Table 5: Challenges with Emerging Technologies for CGTP Manufacturing and Single Sourcing

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Scope:

The power of cell and gene therapy products (CGTPs) to transform medicine for rare, complex, and previously incurable diseases is being unleashed by rapid progress in scientific research, yielding a small but growing arsenal of approved therapies and a teeming pipeline of candidates in clinical trials. There have been rapid advances in manufacturing technologies, such as continuous and point-of-care manufacturing systems and new technologies in release testing, which can expedite delivery of CGTPs to patients but require proper quality and regulatory considerations. Additionally, materials used for manufacturing may be complex, proprietary, and in high demand, with resultant few sources or single sourcing that can lead to supply chain insecurity, as seen these last two years. Emerging technologies, such as Industry 4.0 technologies (internet of things, artificial intelligence, robotics, and advanced computing), can revolutionize not only manufacturing processes and controls but also supply chains and logistics. This roundtable panel will discuss manufacturer and regulator roles in realizing the promise of emerging technologies for CGTP manufacturing, standardizing them across various programs, and opportunities to galvanize supply chains to ensure delivery of safe, high-quality CGTPs to patients.

Questions for Discussion:

1. There is constant evolution in technologies that are employed in the CGTP industry. How can regulators and manufacturers keep up with emerging technologies, in manufacturing and procurement, to set precedent and alleviate regulatory uncertainties?
2. The CGTP environment is complex with a multitude of program categories. How can emerging technologies be standardized across programs and evaluated against existing technologies?
3. Are emerging technologies necessarily better than existing technologies and/or is the ROI sufficient? When is replacement appropriate?
4. These last two years, most manufacturers have felt the pinch in procurement. How has your company approached challenges with single sourcing? Are you using any emerging technologies/automation to resolve single sourcing?

Discussion Notes:

Question 1:

There is constant evolution in technologies that are employed in the CGTP industry. How can regulators and manufacturers keep up with emerging technologies, in manufacturing and procurement, to set precedent and alleviate regulatory uncertainties? Keeping up is challenging because there is a lot of theoretical safety risk but not much manufacturing experience for products that would be first-in-market, and specifications are not set by the industry. It may be unclear what regulatory standards need to be met if the technology is not addressed by available guidance. There is the possibility of being held to standards for seemingly similar technologies that, in reality, may be very different, for example, empty lipid nanoparticles vs. empty AAV capsids. As another example, when the oncolytic virus industry was first coming up to speed, the bar these products were measured against was the same as for vaccines, but that was inappropriate because dosing is much higher for oncolytic vaccines and the intended population is very different. As such, limits for host cell DNA were not achievable with a dosing regimen that needed to be orders of magnitude higher. For emerging technologies, there is currently no one-size-fits-all approach. Therefore, early interactions with regulators are critical to align on the criteria that are set for novel products. It can be difficult to know the right questions to ask regulators because information they have about products under review is not shared with other sponsors. It would be a huge benefit to developers in academia and small companies to have more visibility into their thinking about emerging technologies closer to real-time.

Question 2:

The CGTP environment is complex with a multitude of program categories. How can emerging technologies be standardized across programs and evaluated against existing technologies? The pace of technology is such that there may be something new by the time a guidance is issued. It would be prudent to pay particular attention to regulator's suggestions in any interaction because these may be based on patterns they have identified in the applications they are reviewing. For some questions, the answer may simply be, "We do not know yet." For example, in the cell therapy space with feeder cells there are concerns about residuals, but it is not clear how best to test them. Reviewers may respond, "You might want to do this," with vague, high-level language that is still helpful but not directive. Regulators face the challenge of trying to integrate new technologies into their existing regulatory framework if possible, so prescriptive guidance may not be possible at an early stage. However, transparency does not mean commitment and flexibility is valued, so any information regulators could disseminate closer to real time while protecting confidentiality would be helpful to developers. It would also reduce regulators' burden because they would not continually receive the same questions from developers. Regulators need to offer general feedback that will be meaningful within the complexities of any individual program, which must be challenging given the massive volume of applications in addition to communicating with the industry in this complex space, where seemingly any change manufacturing impacts the final product. FDA does issue questions and answers periodically.

Question 3:

Are emerging technologies necessarily better than existing technologies and/or is the return on investment sufficient? When is replacement appropriate? How should the regulatory authorities then look at this matter – instead of comparability, should there be a more comprehensive reason for going in a particular direction? Emerging technologies can provide cost and time savings. For earlier CGTPs, this question started with animal models vs. *in vitro* studies, which for some aspects of development are preferable. For example, tumorigenicity studies were initially a heavy lift but now there are other ways to tackle this issue. However, in the current NGS space for adventitious agents testing, it is a bigger lift for validation vs. using the existing technologies. How do you make that decision to switch to an emerging technology and how do you justify it to regulatory authorities? For a small company, the decision is financial because time is money. However, when new technologies such as rapid microbial methods enter the space, then everyone has to lift to that new technology regulatory authorities expect. It seems to be mainly industry driven. As regulators look at packages coming in, if one company has a higher bar for testing, then expectations will rise. It starts with regulators suggesting you think about it, then it becomes a guidance. The big companies create the lift. Are you missing anything if you do not perform the extra work? If the answer is yes, you will have to do it. If it is a better orthogonal method, maybe more sensitive, but does not miss anything, where the old technology was suitable but did not give the extra information, then it may not be worth the lift. For example, if there are five methods to measure expression, regulators will not require you to include all five tests in the release specification; rather, additional characterization assays can create a great panel for comparability. It is part of the regulatory strategy to determine what will offer your company a leg-up on characterization vs. what needs to be in the specification. The Agency is headed more towards risk analysis. For example, a risk assessment using FMEA helps to distinguish what is really important and help identify CQAs.

Question 4:

These last two years, most manufacturers have felt the pinch in procurement. How has your company approached challenges with single sourcing? Are you using any emerging technologies/automation to resolve single sourcing? Sometimes companies are forced into a niche where there is single sourcing only. How do you define single sourcing? How do you know it is a single source? Looking for reagents, if only one vendor makes it based on your search, and you confirm with a consultant, you know there is probably only one source. In the raw material section of the filing, what is considered like for like? For example, must bags with the same contact layers but made by different companies both be included in the filing? If there are multiple bags and a company picks what they perceive as the best, then it is not like for like. If you need something for a certain level/function and set those criteria, but then see a real drop off in performance switching, it is not like for like and you may have put yourself in a corner. Why is single sourcing a problem? Regulators expect redundancy in your supply chain, otherwise there can be a shortage and patients will be impacted. Most companies' goals are to introduce redundancy during clinical trials. That way, if there is a supply chain issue but you have clinical data along with stability etc., you mitigate shortage risks to the business and to patients. The clinical team may not want

variability in the raw materials, or materials at edges of the range, to minimize variability in outcomes; however, for CMC, there is a concern for process robustness, and variety in the data is needed. A true single source is one where there is nothing else out there in existence. Then there is single source from your personal perspective in terms of the best material. Is there a way to derisk a true single source? You could reach out to a company and ask them to custom-make the material so there becomes a second source, or you could look for a different type of material, although this can be challenging with CGTP reagents. For the second case of materials that are not like for like, in another pandemic, could you do some development, show comparability, and pivot? At what level of paranoia is it appropriate to build a dataset with additional sources should you need to pivot, or is that too much too soon? A raw material risk assessment could be performed to look specifically for those items. As mentioned during this meeting, COVID made supply chain sexy because everything becomes a critical raw material when you run out of it. Labs were shut down because they could not get tips. When you look at a critical raw material, the question is what impacts product quality and safety, but a risk assessment should also have supply chain/business question and what is considered like for like so you do not have to do other studies again, like stability. For tips, there is a lot of like for like. The assessment could include sterility levels, size of opening, material of construction, potential leachables, etc., but these issues are really all theoretical and the tips should be like for like; however, for a growth factor, a change makes the manufacturing method different. For example, a protein may fold differently, so then it is not like for like and characterization work is needed. For comparability-setting criteria: if both reagents meet the same endpoint but a formal comparability has not been performed, is that sufficient? That is why the Agency has very specific definition of comparable. They never say "identical." The more complex the product is, the harder it is to show comparability, but it may be an improvement. For example, FBS is highly variable, but a new FBS could be a process improvement. Importantly, a lot of reagents are not "GMP-grade" in the CGTP space. There may or may not be significant differences in R&D vs. GMP grade of a reagent, and sometimes the R&D version works better because the scale-up causes problems.

Conclusions:

Challenges with emerging technologies include lack of information for both developers and regulators, which can be mitigated by early interactions. History shows that adoption of emerging technologies by the industry can create efficiencies and savings over time, although the lift may be heavier upfront, in particular for smaller companies. While single sourcing is common in CGTP manufacturing, it can be derisked whether there is a true single source or a preferred source.