Genentech 50th Anniversary

Troubleshooting Technology Transfers Together-
a.k.a. Two Heads are Better than One

Daniel Lagasse, FDA/CBER
Dante Romanini, Gilead
Janney Boone, FDA/CDER
Sarah Kennett, Genentech

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“What we tried to do in the early days of Genentech was to create a culture where anything was possible.”

Bob Swanson | Genentech Co-founder

How do we do this? Product = BsDC

Manufacturer A

- **Dev lot 1** (TOX/small scale) (RCB- clonal)
  - Manufacturing deviation at final UF/DF affecting ~1/3 of material
  - Affected material added back to bulk and mfg change implemented
  - Release tests match earlier material
- **Dev lot 2** (small scale) is reference (MCB – clonal)
  - Release analytics look same as TOX

Manufacturer B

- **Dev lot 1** (small scale, same MCB) – Release tests look similar to Tox and Ref Std – minor differences noted (within QTPP)
- **GMP** (full scale) Similar to Dev lot from Mfg B

Regulatory Strategy

- Full characterization of Reference (derived from MfgA) and GMP (derived from Mfg B) **OR**
- Full comparability of Manufacturer B Dev1 to Reference (RS) – Faster results desired
- Release and additional LC-MSMS on tox to verify PTMs comparable to RS
- Any additional tox study needed? PK with new material?
- Anything else? How do we tell the story (assuming Mfg B material is similar but not the same as MgfA)

Scenario 2 – New Product Variant Identified

- Transfer of DS manufacturing (“standard” process) from Site A to Site B for commercial launch of a protein product
- Goal is IMA submission as soon as possible – CMC is rate-limiting
- New variant detected in technical/engineering run DS at Site B
- Has not been detected in material manufactured using earlier processes and at different sites
- No apparent relevant changes in the process between Site A and Site B – RCA eventually identified a “minor” and “standard” equipment difference between sites
- Variant identified at extremely low level (<0.1%)
- Using analytical method (SEC) updated to enhance detectability, variant was present in earlier material/clinical material at extremely low level, always near method LOQ (or LOD)

- **Does anyone have experience with managing this in the control strategy, control system?**
- **How far do we need to go?**

Scenario 3 – “Modular” Manufacturing

- Transfer of commercial protein product DS manufacturing from Site A to a copy-and-paste Site B
- Sites A and B were originally the same (same footprint, same materials of construction, same equipment, same materials/supplies, same protocols…); however, during the intervening years, an equipment update has been made at site B

- **Experience in managing modular manufacturing?**
- **How lean can we go for PPQ (or verification run(s)?), the regulatory submission?**
- **Does the type of equipment changed/step in the process matter? Or how big a change in the equipment?**

Scenario 4 - Inspections

- Transfer of a commercial product (“standard” protein product) DS manufacturing (“standard” manufacturing process) from ex-U.S. Site A to a U.S. Site B
- Site B is an existing site; however, the product will be manufactured in a new building (not similar to the existing commercial lines on site).
- No other product has yet been manufactured on this line.
- Goal is to proceed to PPQ then submit to the U.S. FDA as quickly as possible (rapid onshoring)
- There is no need for additional Drug Substance manufacturing to support supply.

- **Are there any options regarding the need for a PAI, manufacturing of DS during a PAI?**
- **Any experience with engaging with the Agency to discuss this type of situation?**

Scenario 5 – Evolving Health Authority Expectations

- HAs now require PUPSIT (Pre-Use, Post-Sterilization Integrity Testing) for DP sterilizing filter
- Transfer of DP filling from Site A to Site B to relieve supply constraints
- Site B does not have PUPSIT capability
- It will be a difficult and lengthy process to implement PUPSIT at Site B due to how the line is set up
- Introduction of PUPSIT requires new construction/piping, a skid that does not fit into the space available, movement of the filter from a location within the high quality air space (specifically designed this way) to a location further away from the point of filling

- **Have there been successful justifications for not implementing PUPSIT for commercial DP manufacturing?**
- **Other thoughts for rapid implementation to enable rapid transfer?**

Scenario 6 A = B, B = C does not automatically mean C = A

- Commercial product – DS manufacture:
- Site 1 approved in U.S. (and elsewhere)
- Site 2 not approved in U.S.
- Transfer to new Site 3 was performed from the perspective of supply to EU
- Transfer done from Site 2 to Site 3
- Basis for comparability (criteria setting, direct comparator batches), etc. was Site 2
- Goal is rapid approval in U.S. to support supply due to shut-down of Site 1 – most expedient submission with appropriate use of resources is to “simply” use the Site 2 to Site 3 transfer

- **Thoughts on best way to manage A = B, B= C, therefore A = C issue?**
- **Can this be all paper-based? How much of a comparison to Site 1 do we need to include?**

Scenario 7 – Method Transfer

- We are in a transition phase for the QC network, bringing in a new method (specifically rFc for endotoxin)
- Method is in place at Site A and is used as the commercial method for the DS that will be transferred to Site B
- Site B has not implemented this method
- Intend to use not only for this product but for all others (eventually)

- **Is there a quick way to transfer this method?**
- **Is it different for a compendial method than for an individual product method or other "platform" method – what about for this one, given rFc requires product-specific data for qualification?**

Scenario 8 - PAT

- We are using PAT to support DS manufacturing/controls (cell culture and UFDF)
- It will be a huge effort to set up the same approaches at another site, given differences in equipment and not already having the instrumentation running at Site B

- **Experience with whether it is worth the investment?**
- **Considerations for how to do this for a rapid transfer?**