IPQ INTERNATIONAL PHARMACEUTICAL QUALITY
Inside the Global Regulatory Dialogue

COVID-19 Vaccine Urgency Throws Spotlight on Next-Generation Sequencing for Adventitious Virus Control

[Editor's Note: The following is IPQ's coverage of the December 2019 CMC Strategy Forum Japan. The coverage appeared as Part III and IV of a five-part IPQ story on the collaborative efforts now going on globally to advance the use of in vitro testing in assessing and controlling adventitious viruses for vaccines and biotherapeutics. The first two parts of the story focus on the discussions that took place at the CASSS Europe forum in May 2020, which reflected the high relevance of the adventitious virus issues to the development of COVID-19 vaccines. The story was included in the April/May 2020 IPQ Monthly Update. The issue has been made publicly available so that its content can be as useful as possible in meeting the pandemic challenges. CLICK HERE for the full April/May 2020 issue.]

PART III

A Decade of Regulator/Industry Collaboration on NGS

CBER Office of Vaccines Research and Review [OVRR] Senior Investigator Arifa Khan, presenting at the December 2019 CASSS CMC Strategy Forum Japan, outlined the increasing focus on advanced virus detection technologies over the last decade and shared FDA's collaborative efforts in developing and promoting the use of next-generation sequencing (NGS) for biological product safety testing.

Khan shared highlights from recent key conferences and detailed her department's work on development of model virus reference standards, modernization of a virus-specific database, and outreach activities to manufacturers.

She began by walking the audience through the safety concerns raised by the introduction of novel cell substrates for vaccines two decades ago, and how the need for advanced virus detection technologies including NGS to test for previously undetected viral contaminants became clear with the 2010 discovery of porcine circovirus (PCV) in rotavirus vaccine.

> **Khan then went on to consider the challenges around the use of NGS in virus detection, including validation and bioinformatics – especially the handling of large amounts of data and follow-up strategies to determine the biological relevance and significance of positive signals.**

Applying NGS to adventitious agent testing has been a major focus of her lab team. The Office of Vaccines Research and Review (OVRR) has been active in agency genomic working groups and in external collaborations and organizing conferences.

Outcomes of Recent NGS Meetings Highlighted

Discussing the outcomes of the IABS workshops on NGS for adventitious virus detection in biologics held in Rockville, Maryland in 2017 and in Ghent, Belgium in November 2019, Khan stressed the clear need for "continued collaborative efforts and scientific exchange" in meeting the challenges of applying NGS in the regulatory arena.

She further highlighted a September 2019 workshop on the progress made and gaps remaining to be filled in "standards for NGS detection of viral adventitious agents in biologics and biomanufacturing," organized by FDA and the National Institute of Standards and Technology and held at NIST's Maryland headquarters.

> **The many collaborative initiatives in which Khan and her group have been involved have included publications, developing the panel of reference standards *(see Part I)*, and modernizing the reference virus database (RVDB) to allow the information to be more widely accessible.**

She explained that the RVDB was designed "to have complete representation of diverse virus families" – facilitating the general use of NGS for broad virus detection and aiding in detection of emerging viruses. The database was moved to the University of Delaware in October 2019, she noted, and the goal is to make it more user-friendly, blast-searchable, and regularly updated.

Concluding with a roundup of current and future regulatory guidance and the experience of the OVRR with NGS, Khan stressed the importance of engaging early with her office through technical working group discussions "to reach a consensus prior to initiating lengthy, expensive studies."

The power of NGS and its benefits for potential applications in biologics is recognized, she said, and "therefore, regardless of the challenges, there has been much progress made towards the standardization and applications of NGS." ***[A link to Khan's full presentation at the CASSS Japan forum is provided below.]***

Evolution of European and International Guidance on NGS

The evolution of international guidance and the Ph. Eur. monographs regarding NGS was further discussed by Italy National Center for the Control and Evaluation of Medicines Senior Researcher Domenico Genovese at the CASSS Europe strategy forum in May.

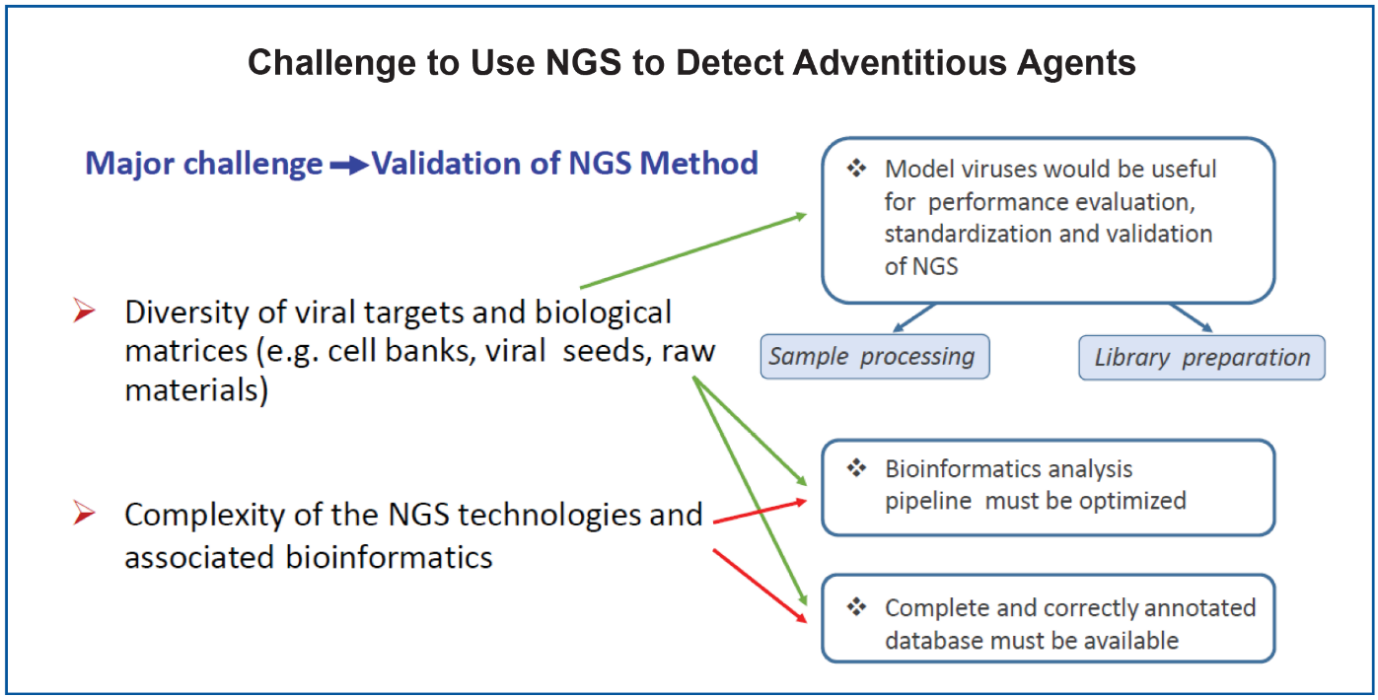
Genovese focused on the requirements for biological manufacturers to demonstrate the capability of the process to remove or inactivate known contaminants. He pointed out that various EMA guidelines provide recommendations on viral inactivation validation and also set specific values for viral clearance levels.

He discussed the limitations of conventional assays to detect viral contaminants, noting – as did Khan – the "evolving regulatory expectations on viral safety" over the past decade and that NGS "is a sensitive and un-biased detection method for adventitious agents."

He then outlined the evolution of the EP monographs. These were updated in 2018 to encourage supplementation and replacement of conventional testing by newer, sensitive molecular methods with broad detection capabilities, and are supported by WHO technical report guidance.

The new/updated chapters include: ● Chapter 5.2.14 – "Substitution of *in vivo* method(s) by *in vitro* method(s) for the quality control of vaccines" ● Chapter 5.2.3 – "Cell Substrates for the production of vaccines for human use" and ● Chapter 2.6.16 – "Tests for extraneous agents in viral vaccines for human use."

> **Acknowledging the challenges of using NGS to detect adventitious agents, Genovese agreed with other speakers at the CASSS session that coordinated work among specialists is important. As examples, he also cited the efforts of the Advanced Virus Detection Technologies Group (AVDTIG), which is gathering together government agencies, industry, service providers, technology developers and academics worldwide, and conferences like that held by IABS in November 2019.**



[CLICK HERE for Genovese's slides from his CASSS Europe forum presentation.]

Genovese echoed many of the messages that Khan presented in the December CASSS strategy forum in Tokyo – referencing her office's work on upstream sample processing and library preparation as well as the efforts by the UK National Institute for Biological Standards and Control (NIBSC) on development of candidate reference material for adventitious virus detection in vaccine and biologicals manufacturing.

Looking to the future, Genovese reiterated the need for further dialogue between researchers, developers, companies and regulators to overcome current hurdles in approving the implementation of NGS and to develop harmonized international guidance on validation, for the benefit of both industry and agency assessors.

During the panel discussion that followed his talk at the CASSS Europe session, Genovese commented that his agency has not yet reviewed applications with NGS, but is preparing to do so through this dialogue. ***[See Part II for the full panel discussion.]***

[CLICK HERE for Khan's presentation at the forum.]

PART IV

Stakeholder Engagement Begins on ICH Q5A Revision

Members of the Expert Working Group (EWG) set up for revising ICH's Q5A guideline on viral safety evaluation are moving forward in their efforts to engage with stakeholders as much and as early as possible to ensure that the revised document is fit for purpose for the future.

Among the venues where that engagement has already taken place are the CASSS CMC Strategy Forum Japan, held in Tokyo in December 2019, and a workshop session at the CASSS WCBP conference in Washington D.C. at the end of January.

> **Driving the dialogue around revision of the ICH Q5A guideline on the "viral safety evaluation of biotechnology products derived from cell lines of human or animal origin" is a concept paper, endorsed by the ICH Management Committee in November 2019, which spells out the rationale and objectives for the revision and the issues that EWG views as most important to be considered in the update.**

The concept paper stresses that the current 1999 version, "while still useful, requires revision to allow for a consistent global understanding of viral safety within the biopharmaceutical landscape."

The revisions, the paper explains, will be aimed at supporting the new product development, use of state-of-the-art technologies, and a more harmonized regulatory approach for newer classes of biotechnology products. Alternative validation approaches are expected to provide increased flexibility for viral safety assessment.

> **A little over a month after the concept paper was released, the issues of virus control in bioprocessing came into sharp relief with the emergence of the coronavirus global pandemic *(see the first section of this story)*.**

Biotech manufacturers are now wrestling with the challenges of making sure that the three pillars of virus control defined in Q5A are in place in the SARS-CoV-2 virus context: ● avoiding contamination via raw materials ● ensuring viral elimination techniques are appropriate and satisfactory, and ● preventing potential contamination via personnel.

The additional complexities of the COVID-19 situation mean that both manufacturers and regulators are having to develop contingency plans to deal with reduced staffing levels, increased need of specialized protective equipment that may be in short supply, and adapting control strategies as more information on the novel coronavirus becomes available.

ISPE Webinar and PDA Virus Forum Continue the Q5A Dialogue

At an ISPE webinar on June 11 moderated by ISPE's new CEO Tom Hartman, GlaxoSmithKline (GSK) TSE and Virus Control Director Anne Stokes shed significant light on the operational controls needed to mitigate the SARS-CoV-2 challenge to the Q5A virus control framework. Stokes represents the Pharmaceutical Research and Manufacturers of America (PhRMA) on the ICH Q5A (R2) EWG.

Along with the control framework, she discussed the planning activities required to prepare for a novel virus challenge to manufacturing facilities and the ongoing virus risk management and mitigations needed.

> **The Q5A revision dialogue between EWG members and stakeholders is continuing at the virtual PDA Europe Virus Forum June 22-23, where Stokes is again presenting.**

Regulators from the EWG participating in the sessions are Paul-Ehrlich-Institut (PEI) Viral Safety Section Head Johannes Blümel and FDA CBER Office of Vaccines Research and Review (OVRR) Senior Investigator Arifa Khan.

Also presenting is FDA CDER Office of Biotechnology Products (OBP) CMC Product Quality Researcher/Reviewer Scott Lute – a colleague of the EWG rapporteur, Joel Welch, who serves as Review Chief at OBP's Division of Biotechnology Review and Research IV.

In addition to representatives from major biopharmaceutical firms, service providers experienced in virus testing and clearance techniques will also be presenting and engaging in discussions at the forum. Service providers are mentioned in the Q5A (R2) concept paper as key stakeholders in the revision process.

Japan's EWG Member Outlines Plans for ICH Q5A(R2)

At the mid-December 2019 CASSS Japan Forum, PMDA's Office of Vaccines and Blood Products Deputy Review Director Akira Sakurai, who serves on the ICH Q5A(R2) EWG, presented on the recently released concept paper and shared information on the composition and plans of the working group.

He outlined the drivers for the revision, progress made at the November ICH meeting in Singapore, and the anticipated development timelines. An initial draft is targeted to be completed by November 2020, with sign-off by topic leaders and endorsement of a Step 2 document called for in June 2021, and adoption of the final guideline in November 2022.

These key milestones were outlined prior to the COVID-19 pandemic, although it was noted in the slide presentation by Sakurai that the formal ICH procedures allow for sign off, endorsement and adoption to be achieved either by face-to-face meetings or electronically. The high relevance of the COVID-19 experience does add to the EWG's challenges and the importance of making the update as valuable as possible.

Sakurai stressed that a common message in the concept paper and all ICH communications is the need for early engagement with stakeholders via public conferences. ***[A link to the CASSS Japan agenda and Sakurai's slide set is provided at the end of the story. The concept paper is also provided in full below.]***

ICH Q5A(R2) Expert Working Group Membership

Dr. Joel Welch, Rapporteur (FDA, United States)

Expert List		
ANVISA, Brazil Ms. Silmara Cristiane da Silveira Andreoli	**IFPMA** Ms. Wei GONG	**PhRMA** Lianchun Fan Anne Stokes
EC, Europe Johannes Blumel	**IGBA** Dr. Andrej Francky Dr. Parag Goyal	**Swissmedic, Switzerland** Dr. Christoph Berger
EFPIA Dr. Marie Murphy	**JPMA** Dr. Nao Nakamura Mr. Kazuhisa Uchida	**TFDA, Chinese Taipei** Mr. Hung Chang
FDA, United States Dr. Arifa Khan Dr. Cecilia Tami	**MFDS, Republic of Korea** Dr. Gi Hyun Kim	**TGA, Australia** Mr. Dennis Dowhan
Health Canada, Canada Dr. Christopher Storbeck	**MHLW/PMDA, Japan** Dr. Akira Sakurai Dr. Yoji Sato	**USP** Dr. Fouad Atouf
HSA, Singapore Dr. Zhang Wei	**NMPA, China** Ms. Meng YANG	**WHO** Dr. Ivana Knezevic

Sakurai led off a session looking at technologies related to viral safety and the ICH Q5A revision, co-chaired by PEI Monoclonal and Polyclonal Antibodies Section Head Steffen Gross and Kyowa Kirin's Kazuhisa Uchida.

Other speakers included FDA's Khan and Kobe University researcher Keisuke Yusa, who spoke on the collaborative efforts to develop and use next-generation sequencing (NGS) for viral safety control in biologics***. [See Part III of this story for Khan's full presentation at the CASSS Japan forum.]***

Yusa demonstrated that a cell specific database can reduce false positive results and the versatility of NGS as a platform for viral safety control of a range of biologic products. Contributing to the research was Japan National Institute of Health Sciences Division of Cell-Based Therapeutic Products Head Yosi Sato, who serves on the ICH Q5A EWG alongside Sakurai.

An industry perspective on CHO cell product virus safety in the context of the Q5A revision was then given by Genentech Process Virology Associate Director Qi Chen. She highlighted the "tremendous amount of virus safety knowledge" accumulated over the 20 years that the current guideline has been in use, which provides strong support for the proposed revisions.

ICH and PIC/S Collaborating to Tighten Review/Inspection Alignment

Joining the panel discussion following the presentations, Health Canada Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics Senior Regulatory Scientist Anthony Ridgway – who had served on the original ICH Q5A EWG – shared his experience on a question relating to platform approaches and modular clearance.

Ridgway commented that he thought modular approaches would stand a good chance of being allowed for in the updated document, noting that it often happens that the scope of a guideline broadens over the years as more information and experience becomes available.

He suggested that regulators are already accepting a modular approach in many ways – for instance, in not requesting validation studies provided by the filter suppliers to be repeated by each product manufacturer. "So, in principle, the concepts of accepting these things are there." Panel participants agreed that appropriate justification would be key in successful regulatory applications.

Another valuable discussion was around the interplay with other ICH guidelines – in particular, ICH Q7 on active substance GMPs.

In the context of this discussion, Genentech Regulatory Policy and International Operations VP Wassim Nashabeh, who was chairing the forum and represents the Biotechnology Innovation Organization (BIO) on the ICH Assembly, pointed out that ICH was in the process of entering into a collaboration agreement with the Pharmaceutical Inspection Co-Operation Scheme (PIC/S).

He explained that the collaboration would be focused on the elements of the quality guidelines that may have an impact on inspection practices or GMP expectations.

The minutes from the ICH November 2019 meeting in Singapore indicate that its Management Committee received positive feedback on a proposal for more routine engagement with PIC/S and that there would be a pilot phase for this collaboration.

"As part of this proposal and in line with ICH processes, PIC/S would be involved in ICH guideline work during the public consultation following Step 2b," the ICH Assembly said in its minutes. "Additionally, as an ICH Observer, PIC/S could also request to be part of Plenary Working Parties (PWPs) which would allow an involvement prior to step 1."

Q5A(R2) EWG Engagement Continues at CASSS WCBP Workshop

The discussion on revising Q5A continued at a workshop during the CASSS WCBP meeting in late January. The workshop was led by the two EWG members from FDA, CBER's Khan and CDER OBP Product Quality Team Leader Cecilia Tami, and by AbbVie Director of Cellular and Molecular Biology Science Lianchun Fan, who represents PhRMA on the EWG along with GSK's Stokes.

Khan began by providing a brief background on the Q5A revision and how the ICH Q5A-E biotechnology product series relates to the other ICH quality guidelines.

She then outlined the five key issues highlighted in the concept paper that the EWG members were particularly looking for feedback on, involving areas where advances have been made over the 20 years since the existing guideline was written.

> **To set up the discussion on each of the issues, the workshop leaders invited participants to share their related experiences, concerns they may have related to the updates, and suggestions for gaps that warranted attention.**

Khan stressed that it was important for the EWG to get the feedback requested, because different manufacturers use the guideline for different types of products, including vaccines. "In the early days," she pointed out, it was mostly used by monoclonal antibody manufacturers.

Final Concept Paper

Q5A(R2): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

Dated 17 November 2019

Endorsed by the Management Committee on 18 November 2019

Type of Harmonisation Action Proposed

It is proposed to revise the Q5A(R1) Guideline "Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" to reflect new biotechnology product types, advances in manufacturing technology, analytical methods for virus testing, and scientific knowledge that have occurred since publication of the original document in 1999.

Statement of the Perceived Problem:

Since the publication of the Q5A(R1) Guideline in 1999, advances in biotechnology product development and manufacturing have occurred. The following advances are not reflected in the original guideline:

- New classes of biotechnology products have been developed, resulting in challenges for consistent regulation of these products across different health authorities.

- Only a limited number of validation approaches for virus clearance are described that can be currently applied. This has resulted in regulatory health authorities adopting different positions on the acceptability of these advances.

- New alternative analytical methods are available for use in virus testing but are not described. The techniques should be discussed, and additional detail included to support the inclusion of future analytical techniques.

- The development of advanced manufacturing (including, but not limited to continuous manufacturing processes) requires additional considerations for implementation of virus validation and risk mitigation strategies.

Issues to be Resolved

- <u>New classes of biotechnology products</u>

In the past twenty years, there has been an emergence of advanced biotechnology products due to the development of new production technologies and biomanufacturing platforms. Specifically, virus-like particles (VLPs), subunit proteins, and viral-vectored products have been developed for vaccines and gene therapies using novel mammalian and insect-based vector/cell expression systems. For some of these products, clearance of virus vector and adventitious agents may need to be demonstrated. The physicochemical properties of known and potential viruses for the species of cell line origin need to be considered in selection of appropriate viruses for the clearance studies.

- <u>Additional validation approaches for virus clearance</u>

Where appropriate, flexibility in validation approaches should be allowed in order to effectively leverage knowledge gained during development of manufacturing processes with extensive experience to support virus clearance. It is necessary to discuss expectations and limitations for the use of data of a purification step for related products or product classes that follow the same virus removal/inactivation unit operation purification step or conditions. Additionally, opportunities to use alternative approaches for virus clearance validation based on experience with well-characterized cell substrates and manufacturing processes should be discussed.

- <u>New virus assays and alternative analytical methods</u>

Technological advances since the publication of the original ICH Q5A(R1) Guideline have occurred that require additional discussion. Specifically, nucleic acid-based assays such as Polymerase Chain Reaction (PCR) and Next Generation Sequencing (NGS) may provide rapid and sensitive detection of adventitious and endogenous viruses in the starting and harvest materials. Additionally, quantitative PCR assays may be considered for assessment of the virus clearance capability of the manufacturing process. However, these nucleic acid-based assays have limitations as they cannot distinguish between infectious and noninfectious particles and therefore detection of a signal may need a confirmatory test with an infectivity assay for risk- assessment. For this reason, additional justification describing their use should be provided. Moreover, general principles for the inclusion of new assays and potential replacement/supplement of existing assays should be presented in order to continue to support future development of new technology.

- Virus clearance validation and risk mitigation strategies for advanced manufacturing

The principles of viral safety described in the ICH Q5A(R1) Guideline apply to emerging or advanced manufacturing approaches beyond traditional unit and batch process operations. However, specific challenges associated with viral safety in advanced manufacturing are not addressed in the original guideline, and would benefit from additional discussion and clarification. These challenges may include:

— Screening for and detection of adventitious and endogenous viruses during continuous manufacturing

— Validation of virus clearance strategies adapted from traditional unit operations

— Suitability of small scale models designed for traditional virus clearance spiking studies to represent advanced manufacturing systems

— Potential considerations for the role of facility design and manufacturing processes (open versus closed systems) in viral safety evaluation

Details for this topic will also support the ongoing development of ICH Q13.

- Aspects of virus clearance validation that have emerged or evolved

Some aspects of virus clearance validation have emerged or evolved since the publication of the ICH Q5A(R1) Guideline and will be discussed. For example:

— The recommended evaluation of chromatographic resin at the end of its lifetime for Protein A resin and potentially other resins

— Additional relevant model viruses for virus clearance studies

— Selection of appropriate model viruses for validation of nanofilters

— Additional discussion on the virus clearance safety margin, including calculation of clearance factors

Additionally, risk mitigation technologies for treatment of raw materials will be discussed.

Background to the Proposal

Consensus has emerged that ICH Q5A(R1), while still useful, requires revision to allow for a consistent global understanding of viral safety within the biopharmaceutical landscape. Moreover, to support both the development of new products and the use of state-of-the-art technologies, updating of viral safety approaches is essential. Implementation of updated assays and alternative validation approaches will benefit both industry and regulators by providing increased flexibility for viral safety assessment. Finally, the revised guideline will allow for a more harmonized approach for newer classes of biotechnology products and new developing technologies.

Type of Expert Working Group and Resources

It is proposed to establish an Expert Working Group with representatives with specialized knowledge on virus-detection technologies, virus clearance strategies, and manufacturing processes.

The Expert Working Group may also engage with external service providers who have experience with performing virus testing and virus clearance evaluations.

Timing

This working group had its first face-to-face meeting in November 2019. It is anticipated that this guideline may take 3 years to complete.

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Which New Classes of Biotechnology Products Does the Guideline Apply to?

The discussion at the CASSS WCBP workshop began with a focus on the considerations that come into play for the new classes of biotechnology products.

Khan clarified for "those who only work on monoclonal antibodies" that the guideline will also apply to some of the other biologics, including vaccines and gene therapy products. However, she stressed that Q5A "is specifically for those that can undergo clearance of virus vector and adventitious agents."

"Currently there are baculovirus-expressed VLPs [virus-like particles], subunit proteins, and viral-vectored products that are already using the principles laid out in the Q5A," she explained. "So we felt that if we were updating the document it is timely to be current and forward thinking to include this category of products."

> **Responding to a question about whether there had been consideration of opening up the guidance to cell therapies – which cannot undergo clearance but still have to follow many of the other principles in Q5A – Khan commented that the EWG felt that those aspects were covered by other existing documents.**

CDER's Tami explained that the guideline was for products derived from cell lines as indicated in the title. While it "took a lot of discussion," she said, "ultimately the decision was not to include cell therapies."

Khan asked if people were actually using the Q5A guideline for cell therapies. Biologics Consulting's Barngrover replied that in her experience they were, and that while the clearance may not be applicable, "certainly some of the new viral assays may very well be relevant."

> **Khan clarified that the new assays were being introduced to catch up with some of the other documents, noting that the WHO and EP have already introduced the newer assay methods and that the FDA cell substrate document is being updated concurrently. "So, we are introducing it here to be prospective in terms of where technologies are going."**

The CBER official stressed that the EWG will preserve the guideline's current format. The aim would be to give some relevant examples. However, she highlighted the challenge of achieving the right balance, "because then people tend to think this is the only way. So, we do want to keep it more in terms of philosophy" allowing people to apply the guidance "according to what they feel best fits for what they are doing."

Tami agreed, commenting that "the idea is that it doesn't need updating in two years when things evolve so rapidly. So it is really going to deal with concepts, principles, and maybe examples, but I don't think it is going to be very specific."

Khan emphasized that "this has been a great document. It has and is still serving its purpose very well. We want to continue in the same spirit, so it will be good at least for another 20 years or more."

How Are New Virus Assays and Alternative Analytical Methods Justified?

The second topic for discussion was the methodology advances since the publication of the guideline – specifically the nucleic acid-based assays polymerase chain reaction (PCR) and NGS, and their use in characterization, detection, and viral clearance validation.

"You may be surprised to see PCR there" Kahn remarked, "when we have maybe been using it for almost as long as the document has been there. Well, PCR is not in the document," so it is being updated to formally include it. "NGS is an evolving, emerging technology and there has been a great deal of progress made on it, so now we do feel comfortable putting it in the document."

She mentioned again that in CBER's office of vaccines "we are also updating our document. It has already been introduced in the European documents, the EP – they are already talking about using NGS to replace some of the *in vivo* testing. So it is moving rapidly. We are not saying you must use it. It will be introduced for you to decide how best it can be applied in the appropriate manner."

> **One of the participants asked for clarification around the methods and whether they could be recommended for testing of unprocessed bulk.**

"Clearly," he said, PCR can be used for viral clearance studies instead of an infectivity method. "With NGS you certainly could do that – I don't know if we all do it – but my question really is if this guidance is considering supporting the use of alternate methods for virus detection in unprocessed bulk or the equivalent in some of these new modalities? Today it is restricted to some kind of infectivity assay, which takes a long time and is pretty challenging. So is that within the scope of this, because I think it would be hugely valuable if it were?"

Khan replied: "Your question is being addressed in various areas and data is being generated in terms of how NGS can be used to complement, supplement or replace the current assays. What we are expecting is that as we are working on the document there will be more information generated before we finalize it, and we will be able to update it with the current information at that time."

> **Kahn was asked about the timeline for the additional supportive data versus the guideline's completion. She replied that the data is expected "to be there by the end of next year or sooner. There will be some data at the end of this year. There are studies ongoing to evaluate NGS with the other assays."**

She pointed to the extensive research and interest group efforts on NGS and *in vitro*/*in vivo* correlations, and noted that the Office of Vaccines had already received submissions in which NGS is being used to supplement and even replace some assays. "So we are looking at it on a case-by-case basis even right now, and all of that knowledge…will build towards information that will go into the document." ***[See Part III.]***

Fan added that PhRMA was collecting feedback from across the industry. "This is definitely one of the points under pretty intense discussion. We are aware that both PCR and NGS have their pros and cons – they could be too sensitive, and how do you deal with false positives? So there will be lots of discussion, and hopefully some of the data will help us to make some decisions."

The Revised Guideline Will Need to Continue to Be Flexible

Asked whether the new guideline would help sponsors with defining some of the criteria for them to do the replacement, Khan responded that it was too early to discuss the details of what the revision will contain. "At the moment," she said, "these are the topics we want to include, and we will have to see how much detail can go in. We don't want to be too specific."

"We still want to keep it flexible so that people can use it for different purposes, but the data package will need to support that [the method] is fit for purpose. We can indicate what should be in the package, but not to be specific in terms of the exact criteria for the methodology, because it is evolving."

Biologics Consulting's Barngrover noted that the current guidance is silent on how much qualification or validation of the virus assay is needed and asked if there was any intention to change that. Khan replied that "again, those are questions that we are taking notes on and will discuss in detail with the EWG."

She reiterated that "the current document has held strong for so long because it was not very prescriptive. It was flexible, so it could be used across product categories." How it is revised will depend on the different product types, she said. "I think for the newer products we might keep it broader, and maybe for the more experienced products we can learn and leverage experience and provide details for that."

In response to a query from Tami about what sort of validation details would be helpful, Barngrover shared that in her experience, some sponsors query whether any validation was needed for assays used for qualifying cells. When Khan referred to the clear validation requirements laid out in ICH Q2, Barngrover pointed out that the Q2 guidance was specifically for assays used for drug substance and product release.

Tami agreed the point was well taken. Further support came from another workshop participant remarking that "some guidance documents talk about using scientifically sound methods, or sometimes validated methods." There can be "uncertainty about which way to go," he said.

Encouraging workshop delegates to provide input, a participant urged: "If you have a strong opinion on what it needs to say, this is the chance to really highlight it for the group, because there will never be a time more open than now to try to hear about what perspectives should be captured."

Decision Tree Suggested for Evaluating PCR/NGS Findings

Daiichi Sankyo CMC Biologics Regulatory Affairs Director Roman Drews, a former CBER official, suggested that a decision tree would be helpful for verifying the results of PCR and NGS used in the GMP/QC context.

Khan and Tami agreed that yes, that would be useful and could be provided as an appendix. Khan referred to the work of the Advanced Virus Detection Technologies Interest Group (AVDTIG), mentioning that this was one of the topics being followed up by them. ***[See Part III.]***

Khan also highlighted that with any nucleic acid-based assay, before embarking on the technology there should be a follow-up strategy in place. Tami added that it was important to have a decision tree "to confirm any positive before you discard a lot."

A participant requested that the discussion around NGS should be described as specifically as possible in the guideline out of concern that everyone would start to do NGS because it is mentioned in the guideline without understanding why, "and this should be avoided."

Khan agreed that it was important to be thoughtful about using NGS and whether it is the best approach. "It will be your decision, but we can lay out the principles for potential applications." Tami again emphasized the concern that examples in a guideline can sometimes lead to being regarded as the best way to go "when it is not necessarily so."

Khan explained that the EWG had been thinking of reducing examples, but acknowledged that it may be important to have some, "like the decision tree or different situations in which these new assays might be applied."

How Can Prior Knowledge be Leveraged in Viral Clearance?

Another area of inquiry identified by the EWG in the concept paper regards the use of prior knowledge and learnings from similar processes and products in validating the viral clearance for a new product.

Chen, who introduced the topic, noted that Genentech has been using modular viral validation for clinical products for many years, and the approach has successfully sped up clinical development. Industry has been accumulating "a lot of knowledge" in this area, she said – raising the potential for Q5A to recognize its viability also for commercial products.

Biologics Consulting's Barngrover commented that she could see where knowledge leveraging might work for viral validation, but questioned how it would work in other areas, for instance chromatography. A concern would be how similar the chromatography would have to be – for example, in terms of protein load and flow rates.

CDER's Tami commented that there are some steps that are very clearly understood, including the parameters that need to be controlled. "Maybe for those, modular clearance works. But with other examples it is more challenging."

> **A discussion followed from Tami's request for thoughts from the audience on what was needed. "Can you use experience from others in industry, from literature, confirmation runs? What would be the most appropriate to claim modular clearance?"**

A session attendee suggested the question is really a scientific one. "It doesn't necessarily relate to how many marketed products you have, but it is more about how many experiments you have performed or have access to the data from – not how much your company did, rather how big the database is, including data from both marketed and clinical products."

CMOs, he pointed out, may also be able to provide the data they have accumulated. "Maybe it wasn't your data, but as long as you have access to all the data – beyond just a log reduction of virus (LRV) value – I think you are able to judge what it means."

> **Khan stressed the importance of publishing as much data as possible so that the information can be leveraged – noting that this is something she encourages and is seeing happen more often.**

Chen commented that the principles should be the same for both clinical and commercial products – involving the need to define your conditions. The approach should apply to well-characterized steps, such as low pH, inactivation by detergent, and retrovirus removal by small virus retentive filters, she maintained.

"You need to define the conditions that are most robust so you can reliably get the same log reduction every time – becoming product independent. When you actually have that knowledge, you can apply this approach. There has already been a lot of data shared by the industry and there are white papers published for all of these well-characterized steps."

Another audience member commented that in-house data for modular clearance could be supported by literature data and white papers as a knowledge base for risk analyses for quality-by-design approaches to process development. "Firm A will not know exactly how Firm B will run their columns or their unit operations, but it certainly contributes to the knowledge base that feeds into risk analyses."

ICH Can't Be Overly Prescriptive, Health Canada's Ridgway Comments

Health Canada's Ridgway weighed in with his experience on multiple ICH EWG's, including that on the lifecycle management guideline Q12 – commenting that the details of what would constitute sufficient information are beyond the scope of an ICH guideline.

What is needed, he said, is to "achieve harmonization on whether that type of evidence will be accepted and considered by regulators. But it is not for the guideline to try and define exactly what is needed to satisfy the regulators. The information is going to change over time and new information will come in after the guideline is finished."

"So I think there are dangers in setting defined parameters about what information would be acceptable or not. The important thing is to determine whether the regulators involved in drafting the guidance document are willing to consider this and leave it at that."

> **Another participant commented on the international acceptance of certain robust, effective steps. He noted that there are certain conditions that have been shown to be very robust and hold up against a wide variety of manufacturing processes, and that some of these steps have been accepted by health authorities internationally.**

"It would be nice for the guidance to mention these steps again – we have had this in other documents – of what is a robust, effective step. Maybe even some of those international references could be included in the guidance, to help people look at and be familiar with them, and how they can apply them to mitigate certain studies."

How Should Virus Clearance Validation Guidance be Updated?

The next issue receiving attention was aspects of viral clearance validation that have emerged or evolved over the lifetime of the current guideline.

Genentech's Chen provided some examples to stimulate discussion, such as whether the mention of the six-log safety margin for retroviral clearance in the current version should be reconsidered.

Echoing concerns expressed earlier about the risks of including examples that later become expectations, an audience member commented that he believed there was a misunderstanding because "people take it as a target."

> **Chen agreed that although the six-log safety factor is included in the appendix, for some reason it has become a standard, "so people always talk about less than one particle in a million doses."**

"But that then translates to about 15 to 20 logs of clearance you have to validate for your purification process. And for well-characterized cell lines such as CHO cells, we know that these particles are not infectious. Over the 30-40 years of history, these particles have never been shown to be infectious. So," she questioned, "is that clearance target reasonable?"

A session participant added that the list of evolving aspects of virus clearance validation provided in the concept paper were "excellent choices – exactly the ones that require an update."

> **He remarked that the evaluation of resin at the lifetime was particularly relevant, noting that the studies that need to be performed currently could sometimes lead to a delay in the submission of a BLA if there were any technical issues.**

He stressed that there is a lot of data available showing that "there is no big additional value coming out of these studies, as the resin at the end of lifetime always, in my experience, has the same clearance capacity as at the beginning of the lifetime."

BMS Downstream Process Development Associate Director Angela Lewandowski joined the discussion, adding, "I am actually pretty excited about these potential updates – the first one in particular…. There is a lot of data collectively within the industry showing that end of lifetime resin has no impact on viral clearance LRVs."

> **Referring to a recent multi-company evaluation done through the BioPhorum Operations Group (BPOG) of cycled resin in viral clearance studies, Lewandowski agreed that these kinds of studies involve "a huge amount of effort, material, and FTEs, when we have never seen a safety impact."** ***[A link to the BPOG study report published in the PDA journal is provided below.]***

Daiichi Sankyo's Drews suggested that the guidance could include defined criteria in cases where lifetime studies for virus clearance could be avoided. Another audience member offered that the guidance could indicate "that if certain criteria are met, then these studies can be mitigated," and that regulators are not expecting to see them.

He added: "In looking at viral clearance and what levels of reduction are needed, it also depends on what the load is. So maybe having some description of how you determine the load and the process to decide how much more you need to clear in the studies would be helpful."

> **Noting that the specific changes being discussed by the participants related to CHO cell production, Khan suggested that the EWG "may have to indicate the basis for why the changes are being made, so the principles are not applied to the new types of product being considered."**

Parexel consultant Kurt Brorson, a former CBER official, pointed out that CHO cell-derived products use similar columns and are an "enormous" class, which includes both antibodies and recombinant therapeutic proteins.

Khan agreed and suggested that the format of the guideline could be modified "to distinguish the product categories where there is more experience versus the newer, emerging products where we have less experience. We will have to figure out how to present that so it is clear and not confusing."

Drews offered that the risk of the class of products would also be an important factor to consider. The panel agreed, acknowledging that even though the guidance was specifically directed at cell-derived products, the principles on qualification of the columns were also being applied to plasma-derived products.

Biologics Consulting's Barngrover suggested that there might be value in combining the wisdom and expertise of the EWG to include some of the reasons for failure of viral clearance studies – for instance, if the manufacturer didn't take into account aggregation of the virus stock that was being used or the need to use a high enough titer. These are things that people should be aware of and "that might be helpful guidance to add."

What About Continuous Manufacturing?

The last of the five areas put out for discussion at the CASSS WCBP session was how the guideline should be updated regarding assessing the risks of and validating viral clearance for continuous processes.

Bayer Regulatory Affairs Senior Director Bob Kozak began the discussion by suggesting that "it might just be helpful in general to outline some of the expectations for residence time. What are some of the parameters that need to be shown and developed to support continuous manufacturing clearance?"

> **Khan explained that the EWG felt the issue of continuous manufacturing (CM) needed to be considered so that the guideline keeps pace with the field and is forward thinking. "Even if we don't have the answers, maybe we can think in terms of what questions we need to address and the expectations."**

Chen agreed, noting that Genentech's exploration of elements of CM has led to questions about viral clearance validation when the process steps are connected. She suggested that the linkage to ICH's Q13 guideline on CM "will also be very helpful."

Khan commented that the Q5A EWG was in conversation with the Q13 EWG to make sure Q5A "is not duplicating but complementary."

> **Another participant at the session added that, "for this area, I think the equipment vendors are going to be very important in terms of providing examples of how to validate a continuous chromatography system, for example. They are starting to publish on this area, so the scientific literature will be useful to follow. It will be an area likely needing a lot of flexibility."**

Health Canada's Ridgway suggested that "there will not be a huge body of real data available with regard to viral clearance during continuous manufacturing by the time this guidance document is coming to completion." As such, it "could allude to possible considerations that regulatory agencies might be willing to consider, but it might be very difficult and a little too early for the guidance document to try to make some firm conclusions on how this can be applied to continuous manufacturing. I think you will need to be cautious."

International Harmonization Needed on Viral Clearance

After considering the different areas for inquiry called out in the concept paper, the audience was asked if there were any other concerns that they would like the EWG to consider.

> **Daiichi Sankyo's Drews underscored the regulatory differences in different regions of the world regarding viral clearance and the dedicated steps involved. He asked if the guidance may be able to help clarify specific requirements.**

Khan responded that Q5A is "an international document that needs consensus and agreement by all of the different regions. So the one thing that is important in addition to all the discussions we are having is that we are made aware of the different publications from the different regions, and we want to make sure we are consistent with the other guidelines that are published or being published."

The differing requirements do make the guideline process challenging. “But, again, based on the experience and the knowledge, perhaps the others may now come to the same conclusions. So, I think that is an important point that we can discuss with the working group.”

Khan concluded the session by noting that the EWG had begun working on the specifics of the revision, and was holding regular teleconferences at which the points raised can be more broadly discussed. The face-to-face ICH meeting planned for Vancouver in May 2020 took place virtually.

Links:

- CASSS CMC Strategy Forum Japan 2019 Agenda
- Sakurai’s Slides on ICH Q5A(R2) from the Japan Forum
- PDA Journal Article (Sept/Oct 2019) on BPOG Viral Clearance Study

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