MANUFACTURING SCIENCE

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Agenda

- Desired State
- Culture Change
- Key Points of Discussion
- Group Specific Issues
- Getting from Here to There
- PAT
- Interim Specifications
Desired State

- Understanding what is critical for quality and design for quality
- Agreement between Industry and FDA on a regulatory strategy that is commensurate with the design
- Regulatory relief where appropriate
- Manufacturing science is dynamic and encompasses research, development, manufacturing, analytical
- Open communication and trust
- Agreed upon levels of information, data and documentation required for changes (specifications, new technology, PAT, comparability protocols)
Culture

• Industry and Agency
  – Trust needs to be built
  – Shift from change is “bad” to change is “good”
  – Move from ‘compliance’ mindset to ‘quality by design’ mindset
  – Need to design the process, specifications, in-process controls that are related to “fitness for use” (safety, efficacy, availability)
  – Increased “manufacturing science” and “quality systems” = decreased reliance on finished product testing
  – Documentation ➔ Data ➔ Knowledge
    • It is not question of submitting more and more data but sharing the right knowledge
    • Development report should demonstrate that we have designed quality into the product and the process
    • If we demonstrate that we have the right quality systems in place (i.e. change control, continuous improvement ) regulatory relief is given
KEY POINTS

• Manufacturing Science is dynamic – the current regulatory process is static
  – Applied the same way to all regardless of where you are with Manufacturing Science
  – Disproportional relationship between Manufacturing Science and Regulatory Process

• Definition: Manufacturing Science
  – More than just technology
  – Research, Development, Manufacturing, Analytical, Behavioral
  – ‘Science’ is well understood and accepted
  – Definition needs to be disseminated within all the areas of the company
KEY POINTS

• Using in-process in-line/at-line/on-line analysis to demonstrate control of process and develop knowledge that certain changes do not impact product safety and efficacy
• More flexibility is needed in regulatory process
• Risk-based approach will help the flexibility
• A new mechanism for sharing knowledge is needed: what knowledge and how much
Group specific issues

• BIO
  – Years ago Biologics were not well characterized
  – That has changed – and they can be well defined and well characterized
    • Should permit more flexibility in regulatory process
  – While products are unique there are some steps that are common leading to standardized approaches to changes
    • Fermentation, filtration

• Animal Health
  – “Status quo” appears to be desired state because there appears to be less value added in implementing new technology
From ‘Here” To ‘There”

• Super supplement
  – Need a new way to supply information – a new process (multiple changes)
  – Industry gains a great deal of information and product knowledge in the first 12 months after approval
  – CAE: Changes Already Effected
    • Based on prior agreement

• Use of INDs/INADs to share process development knowledge
From ‘Here’ To ‘There’

• Expansion and modification of SUPACs
  – Go back and re-assess the guidance documents
  – Do we need a PAT SUPAC-like guidance – prepared in a similar manner to the SUPAC for equipment changes?
  – Current perception: SUPAC doesn’t address multiple changes and relief for specifications
    • If through new technology you have better quality assurance and are adding assurance you should have regulatory relief

• Need to change how we look at specification life-cycle

• Extensive use of statistical modeling for design of processes and experiments

• Address inconsistencies
  – Within agency and industry
From ‘Here’ To ‘There’

• Inspections
  – Broader pharmaceutical expertise needed
    – European model – 5 yrs. Industry (Manufacturing/Quality) experience
  – Training of inspectors
    • Bring training in house to FDA
    • Use Industry/Association experts to train
    • Leverage internal FDA experts
      – Expand current FDA expertise list
    • Industry experience emphasis for new inspectors
    • Sabbaticals: Industry to FDA
      – Training and expertise
From ‘Here’ To ‘There’

• Inspections
  – PAIs
    • Consider moving to “for cause” PAIs
    • Expanding use of PAI “waiver” by district
  – General GMP/Quality Systems
    • Scheduled to have firm prepared and reduce time and focus
      – People, data, plants and information ready – better process
From ‘Here’ To ‘There’

• Risk assessment should take place at the review process to establish what needs to be done to support future changes.

• Need to change the focus
  – Current focus is primarily on documentation
  – Documents are the goal not science
  – Backing off on documentation requirements will build trust and allow time for science
From ‘Here’ To ‘There’

- If you can show there is an enhancement in quality assurance – CAE or CBE
- General protocols for implementing technology depending on the type– rather than doing PAS on every product- have defined the template for the product type that has had agency review prior – then we can do a CBE/Annual report
- Development reports
  - Needs to capture the failures as well
  - Important teaching tool
From ‘Here’ To ‘There’

• Better communication
  – Between Industry and FDA
  – Internally (break down perceptions and misconceptions of approaching FDA between R&D/Manuf/Regulatory

• Evolve better guidance on changes specifically with changes of RM suppliers or RM source (animal to vegetable derived)
  – Currently major regulatory burden

• Better definition of change?
PAT

- Not a requirement, not mandatory (Industry Alignment)
- Incentives for using, without penalties for remaining with the status quo
- Need a flexible regulatory process to address using PAT in existing processes to replace current methods
- Cannot apply today’s specifications which were developed on a significantly smaller sample size
  - Need to determine how to address this
  - Impact on monograph
PAT

• Process validation
  – If PAT can be considered continuous validation
    – does traditional process validation go away?
• Clear it is not for everything
  – Not for every product or every company
• It is not just about reducing finished product testing, there are more benefits
Interim Specification(s)

- Design of experiments and failure mode analysis is crucial to assist in defining final specification
- The data should tell us where interim specifications are appropriate and where they are not
- Approach similarly to Phase IV commitments