4th Conference on NGS for Adventitious Virus Detection in Biologics for Humans and Animals: Validation and Implementation of NGS

December 4-5, 2024

IABS
International Alliance for Biological Standardization

Rules for remote participants

Make sure your camera and microphone are off during talks.

Questions will be discussed after each presentation.

Apologies if all questions cannot be answered due to lack of time

For any questions, please use the Chat Box and state your name & organization

This meeting is recorded

IABS

International Alliance for Biological Standardization

Introduction – Summary of Previous Meetings and Goals of the 4th meeting

Arifa KHAN, U.S. Food and Drug Administration, Center for Biologics Evaluation and Research (FDA-CBER), U.S.A.
Laurent MALLET, European Directorate for the Quality of Medicines & HealthCare (EDQM), France

International Alliance for Biological Standardization

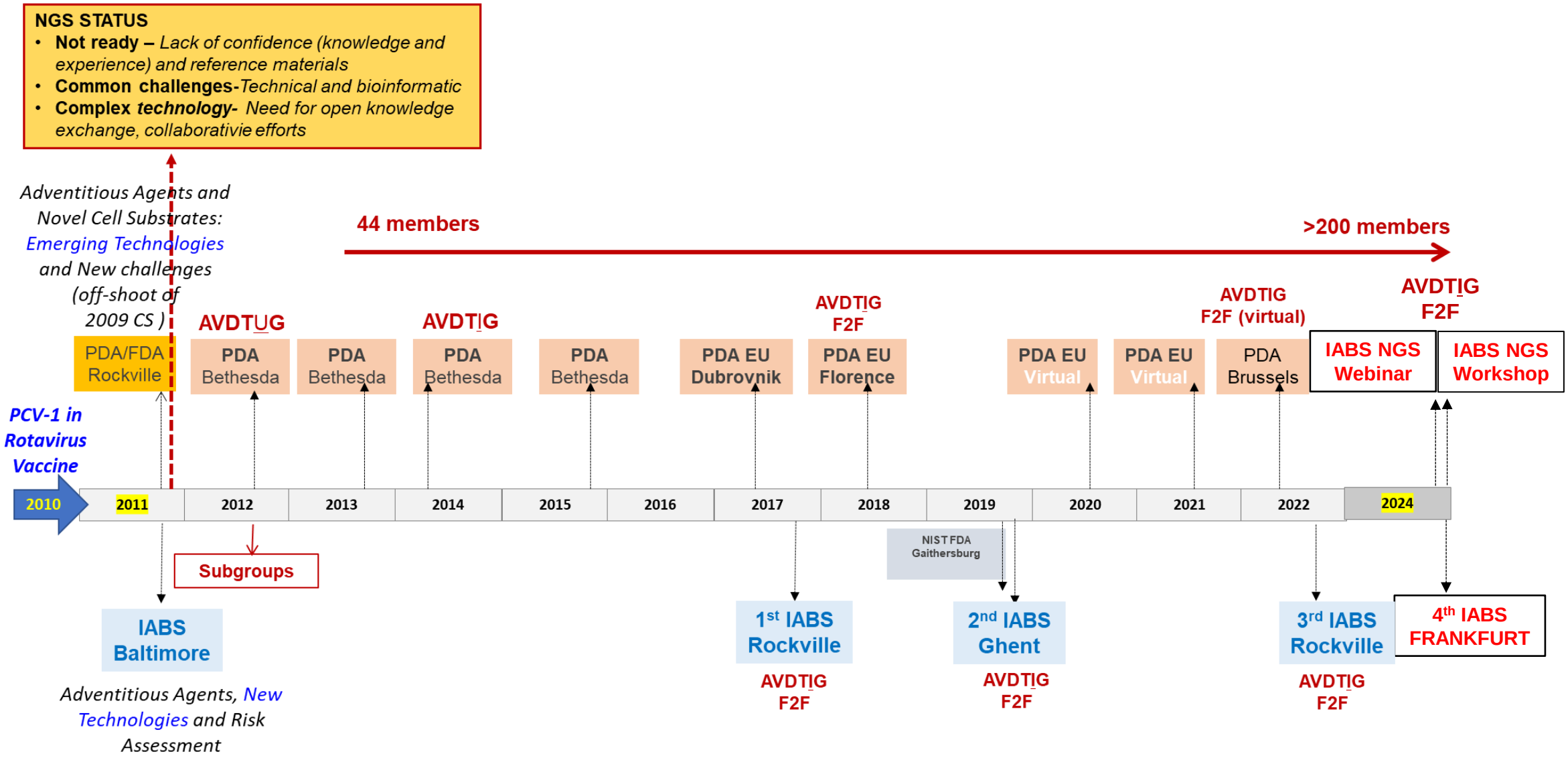
IABS: 4th Conference on Next Generation Sequencing for Adventitious Virus Detection in Human and Veterinary Biologics for Humans and Animals: Frankfurt, Germany. December 4-5, 2024

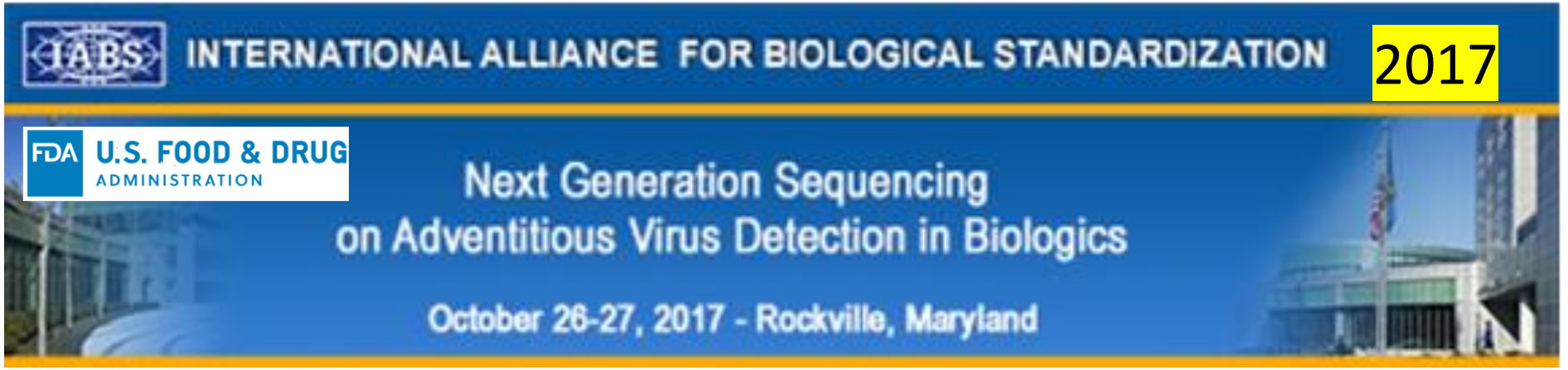
Summary of the Previous 3 NGS Meetings: *Advancing NGS!*

Arifa S. Khan, Ph.D.

OVRR/CBER/U.S. FDA

December 4, 2024


NGS STATUS
• Not ready – Lack of confidence (knowledge and experience) and reference materials
• Common challenges-Technical and bioinformatic
• Complex technology- Need for open knowledge exchange, collaborativie efforts
Adventitious Agents and Novel Cell Substrates: Emerging Technologies and New challenges (off-shoot of 2009 CS)
44 members
>200 members
AVDTUG
AVDTIG
AVDTIG F2F
AVDTIG F2F (virtual)
AVDTIG F2F
PDA/FDA Rockville
PDA Bethesda
PDA Bethesda
PDA Bethesda
PDA Bethesda
PDA EU Dubrovnik
PDA EU Florence
PDA EU Virtual
PDA EU Virtual
PDA Brussels
IABS NGS Webinar
IABS NGS Workshop
PCV-1 in Rotavirus Vaccine
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
2024
Subgroups
NIST FDA Gaithersburg
IABS Baltimore
1st IABS Rockville
2nd IABS Ghent
3rd IABS Rockville
4th IABS FRANKFURT
AVDTIG F2F
AVDTIG F2F
AVDTIG F2F
Adventitious Agents, New Technologies and Risk Assessment



Scientific Committee

Arifa S. Khan CBER / FDA, USA
William Egan GlaxoSmithKline Vaccines, USA
Pieter Neels IABS, Switzerland
Carmen Jungbäck IABS, Switzerland
Luca Benetti Merck & Co., USA
Johannes Blümel Paul-Ehrlich-Institut, Germany
Hansi Dean Takeda Vaccines, USA
Dieter Deforce Ghent University, Belgium
Ivana Knezevic World Health Organization, Switzerland
Alan Fauconnier Federal Agency for Medicines and Health Products, Belgium
Robin Levis,Ph.D. CBER / FDA, USA
Laurent Mallet Sanofi Pasteur, France
Philip Minor National Institute for Biological Standards and Control, United Kingdom
Gayle Pulle Health Canada

- NGS for adventitious virus detection in biologics with focus on applications for human vaccines and lessons learnt from veterinary vaccines.
- The meeting included data presentations and discussions for developing a scientific consensus for **using NGS** for virus detection in selected applications of biologics.

IDENTIFYING THE CHALLENGES OF USING NGS

2017 Meeting Outcomes

- Participants identified needs for:
  - Standard reference reagents
  - Well-annotated databases
  - Large data storage and transfer capacity
  - Clear and simple strategy for follow up of NGS hits
  - Personnel with relevant expertise, particularly in bioinformatics
  - Harmonization of international regulations for testing biologic products and reagents used for their manufacturing.
- It was noted that continued collaborative efforts and scientific exchange by regulatory and other government agencies, industry, academic labs, and service providers will move the NGS field forward with the goal of assuring the safety of biological products that impact on human and animal health.

Biologicals 55 (2018) 1–16

Contents lists available at ScienceDirect

Biologicals

journal homepage: www.elsevier.com/locate/biologicals

Report of the 2017 international conference on next generation sequencing for adventitious virus detection in biologicals

Arifa S. Khan [a,*], Luca Benetti [b], Johannes Blumel [c], Dieter Deforce [d], William Egan [e], Ivana Knezevic [f], Philip R. Krause [a], Laurent Mallet [g], Dietmar Mayer [h], Philip Minor [i], Pieter Neels [j], Guanhua Wang [k]

Scientific Committee

Dieter Deforce, Ghent University / Federal Agency for Medicines and Health Products of Belgium (FAMHP)
Sebastiaan Theuns, Ghent University / PROVAXS
Arifa Khan, U.S. Food and Drug Administration (FDA)
Pieter Neels, International Alliance for Biological Standardization (IABS)
Sven Arnouts, Ghent University / PROVAXS
Johannes Blümel, Paul-Ehrlich Institut (PEI)
William Egan, GlaxoSmithKline Vaccines
Carmen Jungbäck, International Alliance for Biological Standardization (IABS)
Ivana Knezevic, World Heath Organization (WHO)
Laurent Mallet, Sanofi Pasteur
Gerald Schumann, Paul-Ehrlich Institut (PEI)
David Mackay, Advisor Veterinary Vaccinology
Joseph Victoria, Boehringer-Ingelheim

- Bring together industry, academia, technology providers, and international regulatory bodies to discuss current status of NGS for adventitious virus detection in biologics
- Present ongoing efforts on standardization and validation of the technical and bioinformatics steps in NGS for its applications in characterization and safety evaluation of biologics, including human and animal vaccines.
- Develop a scientific consensus regarding **READINESS of NGS** for detection of adventitious viruses in biologics.

2019 Meeting Outcomes

- **NGS could be as sensitive for virus detection as PCR assays and relevant validation data could support its use as a replacement assay.**

- **The need to replace *in vivo* testing with NGS was recognized to align with the 3Rs initiative to replace, reduce and refine the use of animals for medical research and development. *There was support for this consideration.***

- **Further work is needed to replace *in vitro* cell culture-based tests: in particular, to standardise and validate the performance of NGS as compared to that of *in vitro* assays. The risk of false positives is currently limiting the ability of NGS to replace *in vitro* cell culture-based testing.**

- **Further work is also needed to optimise the approach to managing true and false positives and inconclusive results.**

- **In order to replace existing assays, regulations and applicable guidances will need to be revised, if not done so already. (*These already allow flexibility for the use of new technologies such as NGS).***

2019 Meeting Outcomes

- **The importance of moving from prescriptive testing to a risk management approach also needs to be considered in the overall virus mitigation strategy.**

- **NGS technology is evolving rapidly, and it is important to keep up-to-date with the technological advances. Efforts should continue and be more inclusive of all regions for global acceptance.**

- **Concerted efforts should be made toward development of publicly available reference materials that can be used for the entire workflow or specific steps in NGS standardization and validation.**

- **The lack of standards and databases, particularly in the veterinary domain, make it premature at the present time for NGS to be part of compulsory regulatory requirements. However, all stakeholders were encouraged to continue the work highlighted at this meeting with the aim of NGS becoming part of the routine methodological toolkit for manufacturers and regulators.**

Biologicals 67 (2020) 94–111

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Biologicals

journal homepage: www.elsevier.com/locate/biologicals

Report of the second international conference on next generation sequencing for adventitious virus detection in biologics for humans and animals☆

Arifa S. Khan[a,*], Johannes Blümel[b], Dieter Deforce[c], Marion F. Gruber[a], Carmen Jungbäck[d], Ivana Knezevic[e], Laurent Mallet[f,1], David Mackay[g], Jelle Matthijnssens[h], Maureen O'Leary[i,2], Sebastiaan Theuns[c], Joseph Victoria[j], Pieter Neels[d]

3rd IABS Conference on Next Generation Sequencing for Adventitious Virus Detection in Biologics for Humans and Animals

September 27-28, 2022

Rockville, USA

edqm European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

FDA U.S. FOOD & DRUG ADMINISTRATION

IABS International alliance for biological stantardization

Scientific Committee

Arifa S. KHAN	U.S. Food and Drug Administration, Center for Biologics Evaluation and Research FDA-CBER (FDA) – Co-Chair, U.S.A.
Laurent MALLET	European Directorate for the Quality of Medicines & HealthCare (EDQM) – Co-Chair, France
Pieter NEELS	International Alliance for Biological Standardization (IABS) Chair, Human Vaccine Scientific Committee, Belgium
Johannes BLÜMEL	Paul-Ehrlich Institut (PEI), Germany
Jean-Pol CASSART	GlaxoSmithKline (GSK) Vaccines, Belgium
Miia JAKAVA-VILJANEN	Finnish Food Authority
Ivana KNEZEVIC	World Health Organization (WHO), Switzerland
Carine LOGVINOFF	Sanofi Pasteur, France
Siemon NG	Notch Therapeutics, Canada
Michael WALL	Health Canada

Developing consensus for using NGS

2022 Meeting Outcomes

- Impressive progress regarding the implementation of the technology in a number of companies and regulatory agencies
  - validation status of the technology presented by some companies/CROs with at least one publication of a validation study
- Increased number of submissions received by the Regulatory Authorities (FDA, EMA), highlights on regulatory expectations
- The availability of the 5 virus standards from CBER/FDA approved by the WHO ECBS,
- The progress of the AVDTIG activities and deliverables from the subgroups,
- The availability of the Reference Virus Database (RVDB),
- The interest in NGS expressed by many WHO collaborative centres,
- Overall a lot of data has been presented in this 3rd conference

2022 Meeting Outcomes

- Presentation of key draft guidelines (ICHQ5A(R2)) introducing NGS for assessing viral safety of Biological products and Ph. Eur Chapter (2.6.41) outline describing the NGS technology and validation approaches

- Transcriptomics data were presented and further support the scientific rationale to replace *in vivo* tests for adventitious agent testing by NGS.

- The diversity of the approaches (Sequencing, Bioinformatics pipelines...) remains a concern for many stakeholders and the generation of virus standards should be considered as a priority

- Global consensus on implementation of the NGS technology by manufacturers and adoption by Regulatory Authorities was not reached across the different regions

2022 Meeting Outcomes

- PERSONAL MESSAGE to the manufacturers, you may be afraid by the NGS technology, because of the potential detection of signals and the need to interpret them with follow-up investigations. However this is feasible, there are tools to perform this follow-up investigation as we have seen during this conference, and at the end manufacturers are responsible for the viral safety of their products and should not wait for a regulation evolution to explore & implement this technology

Biologicals 83 (2023) 101696

Contents lists available at ScienceDirect

Biologicals

journal homepage: www.elsevier.com/locate/biologicals

Report of the third conference on next-generation sequencing for adventitious virus detection in biologics for humans and animals☆

Arifa S. Khan [a,*,1], Laurent Mallet [b,1], Johannes Blümel [c], Jean-Pol Cassart [d], Ivana Knezevic [e], Siemon H.S. Ng [f], Michael Wall [g], Miia Jakava-Viljanen [h], Carine Logvinoff [i], Ana Goios [j], Pieter Neels [k]

Goals of the 4th meeting

Laurent MALLET, European Directorate for the Quality of Medicines & HealthCare (EDQM**),** France

International Alliance for Biological Standardization

Frankfurt, Germany

December, 3-5 2024

4th Conference on Next Generation Sequencing for Adventitious Virus Detection in Biologics for Humans and Animal

SCIENTIFIC COMMITTEE

- **Arifa S. KHAN** – U.S. Food and Drug Administration, Center for Biologics Evaluation and Research FDA-CBER (FDA) – U.S.A. – Co-Chair
- **Laurent MALLET** – European Directorate for the Quality of Medicines & HealthCare (EDQM) – France – Co-Chair
- **Pieter NEELS** – International Alliance for Biological Standardization (IABS) – Chair, Human Vaccine Scientific Committee – Belgium
- **Johannes BLÜMEL** – Paul-Ehrlich Institut (PEI) – Germany
- **Noémie DENEYER** – GlaxoSmithKline (GSK) Vaccines – Belgium
- **Sigrid DE KEERSMAECKER** – Sciensano – Belgium
- **Blandine DE SAINT-VIS** – Boehringer Ingelheim – France
- **Ivana KNEZEVIC** – World Health Organization (WHO) – Switzerland
- **Carine LOGVINOFF** – Sanofi – France
- **Marie MURPHY** – Eli Lilly & Co – Ireland
- **Siemon NG** – Notch Therapeutics Canada
- **Yoji SATO** – National Institute of Health Sciences – Japan
- **Michael WALL** – Health Canada

Goals of the 4th NGS meeting

International Alliance for Biological Standardization

Bring together representatives from industry, academia, contract research organizations, international regulatory bodies and health authorities for developing a scientific consensus regarding implementation of NGS for detection of adventitious viruses.

- Share the latest scientific data regarding NGS applications and implementation for detection of Viral Adventitious Agents for safety evaluation of biologics
- Share the latest updates regarding the introduction of NGS in regulatory documents
- Discuss the current status of NGS in regulatory submissions and industry applications
- Discuss expectations for the validation of NGS for viral safety of biologics

Goals of the 4th NGS meeting

International Alliance for Biological Standardization

Great opportunity to network and share your ideas, questions, experience and expertise!

IABS meetings	Participants	Countries
1st 2017 (US)	126	14
2nd 2019 (EU)	124	16
3rd 2022 (US)	157	18
4th 2024 (EU)	170	26

The report of this 4th IABS NGS Conference will be published in *Biologicals*

Agenda – 4th NGS Conference

Wednesday 4th of December, 2024

9.00 AM **Welcome Remarks: IABS & Chairs**
Rick HILL – IABS, USA
Laurent MALLET – European Directorate for the Quality of Medicines & HealthCare (EDQM) – France – Co-Chair
Arifa S. KHAN – U.S. Food and Drug Administration, Center for Biologics Evaluation and Research FDA-CBER (FDA) – U.S.A. – Co-Chair

INTRODUCTION

9.10 AM **Introduction – Summary of Previous Meetings and Goal of the 4th meeting**
Arifa KHAN, U.S. Food and Drug Administration, Center for Biologics Evaluation and Research FDA-CBER (FDA) – U.S.A. – Co-Chair
Laurent MALLET, European Directorate for the Quality of Medicines & HealthCare (EDQM) – France – Co-Chair

SESSION 1 – Current Perspectives on Using NGS for Adventitious Virus Testing

Moderators: Laurent Mallet & Arifa Khan

9.30 AM **Next Generation Sequencing and ICH Q5A(R2)**
Johannes BLÜMEL, Paul-Ehrlich Institute (PEI), Germany

10.00 AM **EDQM/Ph. Eur. perspectives on NGS/HTS**
Laurent MALLET, Co-Chair & Gwenael CIREFICE,
European Directorate for the Quality of Medicines & HealthCare (EDQM), France

10.30 PM **FDA**
Arifa KHAN, U.S. Food and Drug Administration, Center for Biologics Evaluation and Research FDA-CBER (FDA), U.S.A. – Co-Chair

11.00 AM **WHO**
Ivana KNEZEVIC, World Health Organization (WHO), Switzerland

11.30 AM *Coffee break*

12.00 PM **Perspectives from the CAACB on the Current Benefits and Challenges of NGS Adoption for Viral Safety Testing**
Charles SWOFFORD, MIT Center for Biomedical Innovation

12.30 PM **EFPIA's Perspectives on the Validation and Implementation of Next Generation Sequencing for Virus Safety Testing of Biological Products**
Noémie DENEYER, GSK, Belgium, Member of the EFPIA WG

1.00 PM *Lunch*

2.00 PM **Panel Discussion**

- Johannes BLÜMEL, Paul-Ehrlich Institute (PEI), Germany
- Laurent MALLET, Co-Chair, European Directorate for the Quality of Medicines & HealthCare (EDQM), France
- Gwenael CIREFICE, European Directorate for the Quality of Medicines & HealthCare (EDQM), France
- Arifa KHAN, Co-Chair, U.S. Food and Drug Administration, Center for Biologics Evaluation and Research FDA-CBER (FDA), U.S.A.
- Ivana KNEZEVIC, World Health Organization (WHO), Switzerland
- Charles SWOFFORD, MIT Center for Biomedical Innovation
- Noémie DENEYER, GSK, Belgium, Member of the EFPIA WG
- Juliati DAHLAN, National Agency of Drugs and Food Control, Indonesia (Virtual)
- Hadeer ABOSALEM, Egyptian Drug Authority EDA, Egypt (Virtual)
- Hamida BEGUM, Bangladesh (Virtual)

Agenda – 4th NGS Conference

Wednesday 4th of December, 2024

SESSION 2 – Reference Materials, NGS Qualification and Validation

Moderators: Sigrid De Keersmaecker, Johannes Blümel

2.45 PM **Transcriptomic NGS assay of cells as a substitute for conventional virus testing techniques**
Marc ELOIT, Pathoquest, France

3.10 PM **Matrix effects on Limit of Detection for NGS-based Adventitious Virus Detection Assays**
Bradley HASSON, MilliporeSigma, U.S.A.

3.35 PM **AVDTWG Spiking Study 4 - Evaluation of Long-Read Sequencing for Adventitious Virus Detection in a Low Complexity Viral Background**
Valeria ZANDA, Merck, Italy

4.00 PM *Coffee break*

4.30 PM **Head-to-head comparison of NGS with in vivo animal assays and in vitro cell culture assays for adventitious virus detection**
Alison ARMSTRONG, Merck KgAG
on behalf of NIIMBL PC3.1-305 project team

4.55 PM **Refinement Efforts on CBER's Reference Virus Database (RVDB) to Enhance Accuracy and Specificity of Virus Detection**
Pei-Ju CHIN, US FDA, U.S.A.

5.20 PM **Next Generation Sequencing: Validation, Regulatory Approval and Implementation of NGS as an alternative In Vivo Testing for Live Attenuated Influenza Vaccine**
Alice ALSTON, AstraZeneca (Virtual)

5.50 PM **Panel Discussion**
Marc ELOIT, Pathoquest, France
Bradley HASSON, MilliporeSigma, U.S.A.
Valeria ZANDA, Merck, Italy
Alison ARMSTRONG, Merck KgAG on behalf of NIIMBL PC3.1-305 project team
Pei-Ju CHIN, US FDA, U.S.A.

6.30 PM **End of First Day of Conference**

Agenda – 4th NGS Conference

Thursday 5th of December, 2024

SESSION 3 – NGS Applications

Moderators : Michael Wall, Blandine de Saint-Vis

8.30 AM **Comparison of Non-Targeted and Broad-Spectrum Targeted NGS for Adventitious Virus Detection**
Gibran Horemheb RUBIO QUINTANARES, Paul Ehrlich Institute, Germany

8.55 AM **Comparison of Long- and Short-Read Sequencing Methods for Recombinant Adeno Associated Virus Sequence and Adventitious Agent Identification in a GMP Environment**
Megan GURA, Regeneron, U.S.A.

9.20 AM **Selecting and developing approaches for adventitious virus detection by HTS, contrasting release testing with investigational follow-up**
Carine LOGVINOFF, Sanofi, France
Song SUN, Sanofi, Canada

9.45 AM *Coffee Break* – **POSTER SESSION**

10.30 AM **Current status for testing of adventitious agents by NGS at Serum Institute of India Pvt. Ltd. and way forward**
Subhashis CHATTERJEE, Serum Institute of India, India

10.55 AM **BLOODVIR – Surveillance system for novel viruses based on next generation sequencing and artificial intelligence**
Martin MACHYNA, Paul Ehrlich Institute, Germany

11.20 AM **Panel Discussion**

- Gibran Horemheb RUBIO QUINTANARES, Paul Ehrlich Institute, Germany
- Megan GURA, Regeneron, U.S.A.
- Carine LOGVINOFF, Sanofi, France
- Song SUN, Sanofi, Canada
- Subhashis CHATTERJEE, Serum Institute of India, India
- Martin MACHYNA, Paul Ehrlich Institute, Germany

12.20 PM *Lunch*

SESSION 4 - Strategies for Optimization of NGS Virus Detection and Follow-up of NGS Signal

Moderators: Siemon Ng, Marie Murphy

1.30 PM **Rapid alignment-free detection of adventitious agents using next-generation sequencing**
Tom J.B. DE MAN, Millipore Sigma, U.S.A.

1.55 PM **Viral metagenomic analysis to complement the viral risk assessment and adventitious agent testing of live virus vaccines**
Vanessa V. SARATHY, Merck, U.S.A.

Agenda – 4th NGS Conference

Thursday 5th of December, 2024

SESSION 4 - Strategies for Optimization of NGS Virus Detection and Follow-up of NGS Signal

Moderators: Siemon Ng, Marie Murphy

2.20 PM **Evolution of a bioinformatics pipeline for adventitious agent detection**
Robert L. CHARLEBOIS, Sanofi, Canada

2.45 PM **Panel Discussion**
- Tom J.B. DE MAN, Millipore Sigma, U.S.A.
- Vanessa V. SARATHY, Merck, U.S.A.
- Robert L. CHARLEBOIS, Sanofi, Canada

3.20 PM *Coffee break*

SESSION 5 – Implementation of NGS in Biologics

Moderators: Ivana Knezevic, Laurent Mallet, Arifa Khan

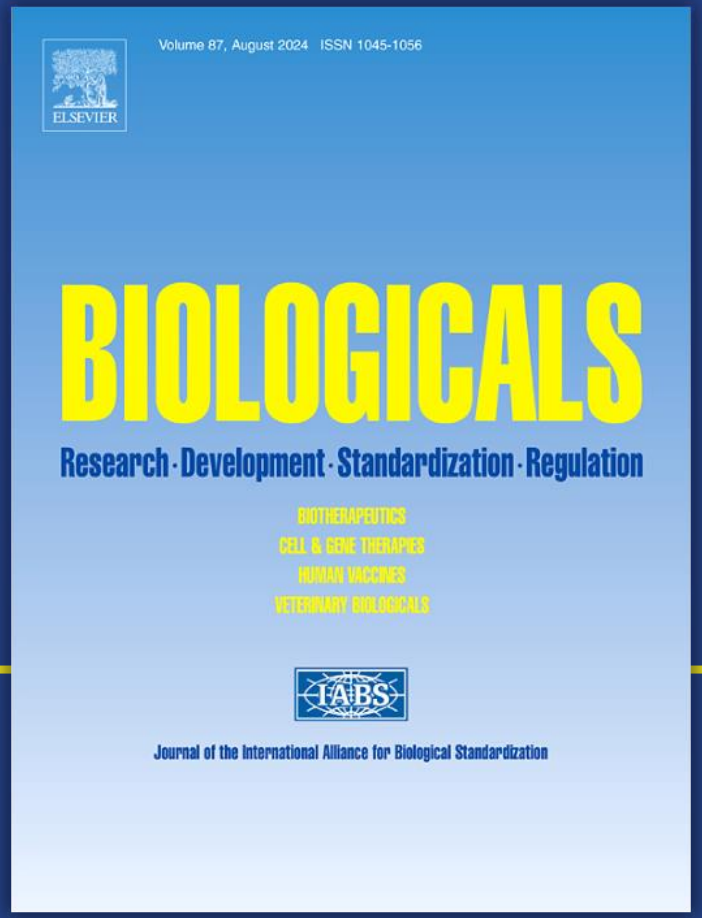
3.50 PM **Final Panel Discussion (Regulators, Industries and CROs)**
- Johannes BLÜMEL, Paul-Ehrlich Institut (PEI), Germany
- Ken KONO, National Institute of Health Sciences, Japan
- Marc ELOIT, Pathoquest, France
- Alison ARMSTRONG, Merck KgAG
- Carine LOGVINOFF, Sanofi, France
- Blandine DE SAINT-VIS, Boehringer Ingelheim Health Animal, France
- Marie MURPHY, Eli Lilly & Co, Ireland
- Siemon NG, Notch Therapeutics, Canada
- Christophe LAMBERT, GSK, Belgium
- Gwenael CIREFICE, European Directorate for the Quality of Medicines & HealthCare
- (EDQM)
- Pei-Ju CHIN, US FDA, U.S.A.
- Ajmeer RAMKISHAN, Ministry of Health & Family Welfare, India (Virtual)
- Koji ISHII, National Institute of Infectious Diseases, Japan (Virtual)
- Igishe USHIE, National Agency For Food And Drug Administration And Control

5.20 PM **Summary & Conclusion**

5.30 PM *Closing Remarks*

5.40 PM *End of Conference*

BIOLOGICALS



Biologicals is a scientific journal that provides a modern and multidisciplinary international forum for publishing peer-reviewed original papers, reviews, and letters relevant to regulatory science as it relates to the development, production, quality control, and standardization of biological products for human and veterinary products derived from novel and established biotechnologies.

Our vision is to provide a forum for the introduction and discussion of scientific topics which impact innovation, lifecycle management, and regulatory strategy. As with most journals, we are dependent on volunteers to serve as members of our editorial board, as well as scientific reviewers.

Biologicals is recruiting volunteers with a strong scientific and/or regulatory background in the development and/or lifecycle management of biological products. We invite you to join the Editorial Board or contribute as a scientific reviewer of a dynamic and influential journal.

If you are interested, please contact the Editor-in-Chief, Dr. Norman Baylor (nbaylor@biologicsconsulting.com).

IABS celebrates 50 Biologicals

Thank you for joining the meeting!

Please take a few minutes to answer the survey and give us your feedback on the conference by scanning the QR-Code:

Thank you

for their support for this meeting

PathoQuest

Boehringer Ingelheim

MilliporeSigma

IABS Vision & Missions

Vision:

Health Solutions for Everyone Everywhere

Missions:

#1 To bring biologicals stakeholders together

#2 To facilitate consensus

#3 To share scientific advancements

IABS
International Alliance for Biological Standardization

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PathoQuest

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