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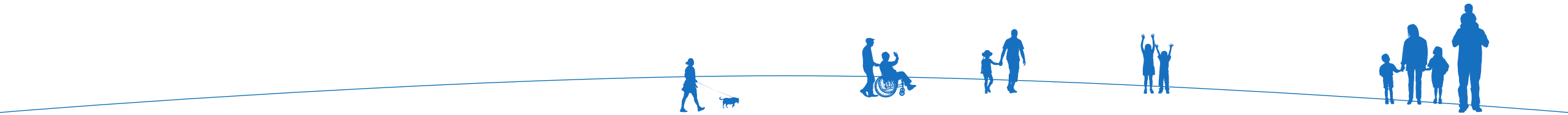
S13 EWG: Non-clinical Safety Evaluation of Oligonucleotide-based Therapeutics

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



Outline

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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Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases Guidance for Sponsor-Investigators DRAFT GUIDANCE (Apr, 2021)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Nonclinical Safety Assessment of Oligonucleotide-Based Therapeutics Guidance for Industry DRAFT GUIDANCE (Nov. 2024)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 Singapore meeting

- ✓ The key milestones so far are as follows:
  - Jun. 2024: Establishment of the S13 informal Working Group
  - Oct. 2024: Completion of Concept Paper
  - 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
- ✓ Regular plenary and subgroup teleconference meetings (for both 1-2x per month)
- ✓ Proposals for outline on dedicated ONT topics prepared by subgroups taking into account regional guidance and white paper/academic paper
- ✓ The draft guideline structure is currently following the structure of ICH S6 with some ONT specific aspects.

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ICH face-to-face Singapore meeting (1/3)

Twenty-three people from the following regulatory authorities and groups participated in person (11/16～19), 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	Mineo Matsumoto	Tetsuya Ohta

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

JPMA
PhRMA
EFPIA
BIO (Biotechnology Innovation Organization)
IGBA (International Generic and Biosimilar Medicines Association)
IFPMA (International Federation of Pharmaceutical Manufacturers & Associations)

Technical writer

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ICH face-to-face Singapore meeting (2/3)

Careful discussions were held on the following points which are also mentioned in ICH S13 Concept Paper(https://database.ich.org/sites/default/files/ICH_S13EWG_Concept_Paper_2024_1028.pdf).

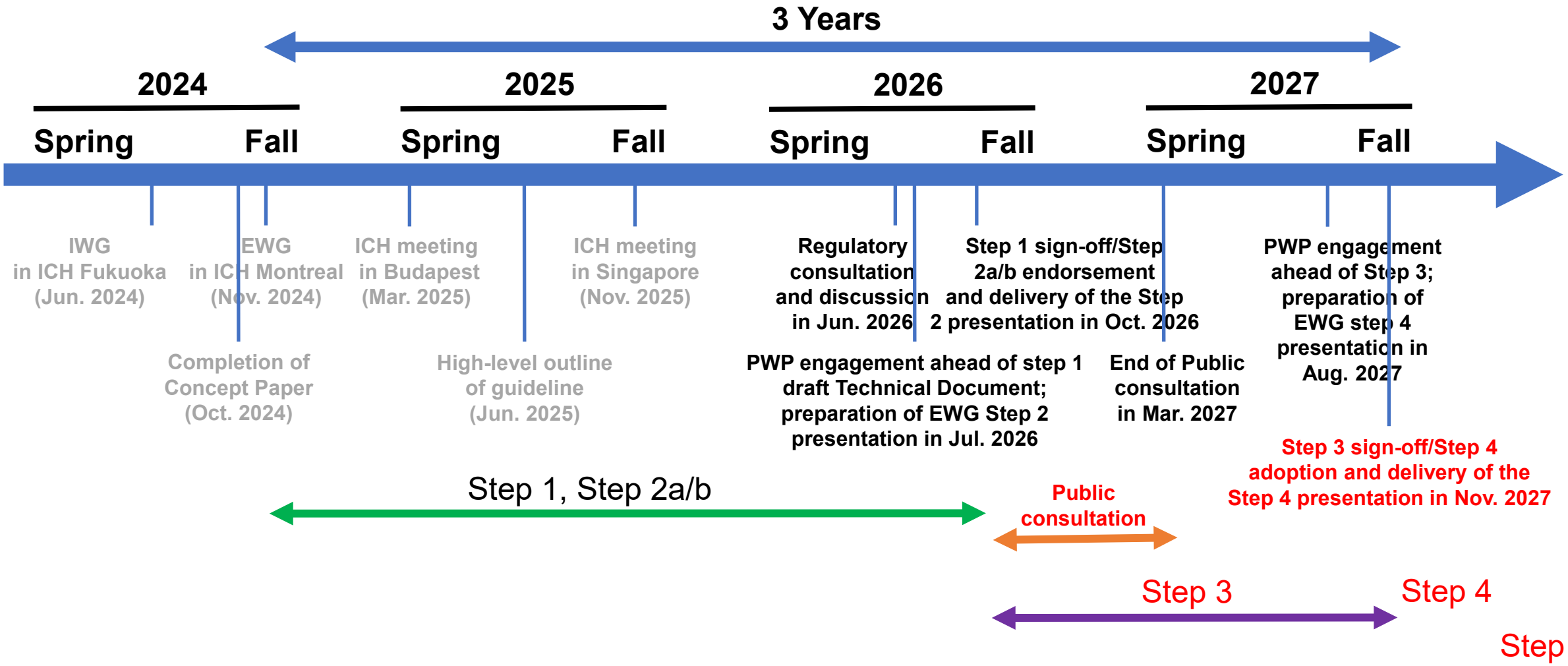
- ✓ ONTs in scope currently encompass antisense oligonucleotides (ASOs), including exon skippers, miRNA inhibitors (antagomirs) and RNA editing oligos (e.g. AIMers/ADAR MoA); small interfering (si)RNAs; miRNA mimics and small activating (sa)RNA. For other ONTs, like oligonucleotide-based aptamers, decoys, transfer (t)RNA and ONTs with CpG-motifs, the guideline will outline which items of the safety assessment concepts will be of relevance in assessing their nonclinical safety.

ICH face-to-face Singapore meeting (3/3)

Careful discussions were held on the following points which are also mentioned in ICH S13 Concept Paper(https://database.ich.org/sites/default/files/ICH_S13EWG_Concept_Paper_2024_1028.pdf).

- ✓ ONTs utilize technologies that potentially allow for leveraging existing safety data from previously authorized ONTs of the same mechanism of action (MoA) and/or similar chemistries and/or targeting moieties, thereby avoiding redundant non-clinical safety studies.
- ✓ ONTs differ from biopharmaceuticals and small molecules in several safety-relevant features, including pharmacokinetics, off-target effects, and species selection criteria.

Anticipated key milestones



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Conclusions

- The draft guideline structure is currently following the structure of ICH S6 with some ONT specific aspects.
- The current EWG discussion is on ONT specific safety aspects with regard to hybridization-dependent off-target effects, general toxicity, carcinogenicity and DART and related ONT specific adapted testing strategies.

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