【レギュラトリーサイエンス財団】
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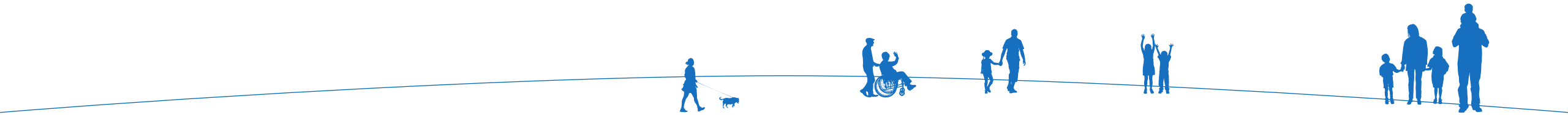
S13 EWG: Non-clinical Safety Evaluation of Oligonucleotide-based Therapeutics

Pharmaceuticals and Medical Devices Agency (PMDA)
Takasumi Shimomoto (ICH S13 EWG Topic Leader)



Outline

- Background
- Status before ICH face-to-face Rio de Janeiro meeting
- ICH face-to-face Rio de Janeiro meeting
- Anticipated key milestones
- Conclusions

Background

With regard to the nonclinical safety evaluation of oligonucleotide-based therapeutics (ONTs), regional guidances were issued to promote the development of ONTs. Afterward, the development has advanced worldwide. Reflecting the global situation, the new topic (ICH S13) was endorsed by the ICH Assembly in June 2023, and the Expert Working Group (EWG) activities for the preparation of ICH S13 began in 2024.

The main current guidances regarding ONTs in Japan, US and EU are as follows:

Japan
核酸医薬品の品質の担保と評価において考慮すべき事項（2018年9月27日）
https://www.pmda.go.jp/files/000270909.pdf
「核酸医薬品の品質の担保と評価において考慮すべき事項について」に関する質疑応答集（Q&A）（2022年6月9日）
https://www.pmda.go.jp/files/000270908.pdf
核酸医薬品の非臨床安全性評価に関するガイドライン（2020年3月30日）
https://www.pmda.go.jp/files/000234603.pdf

US
Nonclinical Testing of Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases Guidance for Sponsor-Investigators DRAFT GUIDANCE (Apr, 2021)
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/nonclinical-testing-individualized-antisense-oligonucleotide-drug-products-severely-debilitating-or
Nonclinical Safety Assessment of Oligonucleotide-Based Therapeutics Guidance for Industry DRAFT GUIDANCE (Nov. 2024)
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/nonclinical-safety-assessment-oligonucleotide-based-therapeutics

EU
CHMP SWP Reflection Paper On the Assessment of the Genotoxic Potential of Antisense Oligodeoxynucleotides (Jan. 2005)
https://www.ema.europa.eu/en/documents/scientific-guideline/chmp-swp-reflection-paper-assessment-genotoxic-potential-antisense-oligodeoxynucleotides_en.pdf
Guideline on the Development and Manufacture of Oligonucleotides Draft (Jul. 2024)
https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-development-manufacture-oligonucleotides_en.pdf

Status before ICH face-to-face Rio de Janeiro meeting (1/2)

- The key milestones so far are as follows:

  Jun. 2024: Establishment of the S13 informal Working Group
  Oct. 2024: Completion of Concept Paper
  (https://database.ich.org/sites/default/files/ICH_S13EWG_Concept_Paper_2024_1028.pdf).
  Nov. 2024: ICH MC endorsement of S13 Concept Paper and transition to S13 Expert Working Group
  Mar. 2025: ICH face-to-face Budapest meeting
  Jun. 2025: High-level outline of guideline
  Nov. 2025: ICH face-to-face Singapore meeting

Status before ICH face-to-face Rio de Janeiro meeting (2/2)

- Specific activities after Singapore meeting are as follows:
  - ✓ Regular plenary or subgroup (general toxicity, carcinogenicity, DART, Impurities, and PK/DDS) teleconference meeting per week
  - ✓ Conducted surveys on ONT repeated toxicity, carcinogenicity and DART studies to incorporate well-characterized ONT concepts into ICH S13 (PMDA/FDA/EMA)
  - ✓ Conducted a survey on ONT phototoxicity evaluation to incorporate the concept into ICH S13 (PMDA)
  - ✓ Preparation of the preliminary draft S13 guideline based on discussions in teleconference meetings referring to the above survey results, existing guideline/guidance/white paper/academic paper, etc.

ICH face-to-face Rio de Janeiro meeting (1/5)

Twenty-one people from the following regulatory authorities and groups participated in person (5/30～6/3), while a little less than 10 others did on the Web.

ICH S13		
Rapporteur	Susanne Brendler-Schwaab (EC/EMA)	
Regulatory Chair	Yoko Hirabayashi (MHLW)	
Japan Member	PMDA	JPMA
Topic Leader	Takasumi Shimomoto	Yutaka Tonomura
Deputy Topic Leader	Mahiro Egashira	Yuichi Takai
Support Staff		Tetsuya Ohta Koichi Goto

MHLW/PMDA
FDA
EC/EMA
Swissmedic
MHRA (Medicines and Healthcare products Regulatory Agency)
NMPA (National Medical Products Administration)
HSA (Health Sciences Authority)
ANVISA (Agencia Nacional de Vigilancia Sanitaria)
SFDA (Saudi Food and Drug Authority)
TFDA (Taiwan Food and Drug Administration)

JPMA
PhRMA
EFPIA
BIO

Technical writer

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ICH face-to-face Rio de Janeiro meeting (2/5)

- At the meeting, the preliminary draft S13 guideline was reviewed by S13 EWG members line by line and the consensus was reached on the draft S13 guideline for the next step (constituent review and plenary working party (PWP) consultation)

ICH face-to-face Rio de Janeiro meeting (3/5)

- ONTs in scope encompass antisense oligonucleotides (ASOs), including RNase H-dependent, splice switching, micro (mi)RNA inhibitors (antagomirs), and RNA editing (e.g., adenosine deaminase acting on RNA [ADAR] MoA); small interfering (si)RNAs; miRNA mimics and small activating (sa)RNA. For other ONTs with MoAs that differ from those listed above such as ONT aptamers, decoy ONT, transfer (t)RNA, and CpG ONTs, the guidance may be relevant to assessing some aspects of nonclinical safety. ONTs are categorised into classes which are defined by their MoA. Guide (g)RNA for DNA editing, prophylactic and therapeutic DNA/RNA vaccines and coding messenger (m)RNA used for therapeutic purposes are out of scope. Drug delivery systems (DDS) used to enhance tissue uptake are in scope

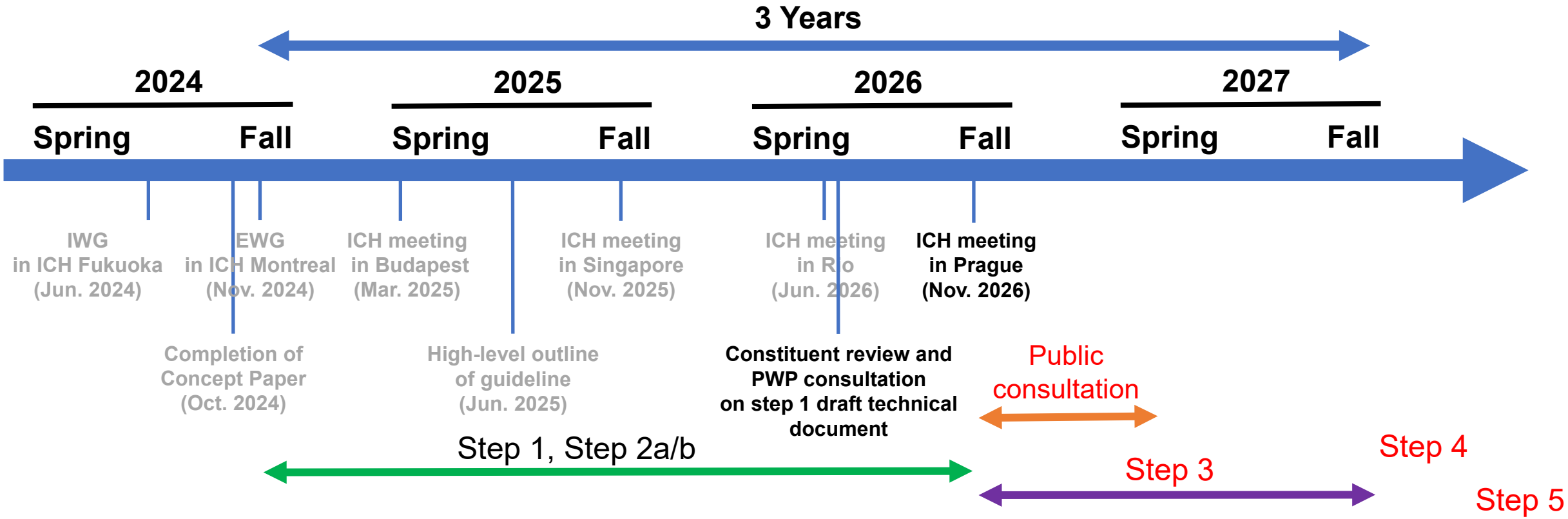
ICH face-to-face Rio de Janeiro meeting (4/5)

- ONTs with adequate nonclinical data may be considered as well characterised (hereafter referred to as well-characterised ONTs). Eligibility for an ONT to be considered well characterised is specific for the nonclinical endpoints being assessed and the route of administration. The concept of well-characterised ONTs may allow the leverage of existing nonclinical data from previous ONTs of the same class with a comparable composition, avoiding redundant conduct of nonclinical assessments and in addition, support the 3Rs principles. These compositions include the types and proportion of chemical modifications e.g., ribose (or other subunits), backbone, base components, number of strands, strand length and/or DDS

ICH face-to-face Rio de Janeiro meeting (5/5)

- The draft S13 guideline incorporates the concept of well-characterized ONT, based on which preclinical safety strategies were developed
  - General toxicity studies
  - Genotoxicity studies
  - Carcinogenicity studies
  - DART

Anticipated key milestones



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Conclusions

- The draft S13 guideline for the next step (constituent review and PWP consultation) was completed
- It incorporates the concept of well-characterized ONT, based on which preclinical safety strategies were developed
- The public consultation is scheduled to begin on late 2026

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