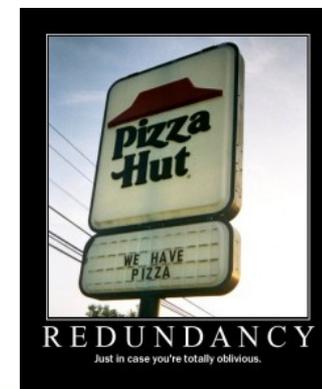
The cost can be enormous, and not just in \$\$, if your submission is confusing

Pet Peeve #1 - CTD format

- It's redundant!
 - Duplication of information within a submission
- It's redundant!
 - Duplication of information in subsequent submissions (amendments or new INDs)
 - **Inefficient use of reviewer time**
- It's not organized in a manner that tells the whole story in a logical manner

Pet Peeve #1 - CTD format

- It can be hard to find specific information
- It's small drug centric. Make it work for biologics
 - C_{10,000}, H_{50,000}, O₅₀₀₀, S₁₆
- It's redundant!
 - (Did I already say that?)



CTD Format

- Do
 - Learn to live with CTD format but
 - Try to make it as non-repetitive as possible
 - Provide sufficient information
 - Present information that is well organized and clear
 - Links to other sections should work
 - Module 2 is for a summary
 - Proofread! Proofread! Proofread!
- Don't
 - Assume it is obvious what you mean – especially if you haven't proofread the submission.

Pet Peeve #2

Poor Communication with FDA

- \$#!+ Happens!
- Incomplete details
- Poorly written submission
- Lack of appropriate meetings with FDA to discuss quality issues



Poor Communication with FDA \$#!+ Happens!

- Do
 - Be honest! It's not what happens, it's how you handle it! (most of the time!)
 - Share information and results of investigations.
- Don't
 - Tell partial story.
 - Come back 2 years later with the whole story.

Poor Communication



Poor Communication with FDA

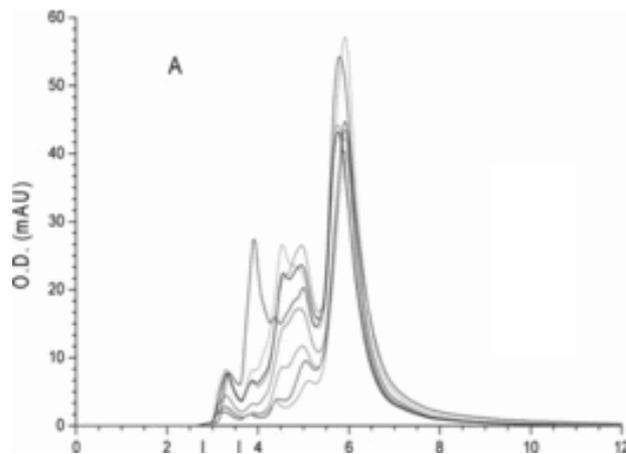
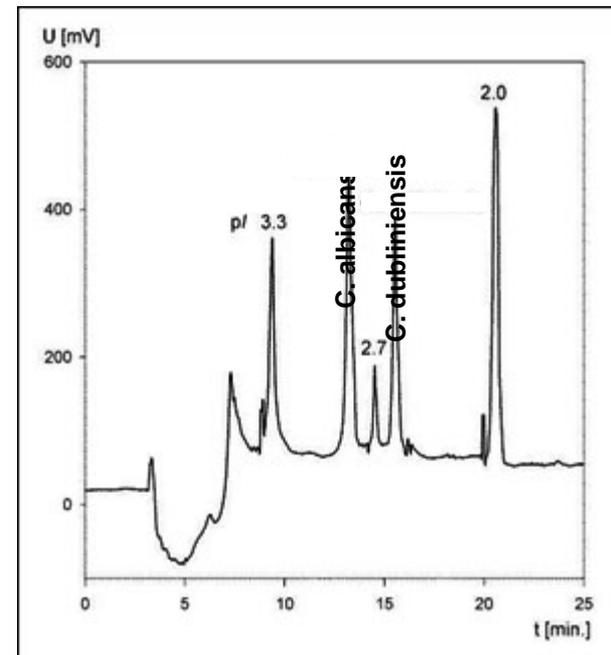
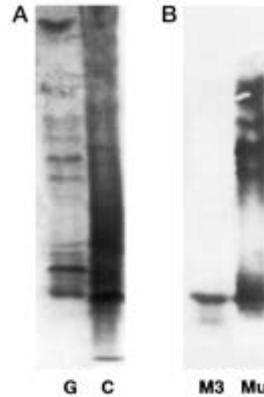
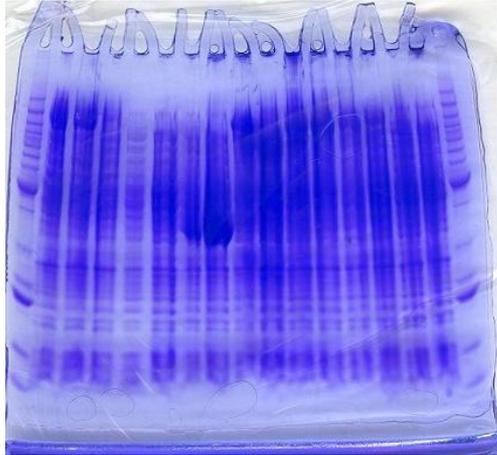
- Do
 - Proofread submissions
 - Ask focused questions at pre-IND, EOP2, pre-BLA or BPD meetings
- Don't
 - Submit poorly written documents
 - Ask too general or overly ambitious questions at meetings

Pet Peeve #3

Data Presentation

- We're scientists – we like to analyze data!
- Missing data
- Poor quality figures
- Confusing tables

Poor Quality Figures



Data Presentation

- Do
 - Pay attention to details
 - Label clearly
 - Lay out in a way that makes it easy to compare peaks, bands etc
 - Include figure legends
- Don't
 - Place text over peaks, especially if the reviewer will be comparing peaks between chromatograms of different lots.
 - Put figures that reviewer will compare on different pages.

Pet Peeve #4

Repeating Mistakes

- Lack of understanding of quality issues at specific phases of clinical development
- Apparent lack of understanding or a disregard of FDA advice



Repeating Mistakes

- Do
 - Show you take our advice into consideration
 - Ask for clarification if you are not sure what we are asking
 - Provide a risk analysis and/or scientific data for a different approach
 - Understand quality issues for phase 1 versus phase 2/3 and BLA
- Don't
 - Ignore FDA comments or advice
 - Marginalize quality concerns

Pet Peeve #5

Poor communication within your company

- Small company with one location
- Large company with multiple sites
- Know your fellow product development colleagues



Poor communication within your company

- Do
 - Share comments from FDA with groups for whom the comment was intended.
 - Share comments from FDA with colleagues in product development associated with different clinical indications.
 - Show you can learn from our comments.
- Don't
 - File the FDA letter without sharing comments with relevant departments
 - Submit subsequent amendments or INDs with same lack of information. You are guaranteed to get the same comments.

Pet Peeve #6

Back up your claims with data

- Your product may be the greatest invention since sliced bread, but we need to come to the same conclusion (and we might not!).
- Protein engineering should accomplish what it was intended to do.



Back up your claims with data

- Do
 - Provide data demonstrating your claim
 - Provide data demonstrating the engineered protein does what the engineering was supposed to achieve
- Don't
 - Hand wave or market to your reviewer
 - Assume your reviewer automatically agrees with your claim

Take Home Message #2

It's not style over substance, but rather it is substance with style!!!!



A complete, well organized, well written submission full of clear figures and tables goes a long way towards making the life of your reviewer a little bit easier.

Take Home Message #3

Trust is an important component of the regulator-sponsor relationship, but it must be earned. Ignoring our advice without a discussion or being less than truthful does not build trust!



**Get ready for specific pet peeves
and roadblocks.....**

The basics: Understand your audience, identify your needs

- The cover-letter - include relevant items for directing the submission to the appropriate review groups (**Pet Peeve #2** Poor Communication with FDA)
 - Identify product type is it a biotechnology product? small drug molecule? A combination of both? This will help direct your submission to the appropriate reviewers.
 - Identify what you are submitting AND your needs e.g.
 - Full response vs. partial response to clinical hold
 - Comparability data for which you would prefer feedback by a specific date (be realistic on timelines, provide submission sufficiently early to give ample time for review. **See Overarching Pet Peeves about pure fantasy**)
 - Meeting request – who will you need to be there based on questions to be answered?

The basics: Proofread! Proofread! Proofread!

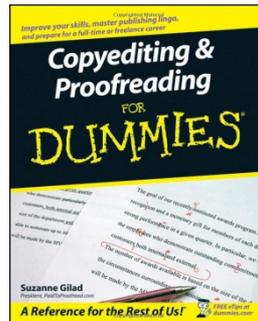
Don't neglect the QA on the written document.

- Clinical protocol stated product “can be shipped at -20 or above” instead of “at -20°C to -10°C”. The reviewer had to request that sponsor check and fix all documents with contractors involved in shipping.
- Conflicts: tables list different specifications or results in different sections, or in conflict with the text.
- Don't mistake “regulatorese” for good quality information. Be specific and provide sufficient data for reviewers to make the appropriate conclusions.
- Don't assume the reviewers know what you're talking about.

Take Home Message #2 Substance with style

Pet Peeve #2 Poor communication with FDA

Pet Peeve #4 Repeating mistakes



Meetings: Take full advantage of that rare opportunity to get the best guidance from the FDA.

Examples of missed opportunities at meetings with the FDA

- Does your meeting package contain sufficient information for reviewers to answer your questions?
 - *“The data package lacks information needed to determine ...”*
 - *“Based on the information provided in the submission package, it cannot be determined whether...”*

- pIND questions that are impossible to answer
 - *“Does the agency agree that the quality data and control strategy would be acceptable for registration?”*

“If you are getting boilerplate answers instead of replies specific to your product, you have not crafted your questions well.” Ruth Cordoba-Rodriguez

Pet Peeve #2 Poor communication with FDA
Pet Peeve #3 Data Presentation



Phase 1 – focus on safety

“The identification of a safety concern or insufficient data to make an evaluation of safety is the only basis for a clinical hold based on the CMC section.”

(CDER/CBER Guidance for Industry Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products November, 1995)

- Sterility, mycoplasma, endotoxin, adventitious agents
- Potency (for dosing consistency)
- Identity (prevent confusions at manufacturing site)
- Purity (relevance of non-clinical data etc.)
- Process and product understanding to enable assessment of safety
 - Is non-clinical lot representative of clinical GMP lot?
 - Is this process within the platform process for which virus clearance is claimed?
 - Are acceptance criteria for provisional preliminary specifications appropriate to assure a meaningful dosing study?
 - Is the product sufficiently stable to assure a meaningful dosing study?

Phase 1 Speed Bumps = Clinical Hold

- Your IND is on clinical hold because the subjects in the proposed clinical investigation would be exposed to a **significant and unreasonable risk** [21 CFR 312.42(b)(1)(i)]
- Your IND is on clinical hold because **insufficient information** has been submitted to allow FDA to assess the risks to the subjects in the proposed clinical investigation [21 CFR 312.42(b)(1)(iv)]



Significant and unreasonable risk

- Unacceptable specifications
 - Endotoxin limit > 5 EU/kg/hr, >0.2 EU/kg/hr for intrathecal, or >0.5 EU/mL for intraocular.
 - Potency assay specifications depend on therapeutic index, toxicity, and dosing.
- Evidence of product contamination
- Insufficient virus clearance
- Mislabeled Product
 - **Pet Peeve #5** poor communication within your company (namely CMC, Reg Affairs and Clinical)
 - **Pet Peeve #4** repeating mistakes (we have found this issue in multiple INDs from the same sponsors)

Track/log comments for other products... never get dinged for the same item twice!
- Joseph Kutza

Insufficient information

- Viral safety
 - Manufacturing scheme is validated for its ability to remove or inactivate retroviruses BUT:
 - Insufficient data provided to support generic/modular clearance
 - No data allowing reviewer to assess appropriateness of scale down models
- Lack of manufacturing information
 - The IND does not contain information on the manufacturing process used for production of the radiolabeled monoclonal antibody.
- Lack of sufficient stability data
 - The stability data submitted in the IND is for a different formulation than that of the clinical drug product
- Lack of sufficient comparison between toxicology and clinical lots
 - Provide data to support the comparability of non-clinical and clinical batches of your monoclonal antibody
- Lack of assurance regarding TSE risk
 - Provide Certificates of Analysis, Certificates of Origin for raw materials of human or ruminant origin,

Take Home Message #3 Trust but verify

Pet Peeve #2 Poor Communication with FDA- *Incomplete details*

Pet Peeve #3 Data Presentation - *Missing data*

Pet Peeve #6 Back up your claims with data

Speed bumps to avoid with Endogenous Protein counterparts

- Immunogenicity assays
 - Ideally will be in place by Phase 1
 - Testing of patient samples should start with Phase 1 trial
- Potency assays
 - Seek most relevant and quantitative bioassay possible (flexibility regarding what is possible balanced with what is quantifiable)
- Assays to assess levels of aggregates
 - More stringent for allowable levels of aggregates (aggregates influence immunogenicity)

Phase 2 and 3 Speed Bumps

- For Phase 2 and 3, FDA's primary objectives include: "to help assure the **quality of the scientific evaluation of drugs is adequate** to permit an evaluation of the drug's effectiveness and safety". (21CFR312.22)
- CMC development should parallel clinical development.
- Product characterization assays should be adequately qualified.
- When modifying or adding a clinical protocol, remember to submit the associated CMC information.
 - Adding placebo controlled trial requires CMC information for the placebo
 - Adding another product in conjunction with your product requires CMC information or letter of cross-reference to the IND, BLA, NDA or DMF.
 - Adding a radiolabel to the product for imaging etc. requires CMC information for the radionuclide and for the radiolabeled protein. (May require a new IND)

Pet Peeve #2 Poor Communication with FDA- *Incomplete details*

Pet Peeve #3 Data Presentation - *Missing data*

Pet Peeve #6 Back up your claims with data



Phase 2 and 3 Speed Bumps

Change happens! and comparability is needed.

- Don't be left without the comparator product - assure sufficient retention of lots to support comparability studies.
- Establish and communicate pre-specified acceptance criteria
- Assure sufficient time to test for comparability and for FDA to review comparability data prior to use of new process material in clinical trial.
See Overarching Pet Peeves about pure fantasy
- Have “plan B”- if processes 1 and 2 do not result in comparable products. You may need non-clinical or clinical cross over studies.

Pet Peeve #2 Poor Communication with FDA- *Incomplete details*

Pet Peeve #3 Data Presentation - *Missing data*

Pet Peeve #5 Poor communication within your company

Pet Peeve #6 Back up your claims with data



Case study - comparability

- During early phase 3 development of a monoclonal antibody, multiple manufacturing changes were made including:
 - removal of animal-derived raw materials from the process
 - new cell clone → new MCB and WCB.
 - Change in DS manufacturing site
 - Scaled up Bioreactors
 - Change to the harvest process and to the downstream operations
- IND amendment included a plan for comparability and introduction of product to the phase 3 trial.
- Plan did not adequately address ICH Q5a (viral safety) risks.
- Plan did not provide detailed acceptance criteria
- Plan did not provide any data on which one would base acceptance criteria.

Pet Peeve #2 Poor Communication with FDA- *Incomplete details*

Pet Peeve #3 Data Presentation - *Missing data*

Pet Peeve #6 Back up your claims with data



Comparability During the Biotechnology Product Lifecycle



Increasing expectations from tox lot to FIH lot, from FIH to mid-stage lots, from mid-stage to pivotal lots and pivotal to commercial lots. Highest bar for post-marketing changes, but expectations are clearer.

Expectations depend on:

- Phase of development;
- Extent of changes;
- Number and availability of development and pre-change clinical lots;
- Characterization of reference standard and pre-change lots;
- General product knowledge;
- Analytical tools (suitable for intended use)

Case 2: Academic to Commercial Sponsor - Post Phase 3 Comparability

- Successful Phase 3 trial, then identified commercial sponsor
 - Met with FDA to discuss manufacturing plans
 - Had preliminary data from lab scale lots; data were encouraging
 - Agreed that if new process resulted in comparable lots, only a bridging human PK study would be needed



Case 2: Academic to Commercial Sponsor - Post Phase 3 Comparability

- Commercial Sponsor - comparability protocol submitted for review prior to studies
 - Methods thorough and current
 - Additional methods to assess MOA
 - Manufactured 3 clinical lots, compared with several lots from academic sponsor manufactured between 1997 - 2010
 - Noted several differences, but associated with oldest lots.
 - Newer lots from academic sponsor and lots from commercial sponsor were found comparable
 - Forced degradation study
 - Tissue Cross Reactivity study



Case 4: Academic to Commercial Sponsor – Phase 1 Comparability

- Old material, limited lots available
 - Old lots stored at 2-8°C, Reference standard available
 - Still meeting original release criteria, but degradation present
- Commercial Sponsor
 - Compared 1 new lot with 1 old lot and old reference standard
 - Methods sufficient for early stage development, could have been more comprehensive
 - Noted several differences likely related to age of original lots
 - These particular differences may not matter for the MOA of this product
 - Age not considered in study nor discussed in IND submission
 - No accelerated stress stability
- Could not conclude materials were comparable, but starting at phase 1
- Sponsor put on hold for other reasons



Breakthrough Therapy Designation

- Based on promising clinical results from early studies
 - Expedited clinical development program
- Within 6 months of receiving BT designation, the sponsor should schedule a multi-disciplinary meeting to discuss development plans
- Product must still meet same quality standards as for product in full development program
- Consider market demand as well as your ability to supply ongoing clinical trials
- Plan CMC meetings during remaining clinical development program
 - All meetings will be Type B (within 60 days of request)
 - Scale up
 - Comparability
 - Validation of process
 - Flexibility needs to be discussed (post-approval agreements)

Back to the basics

- Your reviewers are scientists that base their decisions on data analysis. So back up your claims with quality data!
(Pet Peeves #3 & #6)
- The CTD format is here to say. It can work for you if you let it.
(Pet Peeve #1)
- Communication is key – with FDA and within your company.
(Pet Peeves #2, #4 & #5)
- An open relationship based on trust and information sharing is the best relationship sponsors can have with their reviewers.
(Take home message #3)

Contract Manufacturing and Testing Organizations

- As the sponsor (Owner) of a drug, you are ultimately responsible for assuring the quality of the drug
 - “drugs introduced for interstate commerce are neither adulterated nor misbranded as a result of the actions of their selected Contract Facilities
- Owners and Contract Facilities should establish a written Quality Agreement delineating their respective roles and responsibilities

Contract Manufacturing and Testing Organizations

- “A well-drafted Quality Agreement will use clear language to define key quality roles and responsibilities; establish communication expectations; provide key points of contact for both parties; specify what products and/or services the Contracted Facility will provide to or for the Owner; and establish who has final approval for various activities (Quality Units and other stakeholders).”

Contract Manufacturing and Testing Organizations

- Guidance Documents
 - Contract Manufacturing Arrangements for Drugs: Quality Agreements (2013)
 - Cooperative Manufacturing Arrangements for Licensed Biologics (2008)
 - Quality Systems Approach to Pharmaceutical CGMP Regulations (2006)
 - ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (2001)
 - ICH Q9 Quality Risk Management (2006)
 - ICH Q10 Pharmaceutical Quality Systems (2009)



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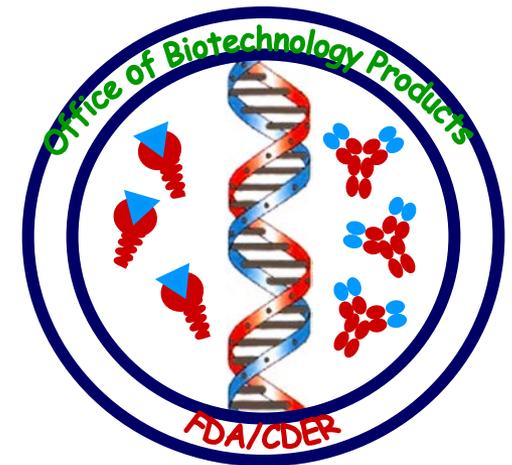
Renaissance Mayflower Hotel
Washington, DC



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Acknowledgments

- All DMA and DTP colleagues who shared their pet peeves and examples – there were many!



FDA or Sponsor?

The BLA – Filing

- ✓ Filing review checks that:
 - All necessary information is contained in the BLA
 - **Incomplete details and Poorly written submission**
 - **Pet Peeve #2 Poor communication with FDA**
 - **Take Home Message #2 Substance with style**

 - Process validation is complete and included in the submission

 - BLA is well organized to enable review.
 - **Pet Peeve #1 - CTD format**
 - **Take Home Message #2 Substance with style**

 - Pre-approval/ Pre-license inspections:
 - All sites should be ready for inspection at time of submission
 - Expectation is that manufacturing of your protein takes place during inspection – plan accordingly, and inform FDA of your manufacturing schedule at time of BLA submission. 21CFR601.20(b)(2)



The BLA – Filing Roadblocks

- Sponsor wanted to provide DP process validation data for a format that was not the to be marketed format. Was cautioned that this could be a reason for RTF so sponsor validated the correct format for BLA submission.
- The manufacturing sites were not ready for inspection at time of BLA submission. BLA was withdrawn until sites were ready for inspection.
- There was no plan to manufacture the product during the BLA review timeline. When sponsor was cautioned that BLA will not be filed, manufacturing schedules were changed to comply.



The BLA – Filing roadblocks

- ***Non-existent or insufficient data in several sections of module 3.***
 - *Section 3.2.S.2.4 (Control of Critical Steps and Intermediates) does not identify all process parameters per unit operation*
 - *Section 3.2.S.2.5 (Process validation and evaluation) is missing information such as: proven acceptable ranges and supporting data per unit operation, validation reports per unit operation, validation of buffers and media hold times, validation of bulk drug substance freezing process, chromatography resin cleaning validation, UF/DF validation report or a validation protocol if concurrent validation is to be performed*
 - *Section 3.2.S.4 (Control of Drug Substance) does not have qualification/validation data for the following methods used for release and/or stability of DS*

The BLA – Filing roadblocks

- ***Non-existent or insufficient data in several sections of module 3.***
 - *The submission does not contain information on the process and controls for the packaging and labeling of the vialled DP by the manufacturing sites listed in the BLA.*
 - *Multiple links are not operational throughout the BLA. For example...*
 - *Appendices and special sections are difficult to navigate due to lack of granularity.*

The BLA – Communicating with FDA

- When is a good time to tell FDA that your facility has not been able to manufacture lots post validation because (bioburden, unknown contaminant, viral contamination, other)?
 - Develop a trust-based relationship
 - Be upfront with the circumstances surrounding unusual issues (reprocessing, reworking, relabeling, OOS's etc).
- **Remember take home message #1 about grumpy reviewers.**
 - The way to keep your reviewer happy is to be open, truthful, and provide the information needed for review and assessment of your process and product.
- Lower quality submissions may be more likely to miss a PDUFA date
 - Multiple rounds of questions and requests for information
 - Post-marketing commitments may be required

The BLA – Review: case studies

- Omission of key data from BLA resulted in delay of approval. Major amendments move the clock timeline.
- Drug Substance stability studies were conducted in containers not representative of the drug substance container material. Stability studies had to be redone, approved with shorter shelf-life
- Drug product long term stability data from pilot scale not representative of full scale. Resulted in a shorter expiration dating than requested.
- Request to drop specific release test for the “to be approved product” was not supported by sufficient information. BLA was approved on time, but sponsor had to include release test that they did not plan on and validate the assay during the BLA review cycle.

**PDUFA V should help eliminate some BLA roadblocks,
but it is up to you!**



Roadblocks that may be identified at various times in product lifecycle

- Inspection
 - GMP, but also verifies that data in submission is accurate
- Contradictory/unclear statements within submission or between OS and amendments
- Key and critical process and product parameters lacking
 - Complex QbD submissions (Priority review)
- Clonality of MCB
- Unexpected adventitious agents
 - MMV, Cache Valley Virus, Vesivirus, Porcine circovirus-1, Leptospira

Additional Comparability Case Studies

Case 1: Commercial to Commercial Sponsor - Phase 3 Comparability

- Old material, limited lots available
 - More DP lots stored at 2-8°C than frozen DS lots
 - Still meeting original release criteria, but degradation present
 - Available data from older methods
- Comparability study thoughtful and thorough, updated methods
- Accounted for changes due to age
- Additional studies to understand predicted differences
 - Related to age, freeze/thaw process etc.
- Additional effector function assays
- Forced degradation study
- Tissue cross reactivity study
- After comparability data assessed, performed human PK study



Case 3: Commercial to Commercial Sponsor – Phase 2b/3 Comparability

- Old material, limited lots available
 - Old lots stored at 2-8°C (6 and 7 years old at time of study)
 - Sample constraints; limited testing on one lot
- Compared interim reference standard (development lot) and reference standard (GMP lot) with two old lots
- Methods could have been more comprehensive but included those most likely to detect important differences
- Differences noted, likely due to age (not considered)
 - Differences favored new product (HMWS and LMWS species)
- Bioassay not reliable, added binding assay for potency
- Conflicting data related to glycan structure
 - Product designed for no effector function
 - Animal PK comparability to address potential concerns related to observed glycan differences



Case 5 : Academic to Commercial Sponsor – Phase 1 Comparability

- 1 lot of frozen DS available(manufactured in 2007)
 - Manufactured into clinical DP lot
 - Minimal characterization
 - Did new release testing, reasonable methods and acceptance criteria
- Starting with Phase 1 clinical trial
- Will need to do comparability study when make next lot(s)
 - Manufacturer and manufacturing process not yet identified
 - Safe-to-proceed letter had comments on our expectations for future lots



Case 6 : Commercial to Commercial Sponsor – Phase 1/2 Comparability

- Phase 1 and 2a trials completed by commercial sponsor (Ex-US)
 - Business decision to drop development
 - Academic formed company to develop product
- Proposed Phase 2b trial (pIND)
- Only a single clinical batch manufactured in 2006 is available
- New manufacturer and manufacturing process identified
- New sponsor does not intend to perform comparability studies
 - Plans to rely on historical release and minimal characterization data
 - Not clear how much reference standard is available or if non-clinical lots are available
 - Told sponsor that we would not be able to make a meaningful assessment, gave many suggestions and requested follow-up tcon.

