Meeting Minutes: Best practices for tech transfer workshop
27 of January 2021

Meeting recording can be accessed here:
https://www.dropbox.com/s/1y46s95qrlusctu/20210127%20Best%20practices%20for%20tech%20transfer%20workshop.mp4?dl=0

Key takeaways

1. **Supply** - Focus on raw materials and consumables early (have a "mass balance"). Build in a plan for "worst case" such as low yields and ensure proper mitigation strategies.
2. **Cultural and language** — assign project manager with right language skills and consider implementing mechanisms to monitor preferences and collaboration between member states.
3. **Documentation** - Have a clear documentation strategy with in the "end in sight"— write each report with a focus on what needs to go into regulatory submissions to reduce redundancy of technical writing.
4. **Teamwork** - Identify decisions and decision-makers upfront and empower them. Define and describe roles and responsibilities. Think out of the box — unite, collaborate and cooperate.
5. **Leverage prior knowledge** (in this case of similar platforms) for risk-based approach to prioritize experiments on unit ops and parameters that are at high risk or with little understanding.
6. **Regulatory** - Early and frequent regulatory communications and engagement throughout tech transfer facilitates a compliant transfer process and final approval.

Announcements:

- CEPI has an open call for an Expression of Interest: Vaccine Drug Products in alternative primary packaging and delivery devices. CEPI and INTACT Solutions are developing a multidose prefilled syringe for pandemic response. The deadline to apply is Sunday 28 February 2021 15:00 CET. Learn more here: https://cepi.net/get_involved/cfps/
- Save the date: Best practices for post approval changes workshop will be held on Wednesday 3 March 15:00-17:00 CET.

ITEM 1iii: [Notes]

Theoretical perspective: Samsung Biologics tech transfer process and protocols– *Andrew Kim, Samsung Biologics*

- What type of concessions were required by the Quality group to facilitate the expedited TT?
    - Never skipped quality but focused on documentation (SOPs etc.) that needed to be met. The DS purified in the DS plant is immediately transferred to DP plant where F/F is performed. There were agreements for conditional release which reduced the process time from 45 to 15 days.
- Can you expand on what is meant by "mass balance on equipment and raw materials"?
    - Based on titer or concentration of the antibody in the cell culture, process volumes and number of batches are projected, and safety margins (e.g. order 20% more than you think you need) are estimated. The sooner you can calculate the amount of raw materials can be calculated the sooner orders can be placed allowing for timely manufacturing.
- In case you change one item from supplier A to B (as you mentioned as an example of filter) would you do it without repeating process validation or any action needed?
    - Samsung did not encounter this scenario. But note, all COVID antibody programs transferred in had not yet been validated at an alternate site. In one case, the sending unit (SU) process was modified to switch the virus filter to a plan B based on what could be sourced to meet the manufacturing schedule. To support this change in plan, the SU site performed additional process development experiments to define operating ranges for the alternative filter. Given the nature of the virus filter operation, there is minimal impact to product quality so a switch to an alternative is more forgiving at this step. Note, this example ties into one of the chief supply issues that has been encountered and is expected to continue

to be an issue in 2021: supply of Merck Vpro virus filters which are an example of a consumable that is in high demand and short supply.

- While no person in plant and SME on 24-hour call, did you use any remote monitoring tools in plant so sender could observe critical operations?
    - Yes, Google glass as a visual remote monitoring tool. At present, there is not a tool in place to allow for real-time monitoring (such as pi monitoring software tools) of the process by the client. However, daily process monitoring updates were provided on critical process information (pool volumes, yields, mass amounts). On a weekly basis, an excel sheet was provided with parameter information from the batches.
- How did you perform training of receiving unit (RU) people with travel ban? Remote training?
    - Training relied on already present RU personnel. I suspect this concern may touch upon a key difference (like the platform process gap) between the COVID mAb projects we transferred into SBL and the various tech transfers to be executed by some of the COVAX members.
- During tech transfer with different process volume (scale) what would be the key requirements expected from the SU?
    - SU would share a detailed process development timeline (with key milestone dates such as process lock identified). SU sharing of mfg. data as it becomes available (500L, 2kL). SU sharing of historical data/experience for other projects based on the same platform process. SU shipment of both master and working cell banks to support our small-scale and mfg.-scale activities. SU drafting of process description documents in a phased approach: each version updated with new or modified ranges. SU availability to address document timeline issues (of which there were many) including document support during holidays such as Thanksgiving or Christmas.
    - What hurt us most are those rare instances when SU was not fully transparent. For example, we observed cell culture growth issues in the shake flask stage for one project. And after the fact we were notified by the client that they had observed the same issue for this project and resolved it by doing XYZ. In this case, if they had shared this potential issue ahead of time, it could have been easily prevented on our end.
- Do you provide standard questionnaires / templates for the donor site to describe their process, so you can implement it easier/faster at your site?
    - Yes. This is a standard element of RFP's early on during business discussions. This is shared with all potential sending sites. For COVID, there were a lot of blanks from sending organizations - which was okay because it was an emergency situation. Estimates were also acceptable.
- At what point would a process be modified to be able to process everything?
    - The common issue was lower than expected titers (not more than expected). It was necessary to return to and revise the mass balance throughout the transfer process as SU developed greater process understanding. Therefore, the max cell culture titer that the purification process could handle (for the high titer projects) was identified. It was agreed ahead of time that any titer above this maximum threshold would result in wasting of the excess during production. This calculation was based on available raw materials. If there were only sufficient buffer solutions to perform 3 cycles of a chromatography step instead of 4 or 5, then 3 would be performed. If there was only enough virus filter supply to perform two cycles of the virus filtration step, then three would automatically be impossible.

ERVEBO® Vaccine for Ebola Virus – A Case Study on Approaches to Accelerate Process Development and Tech Transfer – *Joseph Califano, Merck*

- Did you have to prove comparability between the commercial batches and the very first phase 1 CTM or only between the commercial batches and the phase 2/3 efficacy CTM?
    - Recollection is that there was one set of key data from the CTM. There was one analytical comparability protocol that covered PPQ. Joseph did not have details on the specifics of different phases.

- What was acceptance of global regulatory agencies involved in analyzing comparability and use of scale down model data.
    - Comparability from performance of at scale PPQ batches direct to the clinical batches. Laboratory scale is focused on process characterization and range findings. Understanding variation in those process parameters impacts quality attributes. It was accepted to use a laboratory scale model to make the process more robust. There was a concerted effort to keep many to all the clinical production targets the same as those for commercial production to de-risk.
- In terms of takeaways and now looking back at the initial risks identified; would you do things differently (e.g., start certain workstreams earlier) to accelerate TT-process as well as having first commercially (fully released) doses available?
    - Facility construction and readiness - always feels like there is never enough time for these tasks. Try to complete gap assessment early.
- Was the regulatory strategy taken into consideration when preparing the documentation strategy?
    - Yes. We had review and support from our CMC regulatory team members to review the content and reduce rework before information when external. Any technical documentation that was authored was prepared to be shared externally.
- You moved away from the CDMO that you used originally. What was the reason for not staying with the CDMO?
    - Do not know all the details but one issue was scale.
- In terms of your parallel activities how closely did you engage with regulatory agencies to share and seek their advice/council. Also how did you identify which agencies to facilitate this with?
    - Merck met regularly with FDA and EMA, as well as WHO.
- When is the best time to introduce the development process into a GMP facility?
    - As soon as possible- use the GMP or pre-GMP space for water runs, engineering runs, or other 'facility-fit' activities that may be difficult to do on paper that require the physical space.

Case Study: Process AZ Flu vaccine – *Christian McLarnon-Riches, AstraZeneca*

- What is the typical size of your Tech Transfer team?
    - In this instance, between originating and receiving teams approximately 60 people in total (including program managers and those doing transfer activities).
- Tech transfer for US-UK has been highlighted, and can you comment on any tech transfer to other countries where different languages, cultures but also pharmacopeias, markets and regulatory aspects may play a role in the communication and process?
    - This product was licensed in US, EU, UK which made the transfer a bit easier. Subsequently AZ did a transfer to Japan and managing relationships was very important. Time zones could make that challenging but having upfront planning (documentation) and understanding (key new market research) is especially helpful.
- How did you reduce resource needs? Typically, shorter timelines require more resources?
    - Upfront focus on having key templates in place. Clearly define roles and responsibilities will help to manage resources. For example, add team members when needed so as not to have excess people allocation when it is not adding full value.
- Did the regulatory framework for the seasonal vaccines against Influenza make the TT easier? Is there anything we can learn and leverage for vaccines against COVID-19?
    - The existing framework for flu works well and the main challenge is timing of submissions. For COVID, engaging early with regulators helps. Defining strategy/intentions/plans also helps.
- Is there need to do stability studies on the process validation batches after performing Tech Transfer?
    - Yes DS/DP transfers go onto stability studies
- How did you manage process improvement without conducting engineering runs? Did you find any risks?
    - Yes - when it comes to DS improvements any improvement work that is associated with that has an engineering run and risks are identified during that process.

- Did the regulators in the receiving end (UK) require that preclinical study be repeated along with having to conduct clinical studies starting from phase 1?
    - There are not requirements for clinical studies in Europe for flu.
- How did you address the Analytical method tech transfer particularly when we do not have specified Pharmacopeial requirements (for pandemic flu). What are the major challenges faced during interactions with NRA?
    - Test requirements for the Influenza vaccine are defined in terms of a spec and license. Methods are validated, and tech transferred via a protocol with acceptance criteria & then associated report. There is also a monograph for seasonal vaccine.

Industry Position: Impact of evolving analytical strategies on comparability, specification, and National Control Laboratories testing – *Cristiana Campa, GSK*

- Do you make comparability studies of the reference standards from different development stages?
    - Comparability studies during development may be needed when process/ scale changes are made (very likely in highly accelerated scenarios), and reference standards are ideally used as comparators (see also ICH Q6B).
- If we use an "in-house" ref std (calibrated against international ref std), can we use an internal control (well characterized) to demonstrate method sustainability to support the bridging of analytical methods (current method versus new developed method)?
    - If you are alluding to control samples used in analytical sessions to monitor method performance, yes, they can definitely help supporting analytical bridging and performance assessment.