ETT Engagement on X-ray Qualification Expectations for Single-Use Bioprocess Systems

1 Executive Summary

Given the urgency to qualify X-ray as an alternative to Gamma for irradiation of single-use systems (SUSs), clear alignment is needed among suppliers, pharmaceutical manufacturers, and regulators on expectations for transition & commercial implementation. On September 8, 2022, a small industry team consisting of members of BioPhorum and BPSA, BARDA and subject matter experts met with the FDA/CDER/Emerging Technologies Team (ETT), including observers from CBER and EMA, to socialize and advocate for the positions published in the 2021 BPSA white paper on X-ray [1], and address concerns expressed by regulators during a prior, December 2021 Type C meeting with the ETT. Specifically, these concerns focused on the need for (I) examples of how sponsors would assess, categorize, and notify authorities when implementing a change, as well as (II) proof-of-concept extractables data for representative worst-case components which verify that there are no unexpected effects under low pH, high pH, or high organic content. The package included (i) the follow-up Type C meeting request which identified key questions on which agency feedback was desired; (ii) the May 2021 BPSA whitepaper; (iii) a recently finished & to-be published technical paper demonstrating the comparability of X-ray and Gamma irradiation physics; (iv) the December 2021 CDER/ETT Type C meeting minutes; (v) a report consisting of 3 primary examples of post-approval changes and additional supporting rationale for the BPSA-recommended approach to extractables & leachables verification testing; and (vi) a general letter of support for the risk-based approach to assessment, verification, and notification of changes from BioPhorum. Following a detailed, interactive discussion on September 8, formal meeting minutes were received from the agency on September 20, 2022. The FDA's summary and description of the consensus met were consistent with the understanding of the industry participants, were regarded as highly positive to the advancement of the initiative, and aligned with the industry's need for practical, risk-based approaches to the transition to X-ray sterilization.

The key questions and responses in the attached meeting minutes address those posed in the meeting request. A brief overview of the key points and aligned positions is below.

A. Sterility assurance

Sterility assurance concerns around transfer of dose from gamma to x-ray may be addressed per ISO 11137 [2] [3]. Specifically, (i) sterility assurance levels may be considered independent of the source-of photon-based irradiation, as established according to ISO 11137-2; (ii) the x-ray minimum dose may be substantiated through sterility dose audit experiments as described in ISO 11137-2, and (iii) dose mapping studies for each process shall establish that the minimum and maximum dose requirements are achieved by operating within established process settings.

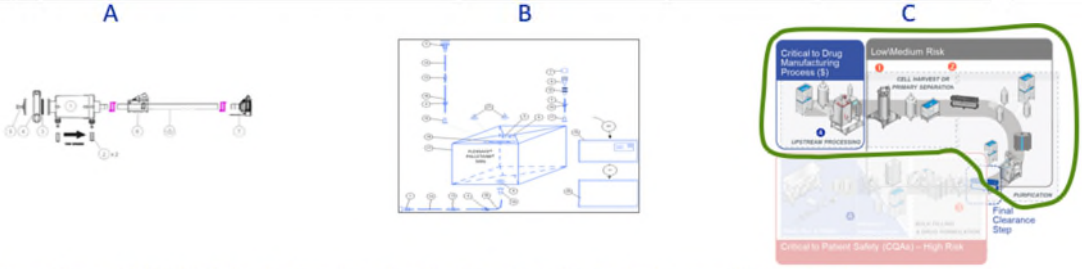
The comments also note that if there is a need to increase the irradiation dose range compared to what was validated for a Gamma sterilization process, then additional studies would be warranted. This case, although worthwhile to consider in the hypothetical, is not expected to manifest with transfer from Gamma to X-ray. Regardless, dose mapping studies will confirm that pre-established dose ranges remain unchanged in transitioning processes.

B. Categorization of changes

Post approval changes that follow the requirements of ISO 11137, and are deemed to be low risk as per the biomanufacturer's assessment may be submitted as part of the Annual Product Quality Report (APQR). This applies to changes that may be used in critical applications such as (A) final, sterilizing-grade filtration assemblies, (B1) formulation buffer mixing assemblies, (B2) applications in which "Gamma irradiation" may have been specifically identified in applicable regulatory filings, or (C) assemblies used in inherently low-risk applications distant to the patient and final drug product.

Case Study	Gamma mentioned in approved filing	Final Risk Determination (Gamma → X-ray)	Regulatory Notification Action	Agency Feedback
Case A: Single-use filtration assembly in final sterilizing-grade filtration step of monoclonal antibody product	No	Low Risk	Annual report	Annual Report*
Case B: Single-use storage bag assembly for mixing and/or storage of formulation buffer	No	Low Risk	Annual report	
	Yes	Low Risk	CBE-30	
Case C: Low risk applications (e.g. associated with or upstream of clearance steps)	No	Low Risk	Non reportable	

A B C



*Such changes, where compliant to ISO 11137 including dose mapping and sterility dose audit studies, may be documented in annual product quality review.

Figure 1: Summary of case study risk assessments, and recommended agency feedback as presented on Sept 8, 2022.

C. USP <665> Moderate Risk (Level B)

USP <665> Moderate Risk (Level B) testing [4] **may be acceptable to verify the equivalence of extractables profiles of x-ray sterilized SUSs in comparison to those sterilized by gamma.** As described under 'Additional Meeting Comments', proof-of-concept studies under low pH, high pH and 100% alcohol for components such as PES filters, TPE tubing and biocontainer films demonstrated comparable extraction profiles and verified that no unexpected recoveries were observed. Such data are available in the public domain [5] [6] [7]. In addition, arguments based on those published in the BioPhorum extractables data review paper [8] were presented to emphasize the richness of the USP <665> Moderate risk approach [4] [9] [10] [11] and its suitability for use in comparing and verifying that there are no unwanted effects on extraction profiles observed upon transition from Gamma to X-ray sterilization.

2 References

[1] Bioprocess Systems Alliance (BPSA), "X-ray Sterilization of SIngle-Use Bioprocess Equipment. Part I - Industry Need, Requirements, and Risk Evaluation," 2021.

[2] ISO 11137-1:2006 , "Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices".

[3] ISO 11137-2:2013, "Sterilization of health care products - Radiation - Part 2: Establishing the sterilization dose".

[4] USP <665>, "Plastic components and systems used to manufacture pharmaceutical drug products and biopharmaceutical drug substances and products," 2021.

[5] R. Menzel, S. Dorey, T. Maier, I. Pahl and A. Hauk, "X-ray sterilization of biopharmaceutical manufacturing equipment - Extractables profile of a film material and copolyester TritanTM compared to gamma irradiation," *Biotechnology Progress,* 2021.

[6] J. Hathcock, "Qualifying X-ray irradiation of single-use sytems to address new challenges associated with single-use growth," Marseille, 2022.

[7] S. Dorey, M. Gauthier, I. Gay, N. Girard-Perier, F. Gaston, N. Dupuy and S. Marque, "Implementing X-ray for single-use systems sterilization," Marseille, 2022.

[8] A. Vaidya, C. Worsoe, G. Madsen, K. Wong, K. Lee and S. Denby, "A comprehensive Review of BioPhorum Standardized Extractables Testing Data: A deep dive into similarities, differences and trends across extraction solvents and timepoints".

[9] "Wang, Ping, "Data Review of Extractable Study Results of Polymeric Product Contact Materials – Necessities of Model Solvents for Extraction", Eurofins 2nd Annual Extractables & Leachables Symposium for Drugs & Devices", Sept 20, 2018, San Francisco, CA".

[10] G. Tumambac, B. Song, X. Li, G. Li, C.-J. Shih and J. Hathcock, "Implementation of the BPOG Extractables Testing Protocols: Comparing USP and BPOG Extractables Data for Autoclaved Polyethersulfone Filters," *BioProcess International,* 2018.

[11] S. Dorey, N. Pahl, I. Uettwiller, P. Priebe and A. Hauk, "Theoretical and Practical Considerations When Selecting Solvents for Use in Extractables Studies of Polymeric Contact Materials in Single-Use Systems Applied in the Production of Biopharmaceuticals," *Industrial & Engineering Chemistry Research,* vol. 21, pp. 7077-7089, 2018.

Meeting Minutes:
Emerging Technology Team (ETT) and BARDA (with Pall Corporation and partners)

Meeting Date: September 8, 2022
8:00 – 9:30 a.m., ET
Teleconference (sponsor provided)

Sponsor Participants	• James Hathcock, PhD, Sr. Director of Regulatory & Validation Strategy Pall Corporation & BPSA Task Force Lead • Samuel Dorey, PhD, Principal Scientist of Materials and Irradiations, Product Development Sartorius Stedim Biotech & BPSA Task Force Lead • Ping Wang, PhD, Director of Research & Development Janssen, Pharmaceutical Companies of Johnson and Johnson • Ken Wong. Critical Material Management Lead, Sanofi S.A. • Tom Oliver, Sr. Process Engineer, BioMarin Pharmaceutical • Thomas Kroc, PhD, Applications Physicist and Head of the Neutron Irradiation Facility, Fermi National Accelerator Laboratory (Fermilab), US DOE • Adam Whaites, Global Sterility Assurance Director, Cytiva Life Sciences & Chair of The Irradiation Panel • CDR Patric Klotzbuecher-Cruz, Senior Biomedical Engineer, DHHS/BARDA/PCI/PVPCR Branch • Lance Garrison, PhD, Domestic Alternative Technology Portfolio Manager, DOE/National Nuclear Security Agency/Office of Radiological Security • Robert Huffman, Supply Chain Management Lead, DHHS/BARDA/Division of Pharmaceutical Countermeasures Infrastructure (PCI) • Joseph Figlio, Chief of Pandemic Vaccine Preparedness Capabilities & Readiness (PVPCR) Branch, DHHS/BARDA/PCI • Frank Flores, Drug/Vaccine Supply Chain Manager, Tunnell Government Services supporting DHHS/BARDA/PCI/PVPCR Branch • Anabela Marca, EMA Liaison to FDA (invited by BARDA) • Maria Jesus Alcaraz Tomas, Regulatory Science & Innovation Task Force, Supply & Availability of Medicines & Devices, EMA (invited by BARDA) • Brian Dooley, Pharmaceutical Qualify Office, EMA (invited by BARDA)

FDA Participants	*Center for Drug Evaluation and Research:* • Bryan Riley, Branch Chief, Division of Microbiology Assessment (DMA), Office of Pharmaceutical Manufacturing Assessment (OPMA), Office of Pharmaceutical Quality (OPQ), and ETT Project Lead • Patricia Hughes, Senior Scientific Advisor, OPMA, OPQ • Neal Sweeney, Microbiologist, OPMA, OPQ • Yiwei Li, Supervisory Chemist, OPMA, OPQ • Sarah Zimmermann, Chemist, Office of Lifecycle Drug Products (OLDP) • Ramesh Raghavachari, Supervisory Chemist, OLDP, OPQ • Joel Welch, Associate Director of Science & Biosimilar Strategy, Office of Biotechnology Products (OBP), OPQ, and ETT Chair • Rick Friedman, Deputy Director for Science & Regulatory Policy, Office of Compliance, and ETT member • Brooke Courtney, Regulatory Counsel, Office of Counter-Terrorism and Emerging Threats, Office of Chief Scientist • Cheryl Kaiser, ETT Project Manager, Office of Program and Regulatory Operations, OPQ *Center for Biologics Evaluation and Research (CBER), invited as observers:* • Manuel Osorio, Senior Scientist for Emerging Technologies and Medical Countermeasures • Lily Koo, Biomedical Engineer

Meeting Package

Background

The Emerging Technology Team (ETT) accepted BARDA's second meeting request to continue discussion on the use of x-ray for the sterilization of single-use equipment.

In advance of the meeting, the ETT provided written comments and position to the questions in BARDA's meeting package. The comments and responses are non-binding and intended to facilitate future regulatory submissions

Question A: If, upon the agency's review, it is deemed appropriate, we ask that FDA discuss their positions on the following:

A. Continued sterility assurance at the same sterility assurance level is ensured with the appropriate transfer of dose from Gamma to X-ray in accordance with ISO 11137.

   a. A minimum sterilization dose required to achieve a Sterility Assurance Level (SAL) of 10-6 is based on product- and component/system manufacturer-specific

bioburden, independent of the source of photon-based irradiation, and to be established according to ISO 11137-2.

b. The X-ray equivalent of a minimum Gamma sterilization dose (achieving SAL 10-6) may be substantiated by X-ray sterility dose audit experiments conducted in accordance with ISO 11137-2 for dose transfer rather than repeating full dose setting for a given product/product load.

c. Dose mapping of each process shall establish that the minimum and maximum dose requirements are achieved within the established processes' settings.

i. If, upon performance of dose mapping, a higher measured maximum dose (VDmax) is observed and adjusting product loads & re-mapping to stay within the pre-defined Gamma dose range is not feasible, then a new maximum dose specification shall be qualified and measured by X-ray dose mapping.

FDA Comments/Position A:

FDA generally agrees with the approach presented in section a, b, and c above for the transfer of dose from Gamma to X-ray in accordance with ISO 11137.

Additional Meeting Comments Position A:

B. Categorization of changes from Gamma to an equivalent, validated X-ray sterilization process for components and SUSs shall be based on a biomanufacturer's assessment of its potential risk to have an adverse effect on the identity, strength, quality, purity, or potency of a product.

a. A risk appropriate, data driven approach shall be taken to determine comparability between the irradiation processes.

b. The total body of data developed by the component manufacturer, SUS integrator, and/or a biomanufacturer's own analytical testing with consideration for significant mitigation factors implemented shall serve as the basis for risk assessment and determination of any regulatory notification/approval actions consistent with 21 CFR §'s 314.70 and 601.12.

i. The case study risk assessments and proposed regulatory notification actions presented in Attachment D, each of which concludes the transition of Gamma to Xray is low risk, are expected to serve as benchmarks for the appropriate regulatory notification action to be taken. These actions include changes categorized as nonreportable, to be included in an Annual Product Quality Report (APQR), and as described below, to potentially be submitted as a CBE-30.

ii. For cases where the pharmaceutical or biomanufacturer, through their internal risk assessment process, determine that supporting data justify a categorization of low risk but that "Gamma irradiation" is specifically identified in an applicable regulatory filing, this would increase the expected level of regulatory action from inclusion of the change in an APQR to submission as a CBE-30.
(Please note that there are no additional or novel risks associated with this case study compared to those above other than "Gamma irradiation" being explicitly stated in the regulatory filing. In context, "Gamma" was used as a buzzword wide throughout the single-use system industry in the transition from moist heat sterilization to ionizing radiation. Many now recognize that it would be more appropriate to indicate "sterilized by ionizing radiation in accordance with ISO 11137" where appropriate.)

FDA agrees that changes categorized as nonreportable should be included in an Annual Product Quality Report (APQR). These changes would typically involve equipment used upstream of the sterilizing filter, unless specifically identified in the regulatory filing as gamma irradiated. For regulatory filings which identifies material as gamma irradiated and is used upstream of the sterilizing filter, the change may be reported in an annual report to update the application with the change.

For sterile product contact material, the switch from gamma to x-ray may be viewed as a like for like change and equivalent so long as the X-ray equivalent of a minimum Gamma sterilization dose (achieving SAL 10-6) is used for the dose transfer and is substantiated by X-ray sterility dose audit experiments conducted in accordance with ISO 11137-2. Dose mapping of each process should show that the minimum and maximum dose requirements are within the established processes' settings. In this case, the change may be reported in an annual report to update the application with the change.

In the event that a higher measured maximum dose (VDmax) or minimum dose is observed during dose mapping studies and product loads need to readjusted and re-mapped and a new maximum dose or minimum dose specification must be qualified and measured by X-ray dose mapping (as described in A.c.i. above), then this change in specifications for the x-ray sterilization of material in contact with sterile product should be reported in a CBE-30 as a moderate risk change.

C. For the assessment of risk presented by extractables and leachables:

a. Based on the justification and rationale in Attachment D, as well as supporting rationale for equivalency of the underlying physics in Attachment B, does the agency concur with use of the moderate risk (Risk Level B) Expanded Baseline Assessment strategy called for by USP <665>?

b. Can extraction solution testing performed according to the USP <665> moderate risk method be considered sufficient due diligence to verify the equivalence of

extractables profiles of X-ray sterilized SUSs in comparison to those sterilized by Gamma?

(a) *The information provided in Attachment D included comparability studies of extractables under high (pH ~ 13.5) and low (pH ~ 1) pH conditions as well as 50% Ethanol in water (moderate risk level per USP <665>). The studies were performed on sterilizing grade filter (PES membrane), polymeric bag (S80 film), and TPE tubing. The study results appear to indicate comparable extractable profiles under the study conditions for the above equipment, and appear to support the comparable leachable risk conclusion between Gamma and X-ray.*

For biologics drug products, the "use of the moderate risk (Risk Level B)……called for by USP <665>" could be supported by the above studies. However, the sponsors may wish to clarify the term "Expanded Baseline Assessment strategy" so that there is a good mutual understanding between FDA and the sponsors.

It is not clear whether the sponsors intend to use the same strategy discussed in C(a) to support the Gamma to X-ray change for small molecule drug products. Given the fact that small molecule drug products can have higher organic content and/or extreme pH, the sponsors should clarify whether additional studies will be performed as part of the risk mitigation strategy.

(b) *Extraction solution testing performed according to USP <665> moderate risk method may be acceptable based on the composition of the material. A risk-based analysis should be provided with justification of extractable conditions based on the polymer composition and susceptibility to ionizing irradiation effects.*

Meeting Presentation and Discussion

BARDA's slide presentation recapped the key points for the qualification of x-ray sterilization for single use systems:

20220907e2 ETT Xray Rationale and Ca

BARDA and ETT members discussed the risk of extractable and leachables, potential system failures from the GMP perspective, X-Ray sterilization of stoppers, and adhesives used in SUS.

Additional Meeting Comments

During the meeting the sponsors provided comparative extractables study results under low pH, high pH as well as using 100% Ethanol as extraction solvent. The studies appeared to have indicated comparable extractable profiles for manufacturing equipment (PES filter, TPE tubing,

and bio-container film) under the above conditions. Based on the available information, FDA generally agrees that the use of the moderate risk (Risk Level B) Expanded Baseline Assessment strategy called for by USP <665> may be acceptable to verify the equivalence of extractables profiles of X-ray sterilized SUSs in comparison to those sterilized by Gamma.

Next Steps

The ETT noted that while CDER and CBER cannot make joint agreements on BARDA's technology, BARDA may request a separate interaction with CBER through CBER's CATT program (or alternatively, by contacting Manuel Osorio). Agreement was made to follow-up offline regarding such a meeting.

BARDA may continue to request interactions with the ETT as future issues in the application of the technology arise (e.g., with stoppers). It was noted additional considerations would apply to this approach for container closures.

Minutes

EMA QIG meeting with BARDA/industry on Qualification of X-ray Sterilization for Single-Use Bioprocess Systems (04APR2023)

1 Summary and Actions on Key Points for Alignment

Given an expected growing shortage in availability of gamma irradiation capacity for sterilization of single-use systems (SUS) used in pharmaceutical and biopharmaceutical processing, and the move to adopt X-ray as an equivalent alternative sterilization technology, members of the EMA Quality Innovation Group (QIG) met with industry representatives to review and provide comments on industry aligned proposals for risk assessment and implementation of X-ray for sterilization of single-use bioprocessing systems. FDA members attended as observers. Six (6) key areas of alignment were reviewed as part of the discussion. Overall, there was strong alignment on the risk-based implementation approaches with supporting feedback and follow-up actions documented further below.

ACTIONS

- **EMA/QIG** (*Giampiero Lorenti, AIFA (IT)*) to consider how they can communicate applicability of Annex 12, either through Q&A or other communication. *(See notes further below)*
- **EMA**. For variations - EMA to provide guidance, through either Q&A or other communication, on when a variation submission would be required and when a Type IB may be appropriate as compared to a Type IA. *(see notes further below, including expected number of impacted filings)*
- **Industry Team.** Share meeting minutes within ten (10) business days. If no objections to the minutes, then will aim to share overview with industry organizations in which we participate.

2 Overview of Meeting

Time & Date: 03:00-05:00pm (CET)/09:00-11:00am (EDT) on Tuesday, 04APR2023.

Attendees:

Cesnule Gilija	EMA (host)	James Hathcock	Pall
Anabela Marcal	EMA	Samuel Dorey	Sartorius
Brian Dooley	EMA	Ping Wang	Janssen
Barbara Stubbe	FAMHP, BE	Aidan Sexton	Janssen
Bream Robert	EMA	Anderson Wong	Sanofi
Christof Krummeich	BfArM, DE	Ken Wong	Sanofi
Conocchia Roberto	EMA	Adam Whaites	Cytiva/Irradiation Panel
Giampiero Lorenti	AIFA, IT	Tom Oliver	Biomarin
Hernan Dolores	EMA	Bryan Riley	FDA/CDER
Klaus Kruttwig	EMA	Elisa Nickum	FDA/CDER
Leticia Martinez	ANSM, FR	Patricia Hughes	FDA/CDER
Marcel Hoefnagel	MEB, NL	Rick Friedman	FDA/CDER
Rene Thurmer	BfArM, DE	Ramesh Raghavachari	FDA/CDER
Frank Flores	BARDA	Lily Koo	FDA/CBER
Robert E Huffman	BARDA	Manuel Osorio	FDA/CBER
CDR Patric Klotzbuecher	BARDA	Katherine Tyner	FDA/OC
Thomas Kroc	DOE/Fermilab	Robert E Smith	DOE/NNSA

Once confirmed that all key attendees were present, immediately jumped into presentation (~40min.) from the industry collaboration team.

Follow up discussion walked through key points highlighted for alignment as indicated below.

3 Key Alignment Questions and Discussion

ISO 11137. May the existing ISO 11137 standard currently used for irradiation sterilization of SUS, and which includes requirements for X-ray, be used as the basis for X-ray sterilization of SUS?

Christof Krummeich: Agree ISO 11137 is a relevant, agreed standard for use of ionizing radiation to minimize microbiological burden of medical devices. It addresses requirements for X-ray as well as gamma radiation and e-beam. There are specific requirements for irradiation sites, who are typically familiar with the technical requirements for how to establish and validate the irradiation process. The ISO 11137 standard provides suitable guidance in detail to the irradiation sites how the irradiation process with X-rays should be performed and validated. It is recommended to perform the irradiation process with X-rays in conformity with the demands of all parts of the ISO 11137 standard and work in a strong collaboration between customer and with the irradiation site. The international standard is the correct approach to establish X-ray sterilization for your products. Dose mapping, as described in the standard, is still a key principle to apply to demonstrate suitability of the sterilization process.

Q&A. Some thoughts shared on energy levels associated with gamma and X-ray. Tom Kroc shared that the relevant high energy level of X-ray irradiation associated with contract sterilization derives from bremsstrahlung and less from the characteristic X-rays.

Q&A. Where are the irradiation sites and are they familiar with the processes followed with gamma. *Response.* Present sites in Europe are Steris Daniken and Venlo (also referenced sites opening in US: Steris Libertyville). This company has extensive experience with gamma irradiation, as the Daniken site has both gamma and X-ray.

Annex 12. Does the EMA agree that language in Annex 12, “Use of ionising radiation in the manufacture of medicinal products”, should NOT be interpreted as restrictive to implementation of X-ray?

Giampiero Lorenti: EMA recognizes that Annex 12 is not the most up to date annex of the GMP guidelines. It is understandable why manufacturers could interpret Annex 12 as restrictive to gamma and electron beam. EMA considers the intent/principles stated in the annex are applicable to X-ray, in addition to gamma and e-beam. Updating language in the Annex is a long-term approach, requiring significant time and resources. EMA will explore internally any regulatory tools (e.g. Q&A, or short communication) that could help in the short term for the industry to use for X-ray sterilization of SUS. Although the current version of Annex 12 is dated, the principles of Annex 12 are applicable, and the document should not be seen as preventing a risk -based approach to X-ray.

E&L Assessment. Does the EMA agree that the risk of leachables from X-ray as compared to gamma, may be assessed based on an

1) understanding of the underlying physics,

2) materials impact evaluation, and

3) using the USP <665> moderate risk testing approach to VERIFY (not revalidate) that there are no meaningful adverse effects to the extraction profiles?

Leticia Martinez: Asked about rationale for USP <665> low, moderate, high profile. *Response*. Shared that the <665> moderate risk approach defined a solvent and timepoint that provided a meaningful profile to verify no impact to the materials. Other solvents (low and high pH for instance) were used to illustrate proofs of concept that equivalence is achieved. The purpose is verification and not a re-qualification.

Leticia Martinez: The evaluation approach based on the materials and underlying principles makes sense. In reference to <665> risk level, it is understood this refers to the choice of the solvent model. Lots of materials and types of testing (physical, chemical, biological) are covered. The assessment seems reasonable and we do not have any objection at the moment. The approach you are proposing is scientifically sound and we are aligned.

Categorization. Does the EMA generally agree with the post-change approval/variation levels proposed in the risk assessment case studies? Specifically, in cases where changes are

1) implemented in accordance with ISO 11137 and

2) a sponsor/authorization holder risk assessment concludes that the transition from gamma to X-ray is low risk,

should this be implemented as a **Type IA** variation?

In cases identical to the above, but where "Gamma" is mentioned in the regulatory filing, does the EMA concur that these should also be treated as a **Type IA** variation?

Brian Dooley: If the sterilization process is not mentioned in the Module 3 Quality dossier, then no variation is expected. Normal internal quality procedures (such as change control assessment) are expected to be sufficient. **(ii)** Where the sterilization is mentioned in the dossier, a variation submission will be needed. Which category of variation for sterilization of SUS, this will be an unforeseen variation category. Will probably be a minor change in the manufacturing process.

There was good discussion that for many cases the Type IA may make sense. QIG will review through Q&A whether Type IB may be appropriate in some cases (e.g."gamma" mentioned in filing, some biologics).

Question: What is the number of authorizations that may mention "gamma" for SUS?

Response: The mentioning of "gamma" in the filings depends very much on the pharmaceutical manufacturer. Some did mention "Gamma" much more so than others but have since moved away from this practice. There are likely a large number of filings that mention "Gamma", but they will be manufacturer-dependent and typically span a given time frame.

Consensus Feedback. Can the EMA provide consensus feedback that can be used by the industry to mitigate fear of regulatory uncertainty and strengthen confidence for the proposed risk-based approach?

Marcel Hoefnagel: Overall feedback during the meeting has been positive with regards to the proposed strategy.

The thinking is that there will be a public Q&A or short communication, but this will take time. EMA will review internally at monthly internal QIG meetings. It is not appropriate/possible for EMA to respond to every industry group and product, separately. The topic is generally the same for all related materials, and thus, can explore mechanisms to share a consensus view.

(note) Advised earlier that the industry team should take notes and share within 10 days of the meeting.

Future Assessments. The biopharmaceutical industry is currently developing an industry-aligned risk assessment approach targeting higher risk applications such as drug substance storage. Does the EMA have experience with filings related to X-ray or have special concerns with a similar risk-based approach?

Leticia Martinez: EMA does not have experience at the moment with filings related to X-ray sterilization of containers for drug substance (DS) or drug product (DP) storage. But we can agree with a similar scientific risk-based approach. Concerned that with DS or DP storage, the time is longer and there are particularities to be considered in the risk analysis. The general approach to this type of risk-based assessment is acknowledged by us.

It is likely each situation will be case dependent, and it is not possible to provide a general overall one-size fits all acceptable approach. It may be worthwhile to come for scientific advice with more details as to how this would work for a specific product. Individual variations.

Closing remarks

Marcel Hoefnagel: The team will aim to move swiftly and discuss with broader QIG. Thanks to the team, EMA is very impressed with the preparation of content to support a positive meeting.

Minutes

PMDA (Japan) Meeting with BARDA/Industry on Qualification of X-ray Sterilization for Single-Use Bioprocess Systems (01JUN2023)

1 Summary and Actions on Key Points for Alignment

Given an expected growing shortage in availability of gamma irradiation capacity for sterilization of single-use systems (SUS) used in pharmaceutical and biopharmaceutical processing, and the move to adopt X-ray as an equivalent alternative sterilization technology, members of the PMDA met with industry representatives to review and provide comments on industry aligned proposals for risk assessment and implementation of X-ray for sterilization of single-use bioprocessing systems. Four (4) key areas of alignment were reviewed as part of the discussion. Overall, there was an alignment on the risk-based implementation approaches with supporting feedback documented further below. Necessary post-approval regulatory procedures will be further discussed by PMDA.

2 Overview of Meeting

Time & Date: 11:00-12:00 (JST) on Thursday, 01JUN2023.

Attendees:

櫻井 陽 (Akira SAKURAI)	PMDA (Sr Scientist for Pharmaceutical Quality)	ハスコック ジェームス （James HATHCOCK)	Cytiva
岸岡 康博 (Yasuhiro KISHIOKA)	PMDA (Review Director, Office of Cellular- and Tissue-based Products)	Samuel Dorey	Sartorius
原 賢太郎 (Kentaro HARA)	PMDA (Division Director, GMP Inspector, Office of Manufacturing Quality for Drugs)	Ping Wang	Janssen
粟津 洋寿 (Hirotoshi AWATSU)	Cytiva	Aidan Sexton	Janssen
CDR Patric Klotzbuecher	BARDA	Anderson Wong	Sanofi
Frank Flores	BARDA	Ken Wong	Sanofi
Thomas Kroc	DOE/Fermilab	Noriko Namba	Cytiva
Kazunori Nagaki	Cytiva	Takeshi Okayasu	Cytiva

Once confirmed that all key attendees were present, immediately jumped into presentation (~24 min.) from the industry collaboration team.

Follow up discussion walked through key points highlighted for alignment as indicated below.

3 Key Alignment Questions and Discussion

(PMDA) General comments that the use of X-ray sterilization is a relatively new topic for us, and we thank you for sharing the information.

ISO 11137. May the existing ISO 11137 standard currently used for irradiation sterilization of SUS, and which includes requirements for X-ray, be used as the basis for X-ray sterilization of SUS?

(PMDA) 'Yes. We agree ISO 11137 may be used as the basis for qualification of X-ray. There are no objections.'

E&L Assessment. Does the PMDA agree that the risk of leachables from X-ray as compared to gamma, may be assessed based on an

1) understanding of the underlying physics,
2) materials impact evaluation, and
3) using the USP <665> moderate risk testing approach to VERIFY (not revalidate) that there are no meaningful adverse effects to the extraction profiles?

(PMDA) 'Generally the strategy and rationale may be acceptable; data presented looks fine'.

Categorization. Does the PMDA generally agree with the post-change approval/variation levels proposed in the risk assessment case studies? Specifically, in cases where changes are

1) implemented in accordance with ISO 11137 and
2) a sponsor/authorization holder risk assessment concludes that the transition from gamma to X-ray is low risk,

these may be managed as part of their internal risk control process within their Pharmaceutical Quality System as 'non-approved matters'?

(PMDA) The rationale needs to be documented, but generally there are no concerns with this approach. As long as the SUS is irradiated by a "validated" method (per ISO-11137), it doesn't matter which method (gamma or X-ray) to achieve sterility claim.

In cases identical to the above, but where "Gamma" is mentioned in the regulatory filing, does the PMDA concur that these should also be treated as a 'non-approved matters'?

(PMDA) If the filing uses terminology such a 'validated sterilization method', or 'ionizing radiation' then generally there is no conflict. In cases where 'gamma' is specifically mentioned in the filing, post-approval regulatory submission will be required. Based on the information presented today, 'minor change notification' together with 'Brief Consultation' can be considered provided that the change is well assessed and may not lead to an adverse impact on product quality.

(Industry Team. Ken) Follow up question: Independent of the X-ray implementation, what does it take to update the dossier to remove "Gamma" by replacing it with 'validated sterilization method', or 'ionizing radiation' as our first step? Would this be a viable alternate path to implement X-ray sterilization method for low risk SUSs in 2024 after the dossier update.

(PMDA) Asked estimates for the number of impacted filings, which may have specifically used the term 'gamma'.

(Industry Team) As a rough approximation, single-use integrators may be targeting approximately 20% of assemblies in 2024, and perhaps 25% of them may have 'gamma' mentioned in the filings. This is of course an estimate, and depends on the authorization holder, and time of the filing. Overall maybe 5% of filings may be impacted by the first wave of X-ray qualifications.

(PMDA) The 'Brief Consultation' process, which could be used for one product as a representative from similar products from a single holder, will allow us to better coordinate the approach to these types of cases and prevent misalignment.

(Industry Team) Can a group of end users approach the PMDA together on this topic to more expeditiously align?

(PMDA) We cannot provide a concrete answer for all such cases today, but will review internally.

Consensus Feedback. Can the PMDA provide consensus feedback that can be used by the industry to mitigate fear of regulatory uncertainty and strengthen confidence for the proposed risk-based approach?

(PMDA) The meeting minutes may be shared with industry groups. We suggest the industry team share the minutes with the PMDA representatives , and then if no objections or corrections, can share more broadly with industry groups.

Executive Summary – CATT Engagement and Feedback

Following a meeting between the FDA CATT, BARDA, and industry group members in Q4' 2023, written feedback from the CATT team was received in late 2023. This feedback demonstrated strong interest in the fundamental concepts associated with X-ray and gamma, and generally supported the key arguments advocated in industry publications. Citing the diversity in applications covered by CBER, the feedback stopped short of a generally applied post-change approval strategy (e.g. always treat as annual reportable), and mentioned risk considerations that may, on a case -by-case basis, require assessment as part of the broad range of applications covered by CBER. Further clarity was requested by the industry team in Q1'2024, with a brief response received in Q2'2024 indicating that it would be difficult to provide further generalized, product/process-agnostic clarification, and that sponsors may receive formal, binding, product-specific feedback through 1:1 consultations.

A.1 Initial CATT Feedback (14 DEC 2023)

Please see attached, "CBER Advanced Technologies Team Written Responses".

B.1 Clarification Request (12 MAR 2024)

BARDA and the constituent members of the BioProcess Systems Alliance (BPSA) thank you for the 14DEC2023 CATT written responses to our meeting on "Conversion from gamma irradiation to X-ray sterilization of single-use systems (SUS) in the context of biomanufacturing", held 10OCT2023. Our interdisciplinary team has digested the responses and is seeking to clarify industry's interpretation of some key wording to ensure the alignment of scientifically-based principles and risk-based approaches with regulatory expectations (see the **Interpretation of Response** section below). In addition, we would like to share some recent industry updates and publications related to the industry-aligned risk assessment strategy.

B.2 Recent industry updates and outputs

ATTACHMENT A: (2023) BPSA X-ray Sterilization of Single-Use Bioprocess Equipment, Part II – Representative Qualification Data. *This paper highlights representative data for multiple types of single-use systems (SUSs) and components. The paper is not intended to be a blanket qualification for all supplier components and materials, but rather, it provides representative examples of comparability assessments.*

ATTACHMENT B: (2023) BioPhorum Guidance for Risk Evaluation of X-ray Irradiation of Single-Use Systems. *This paper summarizes a risk evaluation strategy and provides tools for risk evaluation of transitioning SUSs from gamma to X-ray sterilization for four (4) different risk levels.*

ATTACHMENT C: (2024) Assessment of Cell Culture Data following X-ray sterilization of SUSs.

B.3 Interpretation of Response

The table below summarizes the CATT's written responses, as well as the industry team's interpretation and requests for further clarification.

CATT Questions & Responses	Industry Team Interpretation
Question 1: Does CBER agree that the existing ISO 11137 standard currently used for irradiation sterilization of SUS, and which includes requirements for X-ray, may be used as the basis for X-ray sterilization of SUS?	
CBER Response: ISO 11137 is still appropriate for X-ray sterilization. The physics appears to support the behavior of X-rays being similar to gamma rays in terms of sterilizing capability.	The fundamentals physics of ionizing radiation appear to be well-understood, as well as the appropriateness & applicability of ISO 11137 for use as the standard defining requirements of both gamma and X-ray sterilization.

Question 2: Does CBER agree that the risk of leachables from X-ray as compared to gamma, may be assessed based on i. an understanding of the underlying physics, ii. materials impact evaluation, and iii. using the USP <665> moderate risk testing approach to VERIFY (not revalidate) that there are no meaningful adverse effects to the extraction profiles.	
CBER Response: Based on the available information, CBER generally agrees that the use of USP <665> moderate risk testing approach to verify the equivalence of extractables profiles of X-ray vs. gamma sterilized SUS may be acceptable for many of the CBER products.	We acknowledge that the USP <665> moderate risk testing approach may be suitable to verify the equivalence of extractable profiles of gamma vs. X-ray sterilized SUSs given adequate, scientifically sound justification to support that risk-based decision. USP <665> moderate risk level testing employs a single-solvent and timepoint that is, in

A risk-based analysis should be provided with justification to support the relevance of the testing approach and extractable conditions based on SUS material composition, intended use, and representative process conditions (e.g., contact duration, pH, solvent/media/reagents). Additional testing may be required as part of the risk mitigation strategy and will be evaluated on a case-by-case basis. For example, extended product contact time in a bioreactor may result in elevated extractable and leachable risks to cell and gene products that rely on the metabolic activity of living cells for their primary function. In such case, more extensive E&L studies may be required.	general, highly characteristic of the component extractables profile (i.e., compounds that may leach from plastics and contact durations common of the component types). Given the fundamental similarity of the physics of gamma and X-ray and absent any other changes to intended use or process, this approach may serve as an appropriate means to verify that materials are not adversely affected by X-ray as compared to gamma. However, in the event an adverse impact is observed in the extractable profiles obtained by USP <665> moderate risk verification testing, taking into account experimental variation in the data set, then additional testing may be appropriate as part of an enhanced risk mitigation strategy. Similarly, the inherent process/product quality risk of the SUS under evaluation should be factored into the risk-based analysis of the change from gamma to X-ray sterilization. In instances where inherent process or product quality risk are high (i.e. based on where and how the materials are used in the drug manufacturing process) and the demonstration of equivalent extractable profiles under USP <665> moderate risk level test conditions alone are not sufficient to show a reduction of risk introduced by the change to an acceptable level, then additional risk mitigation factors, to include additional or more extensive testing strategies, may be appropriate. For example: 1) The BioPhorum guidance included as **Attachment B** specifically identifies prolonged bulk drug substance storage in the highest risk category, and thereby requires additional assessment. 2) In accordance with the BioPhorum guidance of **Attachment B**, changes made to the SUSs used in processing Transformed Cell Therapy products with direct “drug product” contact also fall into the high-risk category, and thus require additional assessment. For the avoidance of doubt, we wish to confirm that the specific references to “contact duration, pH, solvent/media/reagents” and “extended product contact time in a bioreactor” are used as examples of intrinsic process risk factors which shall be considered in a holistic, risk-based analysis of the change. While operating

	parameters associated with some processes may be inherently high-risk (i.e. high/low pH, contact time, etc.), these are not prescriptive of the need for full revalidation. Rather, **these process risk factors shall be considered** in addition to the comparability of E&L profiles when assessing the risk introduced by changeover to X-ray sterilization.
Question 3: Does CBER generally agree with the post-change approval levels proposed in the risk assessment case studies. Specifically, in cases where changes are • implemented in accordance with ISO 11137 and • sponsor/authorization holder risk assessment concludes that the transition from gamma to X-ray is low risk, ➢ this may be implemented via Annual Report (FDA), Type IA (EMA), or 'non-approved matters' (PMDA)? In cases identical to the above, but where "gamma" is mentioned in the regulatory filing, does CBER concur that these should also be treated as Annual Reportable?	
CBER Response: CBER does not agree with a generally applied post-change approval reporting category of Annual Report due to the variable and complex nature and form of many of our products and product-/process-specific considerations. We recommend a risk-based approach that is dependent on product risk. The following regulatory reporting classifications for the use of X-ray as an alternative to gamma irradiation for in-scope SUS used in the manufacturing of products (regardless if "gamma" is mentioned in the regulatory filing) are considered appropriate:	We agree that there is no "one-size fits all approach" to qualifying the change from gamma to X-ray sterilization of SUSs. Although some irradiated components and SUSs may be used in inherently high-risk processes/product applications, we acknowledge that scientifically sound risk assessments shall be developed to evaluate 1) how the change in irradiation process may affect their performance in a validated biomanufacturing process, 2) how these inherent process/product risks are mitigated to acceptable levels, 3) and how the change may require new/additional risk mitigation strategies.

(additional rows inserted for ease of reference)	In the event a Market Authorization Holder concludes that changing the irradiation process for a SUS would introduce a significant, unacceptable risk to a validated biomanufacturing process that could not be effectively reduced by a scientifically sound risk mitigation strategy, implementation of that change shall be rejected.
• CBE30 for drug product filters, bioreactors and mixers, and container closure system used to store media, bulk, or final bulk.	1) We understand this comment to recommend submission of a CBE30 for a change in the irradiation process of sterilizing-grade filters used for final filtration of drug products. Changes in the irradiation process of sterilizing grade filters used in other applications further upstream may or may not require submission of a CBE30 if appropriately supported by a scientifically sound risk assessment. 2) Independent discussion: We would like to clarify if the CATT is recommending that changes made to the irradiation process of SUSs used in ***all bioreactors and mixers*** be submitted as CBE30s. We do acknowledge that unique bioreactor technologies associated with novel cell & gene therapies may require additional assessment. Similarly, we acknowledge that changes to the irradiation process of some SUS mixers used for finished drug product (e.g. pooling of thawed bulk drug substance prior to filling, with or without sterile filtration) may affect their inherent process risk and require additional assessment as discussed in comments to **Question 2** (above). However, in many other cases the inherent process risk may be considerably lower. For example, bioreactors employing CHO cells for mAb or other biologics production are far removed from the patient and typically subjected to numerous downstream purification and clearance steps. Moreover, additional supporting studies (included here as **Attachments C(1) and C(2)**), have demonstrated no detrimental impact to cell growth when evaluated post-gamma vs. post-X-ray.

	In these later cases, changes to the irradiation process of many SUS applications may be well justified to have minimal or no impact to a validated biomanufacturing process and may be most appropriately reported internally within the Market Authorization Holder's (MAH's) quality management system and/or submitted to the agency in an Annual Report. We acknowledge the CATT's recommendation that changing the irradiation process of container-closure systems used for long-term storage would warrant submission of a CBE30. Long-term storage of bulk drug substance and finished bulk drug product have been beyond the scope of the current initiative to date. However, "bulk" can be broadly interpreted throughout industry as various stages of in-process, intermediate drug substance and "final bulk" can be read as final bulk drug substance, post-formulation bulk drug product, and/or finished drug product. For the avoidance of doubt, we would like to confirm that the CATT's recommendation applies to changes in the irradiation process of container-closure systems intended for long-term storage, which traditionally require stability studies. This recommendation would apply to SUSs used for storage of bulk drug substance and finished drug product over extended durations whereas the impact to SUSs used for interim storage of in-process (or work-in-progress) bulk, which traditionally require hold time studies, may be assessed in a risk-based manner and reported accordingly. Similarly, we believe SUS applications for storage of cell culture "media" should be assessed, according to both their intrinsic process risk and the risk introduced by the change in irradiation process, in a manner as described for bioreactors above and reported as appropriate.
• Annual Report for other product contact materials	We understand the CATT's recommendation for "product contact materials" as applicable to those SUSs which have direct contact with finished bulk drug substance or drug product.

	We would like to clarify if the CATT recommends inclusion in Annual Reports the change in irradiation process applied to SUSs which may have (i.) in-process contact with drug substance, or (ii.) indirect process flow contact. i. Examples of in-process contact with drug substance include a wide range of fluid handling SUSs downstream of the bioreactor, including depth filtration, chromatography, virus inactivation, and so forth. SUSs utilized during these unit operations generally pose a lower inherent process risk than the "product contact materials" used for handling finished bulk drug substance and drug product. Depending on the risk-based assessments conducted by a MAH for those SUSs used in-process, changes to their irradiation process may be included in Annual Reports or managed internally through their pharmaceutical quality system, as appropriate. ii. As an example of indirect process flow contact, changes to the irradiation process for buffer transfer sets, which are used to feed various buffer solutions into the bulk drug substance processing stream, could be an inherently low risk application that may be most appropriately managed by the MAH's internal pharmaceutical quality system. We seek to gain consensus with the CATT that changes to the irradiation process of SUSs with (i.) in-process contact or (ii.) indirect process flow contact may be submitted in Annual Reports or evaluated through a MAH's internal pharmaceutical quality system, as deemed appropriate by scientifically sound assessments on a case-by-case basis.
• Internal Change for non-product contact items	We acknowledge the CATT's recommendation that changes to the irradiation process for non-product contact be managed by the change control process of the MAH's internal pharmaceutical quality system.
As CBER gains experience and assurance that no adverse product	Understood, and we welcome the opportunity to continue engaging with the agency and further

impact is associated with the conversion from gamma to X-ray sterilization, future dialogue is encouraged to consider alternative post-approval change reporting strategies.	developing the body of data & knowledge to support supplementation of gamma with X-ray, where technically feasible and appropriate, in accordance with sound quality risk management principles.

C.1 CATT Response (23 APR 2024)

The previous CATT comments are considered non-binding feedback to provide general, non-prescriptive guidance in response to the general, product- and process-agnostic questions posed by BARDA during the October 10th, 2023 CATT meeting. CATT is not able to provide further clarification because CBER-regulated products are highly diverse, variable, and complex, and additional recommendations would require product- and process-specific considerations on a case-by-case basis using a holistic, risk-based approach. For product-specific guidance, we recommend that manufacturers who consider making the changes to their process(es) contact the product-specific CBER office for binding advice through regulatory submissions and/or formal meetings. Specific advice provided therein will supersede the general, non-binding CATT comments.

CBER Advanced Technologies Team

Written Responses

Meeting Date: October 10, 2023

Meeting Requestor: BARDA

Meeting Subject: Conversion from gamma irradiation to X-ray sterilization of single-use systems (SUS) in the context of biomanufacturing.

Response Date: December 14, 2023

Question 1:

Does the CBER agree that the existing ISO 11137 standard currently used for irradiation sterilization of SUS, and which includes requirements for X-ray, may be used as the basis for X-ray sterilization of SUS?

CBER Response:

ISO 11137 is still appropriate for X-ray sterilization. The physics appears to support the behavior of X-rays being similar to gamma rays in terms of sterilizing capability.

Question 2:

Does the CBER agree that the risk of leachables from X-ray as compared to gamma, may be assessed based on

i. an understanding of the underlying physics,

ii. materials impact evaluation, and

iii. using the USP <665> moderate risk testing approach to VERIFY (not revalidate) that there are no meaningful adverse effects to the extraction profiles.

CBER Response:

Based on the available information, CBER generally agrees that the use of USP <665> moderate risk testing approach to verify the equivalence of extractables profiles of X-ray vs. gamma sterilized SUS may be acceptable for many of the CBER products. A risk-based analysis should be provided with justification to support the relevance of the testing approach and extractable conditions based on SUS material composition, intended use, and representative process conditions (e.g., contact duration, pH, solvent/media/reagents). Additional testing may be required as part of the risk mitigation strategy and will be evaluated on a case-by-case basis.

For example, extended product contact time in a bioreactor may result in elevated extractable and leachable risks to cell and gene products that rely on the metabolic activity of living cells for their primary function. In such case, more extensive E&L studies may be required.

Question 3:

Does the CBER generally agree with the post-change approval levels proposed in the risk assessment case studies. Specifically, in cases where changes are

- implemented in accordance with ISO 11137 and
- sponsor/authorization holder risk assessment concludes that the transition from gamma to X-ray is low risk,
- ➢ this may be implemented via Annual Report (FDA), Type IA (EMA), or 'non-approved matters' (PMDA)?

In cases identical to the above, but where "gamma" is mentioned in the regulatory filing, does the CBER concur that these should also be treated as Annual Reportable?

CBER Response:

CBER does not agree with a generally applied post-change approval reporting category of Annual Report due to the variable and complex nature and form of many of our products and product-/process-specific considerations. We recommend a risk-based approach that is dependent on product risk. The following regulatory reporting classifications for the use of X-ray as an alternative to gamma irradiation for in-scope SUS used in the manufacturing of products (regardless if "gamma" is mentioned in the regulatory filing) are considered appropriate:

- *CBE30 for drug product filters, bioreactors and mixers, and container closure system used to store media, bulk, or final bulk.*
- *Annual Report for other product contact materials*
- *Internal Change for non-product contact items*

As CBER gains experience and assurance that no adverse product impact is associated with the conversion from gamma to X-ray sterilization, future dialogue is encouraged to consider alternative post-approval change reporting strategies.