Report-out on Topic 1:

Perceived Challenges with FDA/EU/Other Regulatory Review Questions, as well as PAIs

Version 1:

As presented on Day 2 of Workshop

Ground Rules for Discussion

- Intended as a technical discussion
- Intended to facilitate sharing of experience
- Not a Q and A for the Agency
- Questions regarding specific applications or requests for a meeting can be sent to: CDER-OPQ-Inquiries@FDA.HHS.GOV

Communication and openness

- Internal discussions within companies facilitated internal alignment around a lot of the CM related aspects (e.g., batch definition). Multiple companies shared that visits from regulators to sites for CM equipment tours and associated discussions were very fruitful.
- The agency is advocating early and frequent discussions. This will help both the sponsors as well as the regulators to advance the learning and ensure that both are learning at the same time.
- While there may be a number of questions for the initial filing, a lot of the learning will be recycled towards platform understanding and the general expectations from the audience that the number of questions will be lower for subsequent filings as the platform and its understanding becomes more mature.

Shared learning

- Educational visits to operational CM facilities considered very beneficial and worthwhile
  - To educate internal colleagues
  - To educate regulatory agencies
  - To demystify what can otherwise seems like an abstract, potentially complex and challenging mode of manufacture
- With CM, (*a factor that reduces risk is*) that the same equipment set is used for development through commercialization
- CM offers opportunity for increased process knowledge - could permit easier / faster post approval changes in the future
  - Current filing is potentially too static
- With CM, it is expected to have to deal with much larger data sets than conventional batch processes. Clear understanding and expectation is needed to deal with data traceability, data integrity, and ability to address conflicting data from multiple data streams or to deal with aberrant data points.

Shared learning, continued

- Opportunities to share generic learnings from CM experience
  - Pre-competitively
  - Possibly via a wiki or database with some curation
  - Considered potentially sustainable compared to large consortium effort
  - Possible vehicles via IQ or similar
  - A repository of information on what models work well for what operations also considered valuable
- Questions on filings are part of this shared learning
  - Evidence that those questions add value
- The value vs cost/risk of redundant controls in CM:
  - is it possible to utilize all data streams initially to gain more knowledge and then transition to fewer controls long term?
  - A proposal that it may be easier to drop some controls if the sponsor can prove that the associated failure modes are already covered by other controls.
  - This may be easier to implement this way rather than relying only on historical data to justify fewer controls.
  - Different views were also shared to show the potential advantage for redundant controls (e.g., ability to run if one layer is not functioning while other redundant layers are).
  - While it may not be a regulatory expectation to have multiple, redundant controls with CM, it is up to the sponsor to determine the need for redundant controls to assure robustness of the process and product quality.

Do we need guidance? Are we ready for guidance?

- Is shared experience sufficient to support drafting of guidance?
  - Mostly “no” but a few “yes”
  - Have we seen all the innovations that deserve fair consideration?
- Interest in seeing more case studies in the literature
- More forums allowing collaboration and sharing
  - Having these forums is very helpful
  - White paper could provide ~summary of these conferences for those who don’t attend

Overcoming perceived barriers

- Perceived barriers– what agency wants vs what industry thinks agency wants: How to achieve predictability?
- Probably the biggest perceived risk was global regulatory acceptability.
  - However, the participants in the discussion agreed that it was difficult to identify any real life examples where an international regulatory body might have impeded implementation of an innovative technology. Nonetheless, the participants agreed on the value of sharing data as well as proceedings from a conference like this one with the global audience, as well as conducting tours/visits to further lessen this perceived risk.
- Some of the perceived barriers were whether CM was approvable. Now that a CM process has already been approved, that perceived risk has been lowered.
  - Some of the perceived barriers within individual companies are around the fear that CM will not be approved or that it wont be approved within the specific project timeline.
- Perception that regulators have narrow experience in CM applications
- Industry: concerned that CM will follow same pattern as QbD
  - Initially, shared learning and many questions
    - Some questions were not possible to answer, not relevant; # of q's is not always the problem
    - The quality of questions is improving, more pertinent
    - Not always clear on which questions driven by technical curiosity, which are roadblocks to approval
  - Scientific Understanding a given, but regulatory flexibility elusive
  - Incorporated lessons learned – to improve or adjust presentation of data
  - Industry and regulators to build on this to improve experience for CM

Overcoming perceived barriers

- Fear that if provide wrong data will be locked in to untenable constraints
- Regulatory harmonization: willingness of regulatory authorities outside ICH to support CM processes
  - Improve communication?
- Knowledge management: multiple dimensions
  - Tons of data: how to manage?
- Sponsorship and support within companies?
  - Forums exist where high level people attend
    - There is a range of approach – from new idea welcome to “show me robust roi etc”
  - How to balance risk fear opportunity etc?
- How much change is needed for internal quality systems to adapt to CM? An example was shared where a company reviewed all QMS and only a handful needed to be revised.

Overcoming perceived barriers

- Practitioners indicated that initial skepticism had been overcome by the practical experience of seeing CM really working
  - No longer phased by potential complexity or data volume
  - Seeing opportunities to take advantage of several drives in multiple processes
- Company culture issues
  - Considered important to have chemical engineers in the right roles in order to facilitate uptake of CM

Challenges for submission and validation

- Have deep technical knowledge about your process and controls
  - this knowledge partly counteracts risk of bringing on new tech
- How much detail to include?
- Concerns on peoples' minds
  - How to handle outliers in real time __?
  - Differentiating between robustness of system and controls needed to keep system stable
- Interaction is good
  - Conversation with agency addressed this
  - Feedback loop, lessons learned helps
  - Where to put post approval changes?
  - Agency is not too picky about what goes in which sections
    - do orgs have/will produce cheat sheets for what goes in what sections? Useful?
- Validating CM processes
  - Aligning CM processes with validation guidances in US and EU
  - Continuous validation and verification – what does this mean?
  - What constitutes validation? Are there different ways/strategies/approaches?
    - Acknowledging Risks of scale up/scale out
- Need to learn by doing.

Possible actions

- More visits to operating CM facilities
- More industry publications of learnings, pre competitive
- More workshops and forums of this type
- Possible white paper from regulators
- Possible wiki or other vehicle to share
  - Potential to be global, could assist challenges in other regulatory regions

- Other dissemination opportunities at forthcoming meetings in 2016
- Multiple, separate efforts are ongoing to capture approaches for CM, including this workshop, CMAC, the upcoming ISPE conference, IQ, as well as other consortia.
  - There will be a great value in aligning different buckets of work that are being addressed separately in these different forums so that topics are distributed and the various efforts complement each other rather than competing on the same subjects.
- (Direct follow on workshop
  - in Ireland Feb 2017 led by SSPC: manufacturing focus)

Notes of Topic 1 report-out discussion

- Extra items to add:
  - Modeling
    - Should be included as a section in the wiki
  - Validation
    - how to determine the right running time (vs 6 month run time in practice)
  - iQ and SSPC willing to work on wiki
    - Some concerns about ensuring information quality
    - Valuable to also share questions received on filings
  - Important for the resource to be open to all
    - Industry, regulators, academics