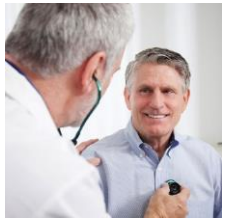
European Federation of Pharmaceutical Industries and Associations

Moving Towards ICH Q5A(R2): Use of Next Generation Sequencing for Viral Safety Testing of Biotechnology Products

Elodie Charbaut Taland, Merck KGaA, on behalf of EFPIA Supportive Group "Clonality, Characterisation and Viral Safety of Cell Lines"






CASSS CMC Strategy Forum EU
October 16, 2023

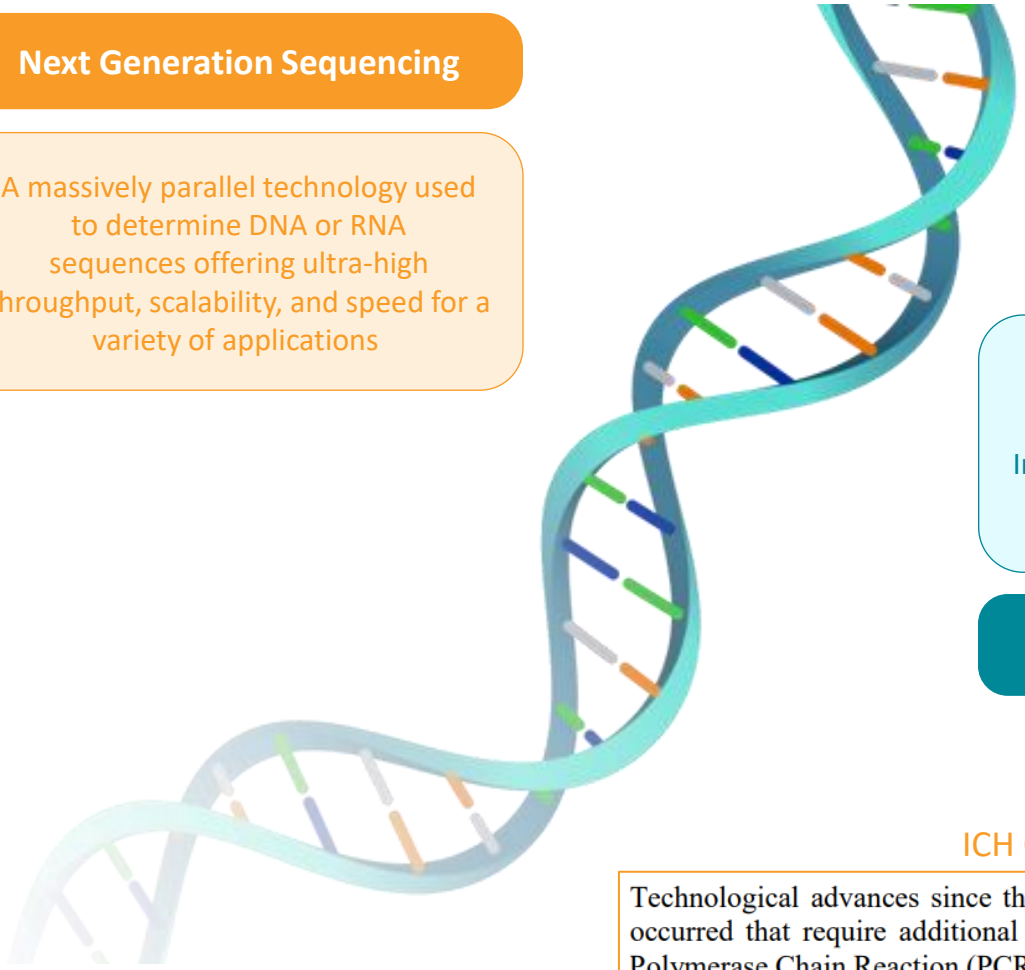
Presentation Outline

1. CMC Applications of Next Generation Sequencing (NGS)
2. Biomanufacturing Supportive Group: Clonality, Characterisation and Viral Safety of Cell Lines
3. Objective of the Position Paper on Next Generation Sequencing for Viral Safety Testing of Biotechnology Products
4. Status of the Position Paper

CMC Applications of Next Generation Sequencing

Next Generation Sequencing

A massively parallel technology used to determine DNA or RNA sequences offering ultra-high throughput, scalability, and speed for a variety of applications



Main CMC Applications

Cell Banks
Viral Seeds
In-Process Controls
Drug Substance

Viral Safety Testing
Genotypic Characterisation
Clonality Evidence
Identity, Purity
Stability

Recombinant Proteins, Vaccines, ATMPs

ICH Q5A(R2) Concept Paper (2019)

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

Clonality, Characterisation and Viral safety of Cell Lines

The EFPIA MQEG Biomanufacturing Supportive Group was initiated in 2019.

Project Aim

- Facilitate the implementation of advanced analytical **NGS technologies** in relation with clonality, cell line characterization and viral safety for **biotechnological products** by sharing and leveraging industry expertise / experience and best practices.
- As a first priority, develop, promote and provide guidance for implementation of NGS as an alternative for current standards on **viral safety testing**
- Present industry position in perspective of shaping regulatory landscape for smoother implementation and acceptance by Heath Authorities

Scope

- Technology of interest: NGS
- Applicable for viral safety testing on Biotechnological products (ATMPs out of scope)
- **EU, US, ICH/WHO** regulatory landscapes

Deliverables

- Drafting of a Position Paper: acting as a practical implementation guide by providing an industry position for discussion with the Regulatory Authorities.
- Presentation of the Industry position within congresses/ conferences

16 Companies Participate to the NGS Supportive Group

Objectives of the Position Paper

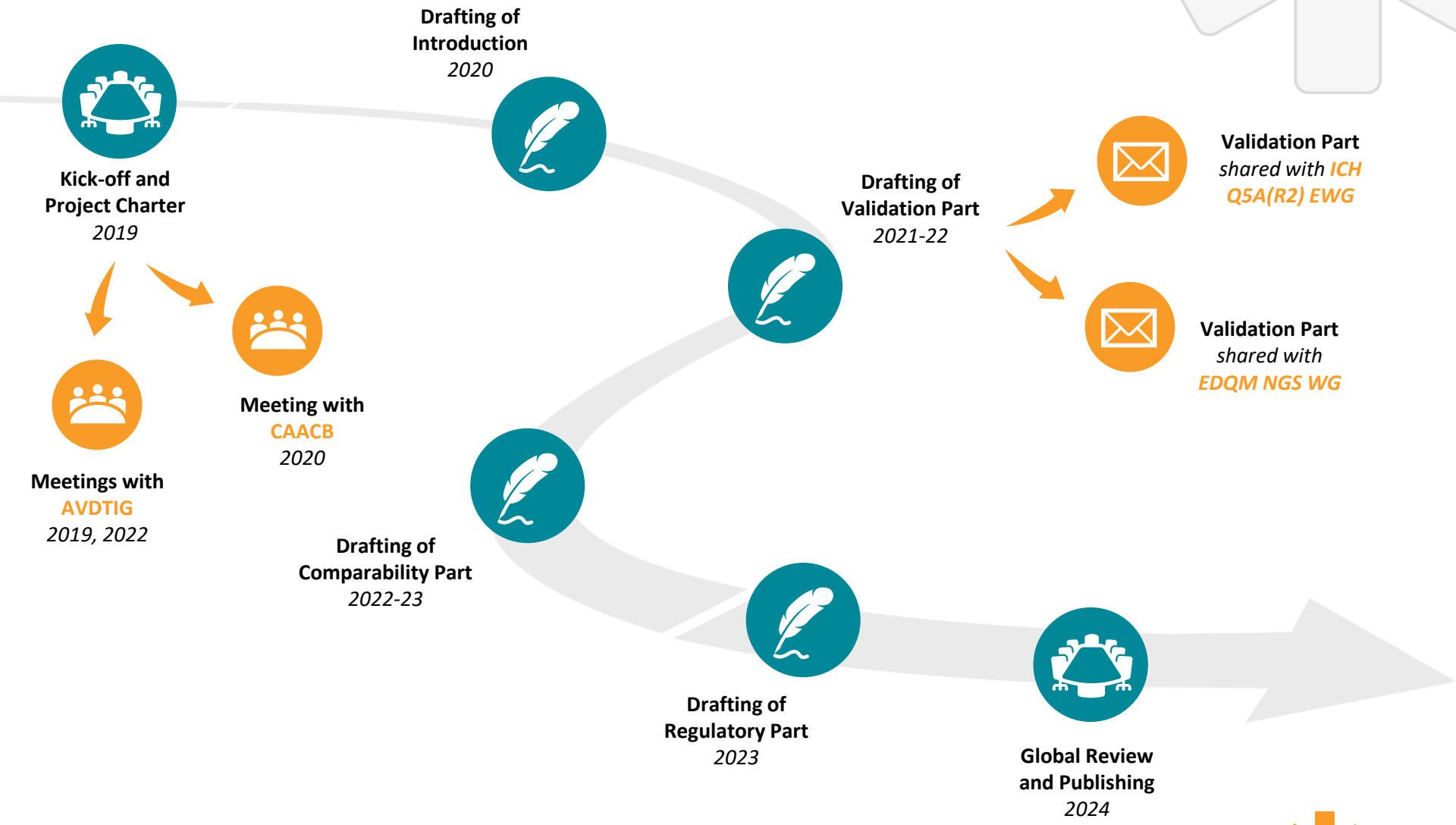
Envisaged as a practical implementation guide providing a position from Industry for dialogue with Regulatory Authorities.

Completion

100%	**Introduction: Why NGS?** Characteristics of NGS technologies and comparison with current virus safety tests
100%	**Validation** strategy for NGS methods
95%	Assessing **Analytical Comparability** of NGS with *in vivo* / *in vitro* virus safety tests
70%	**Regulatory** strategy for NGS **implementation**
	~~**Regulatory lifecycle management of NGS methods**~~

- Support drafting of ICH Q5A(R2), as needed
- Influence potential drafting of a Compendial General Chapter
- Support creation of an ICH Q2(R2) Annex for NGS

Progress of the NGS Supportive Group Work



Status of the Position Paper

Introduction

- Key **features** and expected performance of **conventional virus detection assays** (*in vivo*, *in vitro*, retrovirus), as well as molecular assays such as **PCR and NGS** for the purpose of virus detection
- Comparative table highlighting their **complementarity and orthogonality**
- Initial considerations for introducing NGS-based methods for virus detection, possibly as replacement of routine assays
- To add: the description of different **NGS method formats** (genomics, transcriptomics, viromics)

Validation of NGS-based Methods

- **Validation parameters**: Specificity, Limit of Detection, (Breadth of detection)
- Specific challenges related to specificity and LOD determination
- Limitations of validation studies and necessity to use **representative model viruses**
- Validation strategies: end-to-end vs step-by-step, **reference materials** depending on the NGS method format
- Elements coming from **method development**: robustness, bioinformatic analysis, System Suitability Test
- **Life-cycle management** considerations: e.g. viral genome database update, partial revalidation

Status of the Position Paper

Comparability with Current Tests

- Discussion on significance and limitations of an **analytical comparability study** when replacing a conventional virus test by NGS
- **General methodology** to identify potential challenges for a comparability study
- **Specific examples** are presented in more detail: in vivo, in vitro infectivity tests, PCR
- **Key challenges to analytical comparability**: differences in Critical Quality Attributes, absence of validation data or limitations to their comparison, result interpretation

Regulatory Implications

- Existing **regulatory pathways and requirements** to register NGS for viral safety testing (clinical vs commercial, IPC vs Cell Banks vs DS)
- **Regulatory strategies** that can be used to facilitate acceptance of NGS (depending on product lifecycle stage and intended purpose of the method) e.g. PACMP, HA interactions
- Opportunities to use **technology-driven regulatory mechanisms**, e.g. Innovative Technology Forums (ETT, QIG), future Platform Technology pathways

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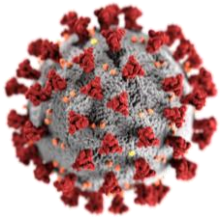

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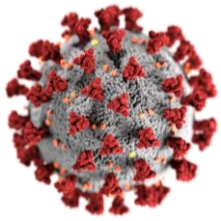

Thank you

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