Developing a Culture of Quality: from Early Development of Novel Therapeutics to Market-a panel discussion: presented live Oct. 26, 2020. (presented on the BioTechniques platform)

Introduction

Many innovative ideas for novel therapeutics come out of academia. While the startup companies formed to advance these ideas are generally founded on scientifically sound principles, they often lack the experience, especially with regards to quality systems needed to translate their ideas into viable product candidates. This experience gap often results in delays, or even failures, in development. A panel discussion including subject matter experts who shared examples of the challenges faced by developers of novel therapeutics and best practices to accelerate their success was held on Oct. 26, 2020.[1]

Panel

Nadine Ritter (NR)
President/Senior Analytics Advisor
Global Biotech Experts/CASSS Board
Nadine Ritter has been a protein scientist for over 30 years, with 10 years basic academic research followed by 20+ years in biologics CMC. She has provided technical, regulatory, and quality elements to the success of over 150 global INDs/IMPDs and BLAs/MAAs and over 30 PAI/GMP inspections. Currently, Nadine is chair of the Board of Directors of CASSS and is a founding member of the CASSS CMC Strategy Forums. She is a past member of the Biopharmaceutical Advisory Board of the Parental Drug Association (PDA; MD, USA) and contributed to the PDA Method Qualification and Method Validation Technical Reports. Most recently, she was co-chair of the 2019 EU PDA Pharmacopeial Harmonization Conference. Nadine is frequently invited around the world to speak, consult, and train on analytics associated with the development and commercialization of biological/biosimilar products and GMP compliance for in-house and contract testing laboratories.

Wesley Workman (WW)
Principal
Workman Biotech Consultants, LLC
Wes started Workman Biotech Consultants, LLC in 2019. Prior to that he led teams that provided analytical technical services support to biologics development and manufacturing in Pfizer (NY, USA) and legacy companies for 34 years. Marketed products that Wes supported include recombinant proteins and antibodies, PEGylated proteins and oligonucleotides, antibody-drug conjugates, heparin, vaccines, enzymes, blood products and antibiotics. Wes has served as a USP volunteer since 1992 during which time he chaired and was a member of numerous USP expert committees and panels. Most recently he served on the USP Council of Experts (2010–2020).

Hynda Kleinman (HK)
Senior Science Advisor/Consultant
Various Organizations
Hynda K. Kleinman received an MS and Ph.D. from MIT in 1971 and 1974. After a postdoctoral fellowship at Tufts University from 1973–1975, she directed a research lab at the NIH from 1975–2006. Since 2006, she has been a consultant to biotech companies. She has published over 430 papers and

[1] https://www.biotechniques.com/webinars/us-pharmacopeias-panel-discussion-on-developing-a-culture-of-quality-from-early-development-of-novel-therapeutics-to-market/

has 9 patents, several of which have been commercialized. Matrigel is used worldwide for *in vitro/in vivo* assays, including the patented invasion assay. The regenerative protein thymosin beta 4 is currently in phase 3 trials for ocular and dermal injuries.

Piergiuseppe Nestola (PN)
Senior Platform Technology Consultant, Viral-based Therapeutics Segment
Sartorius Stedman Switzerland AG
Piergiuseppe Nestola is a Senior Platform Technology Consultant at Sartorius Stedim Biotech (Göttingen, Germany) responsible for providing scientific leadership and identifying the best technologies and processes for the viral-based therapeutics segment. Since 2018 Piergiuseppe has also been a judge at the Mass challenge and Bioexpert network incubators supporting startup life science companies. Piergiuseppe holds a PhD degree in Chemical and Biochemical Engineering from Universidade Nova de Lisboa and performed his research at iBET (both Lisbon, Portugal) developing virus purification processes for vaccines and gene therapies. Piergiuseppe has a Master's Degree in Industrial Biotechnology from University of Turin (Italy) and a certificate in disruptive innovation from IMD Business School (Lausanne, Switzerland).

Michael Hidock (MH)
Principal Consultant, QCS Services
IQVIA
Michael Hidock has 19 years of Quality Management experience within pharmaceutical and medical device manufacturing to support company and client leadership. He has expertise in the development, implementation, and management of core Quality Management Systems (QMS).

John F. Kokai-Kun (**JK-K**, Moderator)
Director, External Scientific Collaboration
United States Pharmacopeia (USP)
Dr. Kokai-Kun received his PhD in Microbiology from the University of Pittsburgh, School of Medicine (PA, USA). He has more than 20 years of experience in drug development and has held various positions with several biotechnology and pharmaceutical companies where his research and development efforts have focused primarily on anti-bacterial drugs, biologics, and vaccines. He has published more than 40 peer-reviewed publications regarding various aspects of drug development and microbial pathogenesis. Dr. Kokai-Kun is also an Adjunct Assistant Professor of Microbiology and Immunology at the Uniformed Services University of the Health Sciences and is retired from the United States Army.

Questions and Responses:

What is quality and why does it matter?

NR – Quality is the evidence that a company is doing what it claims to be doing. If the evidence for quality is not readily apparent to regulators, then a company has failed in establishing its claims. The documentation used to demonstrate quality and adherence to quality practices must stand on its own. The documentation of the work must be so clear, concise, and complete that it can be understood and repeated based only on the documentation. This can be a major paradigm shift for employees transitioning from an academic environment, where notetaking is not necessarily codified, to an industry environment in which documentation has both legal and economic ramifications.

WW – Quality is directly proportional to a company's effort, resources, and attention to detail when performing work. This is most pronounced in the analytical lab where the attention to detail should be obvious in the standard operating procedures. It should be readily apparent what the lab is using for reference standards and control samples, and whether these reagents support regulatory inspection. The necessary information to establish these standards can be obtained by speaking with consultants and engaging with standards-setting organizations like the United States Pharmacopeia (USP).

HK – Quality is the people. It is a company's employees and the consultants it hires. Quality starts with a workforce that is honest, knowledgeable, and experienced. From a clinical development perspective, the employees and consultants must understand the requirements, advantages and disadvantages of clinical trial phases and should be able to advise on how to present a therapeutic product to regulatory agencies. The leader of a company's quality initiative needs to be persuasive, yet approachable, because this person will represent the organization to investors and regulatory agencies.

PN – Quality is about managing the transitions in pharmaceutical development, especially in going from process development to GMP manufacturing. Many companies perform the required process development activities to set up their process, but do not plan appropriately for maintaining quality as they scale to larger production volumes. Process development is not equivalent to manufacturing; it is only an interface between discovery and manufacturing. It is during this interface phase where any problems need to be identified and understood. For example, the limits of any analytical assays must be addressed before attempting to scale-up production. Otherwise, the company will experience significant problems when expanding to a GMP environment.

MH – Quality is a firm's license to operate. All companies from startups to mid-size to large pharma will not survive without quality by design and a quality facility or a robust culture of quality even if they are financially sound. A culture of quality is founded upon honesty and integrity. When a company cuts corners with respect to quality and is not transparent, then it creates a culture of mistrust. Eventually this will be uncovered by regulators, which is very damaging. A broken system can be repaired, and processes can be corrected, but it starts with establishing a corporate culture passionate about quality.

What is the first step to develop a culture of quality

PN – Having the right processes in place to manage the data and support those data over time. Companies develop a lot of data early in the journey. Those data need to be stored and analyzed properly. Data are the product.

MH – Companies need to understand, what is their market? Because each market has a specific set of regulations and requirements, different products and markets have different expectations.

WW – Most early stage companies have a business plan, but they should also have a quality plan. Safety, identity, purity, potency, and strength; just those terms can provide information on what regulators expect and how they can be addressed. Start-off with a quality plan that sets out how you will address those issues. It may change as you progress through the different phases, but it gives you a starting point to approach and discuss with regulators.

HK – Companies need to have their intellectual property (IP) in order. When companies are starting out, they often bring in IP from a university, and it is usually sloppy and not done properly. The best advice is

to have a lawyer file the patents properly and get as many areas covered because IP is the foundation for raising money, getting investors, and growing the company.

NR – Start with the basic science practices at the bench. How are the data being generated? Are the instruments calibrated every day? Are they using positive controls and negative controls? Are the positive controls pure? Have the negative controls degraded? It is also important to understand the goals. There are legally required studies that must be started very early in development to get materials into human clinical trials. There are 12 analytical study packages that are required everywhere in the world. They must be completed for any product to get it into first-in-human studies. In summary, the benchwork must be completed in a manner which has integrity and reproducibility, and the company must be prioritizing the correct studies. Otherwise, the company will waste time and money, and risks compromising a product with potential. Everything in between can be built and bridged into it.

How does a thought process need to shift when translating a therapy concept into an actual drug development program?

WW – There have been a lot of companies that have gone down this path, so benchmarking is important. A startup company should pick one as a model for creating a path. It is also important to stay focused on the product attributes, specifically, safety, purity, strength, and potency. As the company grows, there will be obvious gaps in these areas that will need to be addressed. Some of these areas will require knowledge and experience not present within the company, so the managers will have to seek out that expertise elsewhere. It is difficult to go back and correct work that was done improperly or do work that was never performed when it should have been. Most startups will be acquired by larger pharma if they are successful, and it is much better if those larger companies understand what work has been completed and why. It decreases the value of a startup when the acquiring company does not clearly understand what it is purchasing or if it has to perform significant amounts of extra work to make the product suitable for a regulatory submission.

What are the important considerations for a company when developing their manufacturing process to allow for a smooth transition from working in animal models towards those first-in-human trials?

PN – Once a company has a product, the important questions are related to manufacturing. It is important to start with the end in mind. Where should the company and the product be in one, two, and five years. The managers should then work backwards from those goals to make sure that all the practical steps are under control. Many of the questions that will need to be resolved revolve around basic, yet critical components, including media, cell lines, expression systems, and purification systems and how these choices can be scaled. The initial priority is to control all the process parameters, but then it becomes complicated because a company needs to adapt all the different unit operations.

There are invariably challenges in any drug development program in terms of quality, what is important to consider when overcoming these challenges?

MH – Many founders of startup companies do not have a background in quality. They stumble when there are quality issues that result in failure during clinical phases. They do not know what the next steps should be, and they end up making the wrong choices. It is important for founders of startup companies to surround themselves with enough good quality people and counsel to make the right choices when compromising situations occur.

What kind of skills and experience should a company look for when building a team to develop a drug? Who should be on that team?

HK – Companies should look to hire people who have had prior success in drug development. For example, a company should avoid hiring personnel without experience with clinical trials. Small companies can look to knowledge opinion leaders (KOLs) that can help with everything from protocol design to recommending clinical sites for studies. Companies should also look to contract research organizations (CROs) that have a team of experts for writing regulatory documents. Regardless of the contractors, a company should always confirm and verify all work performed by a third-party.

What should you look for when hiring an outside organization to be a service provider?

NR – There is a lot documentation about the end of product development. As a company approaches commercialization, there are a lot of regulations, guidance documents, and statutes that must be followed. For early phase product development, however, there is no body of documents that specifies in detail how to build a quality system. This will not change much because most people prefer to interact with other people who are experts in these areas. Knowledge transfer for many of these key topics is an oral tradition propagated by people and not documents. The key is the people within an organization. First, find organizations that have a good track record. Then do research on the people within that organization. There are professional organizations like USP that have personnel that have been in the field for a long time. Look for publications. Look for participation in working panels. Look for task forces. Use LinkedIn to check the pedigrees of key personnel in the company.

What do larger companies look for in terms of quality when assessing product candidates and the startup companies for possible partnership or acquisition?

WW – Large pharma benchmarks against best practices in the industry. Due diligence teams look to see if the developers are following standard procedures such as those outlined in a USP monograph or chapter. If the company is not following those clearly stated procedures, then it makes other forms of compliance possibly suspect. Auditors should be looking for scientifically sound processes. What reference standards are the company using? How were they qualified? Startups can help themselves by utilizing the *USP-NF* General Chapters. The chapters are written by USP Expert Committees that bring together academic, industry and regulatory professionals. It is a very rigorous effort that produces guidance on procedures that is not generally available anywhere else. Many of the chapters cover industry best practices and provide tips on achieving compliance. Also, the *USP-NF General Notices* provide information on procedures and how to perform them properly in a laboratory.

What should a company look for when considering a contract manufacturing organization (CMO)?

MH – A small company will rely heavily on its CMO and its suppliers. It is therefore important to identify people who truly understand the regulations that govern those arenas. It is paramount to qualify and fully vet your suppliers because that is one area that the FDA is really going to investigate. All suppliers must have facilities registered with the FDA if a company plans to market a product in the United States. A small company cannot afford to invest a lot of time and money only find out later that its suppliers cannot pass a regulatory inspection.

What are some of the tools available to a company as it is translating its product candidate into a drug development program?

PN – There are several new software packages that can help scientists to design and run experiments in a structured way, as well as electronic lab notebooks for data management.

What are some of the early decisions that a company should make when considering how to interact with regulators?

HK – The FDA is there to help companies. They are interested in more products getting to market if they are safe and efficacious. It is important to contact the FDA very early on in the process with specific questions. In pre-IND meetings, the FDA can guide a company on what it needs to get done to get to the next step. If there is a problem, it is best to go to the FDA right away and seek their guidance.

How does documentation of results differ between the research lab and the development lab?

NR – A lot of the information that was generated during the research part of the lifecycle of a product has incredibly important clues or information that can be leveraged for development. It is important to document this information in such a way that it can serve as a reliable database for product development. Then, if something should occur down the road, the developers can go back and find out how to solve a problem very quickly.

When should a company start considering quality?

MH – Quality is the building block of any organization; therefore, it should be considered at the inception of the organization.

What is the biggest hurdle a new company faces in terms of quality?

WW – The biggest hurdle is the perception that it is going to cost too much. Companies should not think of quality costs but quality investments. It is important to have a quality plan so that you know where you are going and where you are heading. Regulatory agencies will look at the plan to see how much detail is in it, how many resources have been put into it, how much effort has been put into it. Quality is an investment when trying to build a company that someday could be acquired. If a company approaches quality as an investment that will provide returns with the regulators, investors, and partners, then it changes the way it approaches quality.

How do you recommend getting started looking for a CRO or a CMO with the current travel restrictions?

HK – It is possible to do this remotely. Using traditional conference calls or video conferencing with a slideshow allow CROs to pitch their services. These tools also allow the client to ask questions and engage with the CRO representatives. These same tools can be used for internal conferences within the company to pick a CRO and start working with them. An area that is suffering now is patient recruitment for clinical trials. Patients do not want to come into hospitals and public places, and they do not want to travel on planes. However, companies can lay out all the groundwork now and move quickly to start the clinical trial once patients become available.

Select Questions from the Audience:

How do we know who to call or email for analytical regulations for a company that has a QA department?

MH – You will want to have a quality manager at the center of a quality laboratory. The quality manager should have a fundamental understanding of the analytical regulations.

NR – There are three publications; *Biopharm International, Bioprocess International*, and *Pharmaceutical Technology* that have significant amounts of information. They highlight regulations that are published.

Does USP have a working group to help scientists from the beginning?

JK-K – This panel discussion is an opportunity for USP to begin working with some of these early stage scientists. USP also has a program called "Trust Accelerated" which provides advice to companies. Please also look at https://www.usp.org/courses-search for additional available courses with regards to quality.

The full panel discussion can be viewed here:

https://uspharmacopeia.csod.com/default.aspx?p=uspharmacopeia&c=GP&dlink=%2fDeepLink%2fProcessRedirect.aspx%3fmodule%3dlodetails%26lo%3d0b759122-3dc7-412f-8569-e56105510417