Final Concept Paper

S13 EWG: Non-clinical Safety Evaluation of Oligonucleotide-based Therapeutics

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Endorsed by the Management Committee on 03 November 2024

1. Type of harmonisation action proposed

This concept paper proposes to initiate drafting of a new ICH safety guideline on the nonclinical assessment recommended to characterise the safety of oligonucleotide-based therapeutics (ONTs), intending to harmonise regulatory expectations and accelerate development for this modality. Special focus should be given to the types of non-clinical safety assessments, utilising up-to-date technologies and current scientific thinking. Harmonisation will enable the design and conduct of a more efficient non-clinical program for human clinical trials and marketing authorisation, meeting standards across all regulatory regions, and minimise animal use.

2. Background to the proposal and statement of the perceived problem

ONTs represent a rapidly evolving field with high potential to address a wide array of medical conditions, rare diseases and personalized treatments. 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. Various regional guidance documents and white papers have been published on the non-clinical safety assessment of ONTs. While ICH S6(R1) and S5(R3) mention ONTs, there is no dedicated ICH guideline relevant to the nonclinical safety assessment of this modality. In the absence of dedicated harmonised guidance, developers often refer to ICH M3(R2) for safety evaluations, which does not fully address the unique aspects of ONTs. This lack of a specific ICH guideline for ONTs leads to case-by-case decisions, potentially hampering efficient development strategies. Harmonising safety strategies in a specific guideline for ONTs would lead to more consistent and appropriate non-clinical safety evaluations across different regions. Additionally, it would support the 3R principles (replacement, reduction, and refinement) and improve patient access to ONTs.

3. Issues to be resolved and expected deliverable(s)

The aim is to have an up-to-date and forward-looking guideline that can cover rapid scientific advancements in this field. Therefore, the intent is for the proposed ICH guideline to be a combination of high-level principles and detailed technical guidance, relevant to all patient populations, including pediatrics, and will:

1. Define, in its scope, ONTs with different MoA, such as to induce mRNA degradation, modulate splicing events, restore missing protein, interfere with translation of target proteins or modulate non-coding RNA (e.g. micro (mi)RNA or long non-coding (lnc)RNA).

These ONTs 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. Due to their difference in MoA – guide (g)RNA for DNA editing, prophylactic and therapeutic DNA/RNA vaccines and coding mRNA used for other therapeutic purposes are out of scope. In general, therapeutic platforms capable of delivering ONTs to specific organs or tissues, like chemical modifications, conjugations or drug delivery carrier systems are also in scope. More details on which delivery systems are out of scope besides viral vectors, cells or cell-derived carrier systems, will be outlined in the guideline.

2. Harmonise general recommendations for non-clinical safety assessment of ONTs (on-target and off-target) and their delivery methods (chemical modification, conjugation, or complex delivery systems). These recommendations will relate to pharmacokinetic (distribution) and toxicokinetic studies, secondary pharmacology, safety pharmacology, general toxicity studies, genotoxicity, carcinogenicity, reproductive toxicity, immunotoxicity (both immunostimulatory properties and adaptive response e.g., anti-drug-antibodies), photosafety, juvenile toxicity and characterisation of metabolites and impurities, along with their timing in support of clinical development. In this context ONT-specific safety issues such as the applicability of surrogates to assess on-target exaggerated pharmacology, *in silico* and *in vitro* approaches on the hybridisation-dependent off-target effects, and translation of toxicity study results to humans (e.g., species specific effects, interspecies scaling and safety margin calculation considering route of administration) will be covered.
3. Describe aspects of study design unique to ONTs including in such areas as species selection; dosing regimen; high dose setting; route, frequency and duration of administration and recovery period.
4. Describe possible considerations for leveraging existing non-clinical data from well-established ONTs to allow adaptations of the non-clinical program for ONTs containing precedented chemical modifications.

4. Planning

There is regulatory experience with the nonclinical safety assessment of ONTs. Available recommendations from literature and local guidance documents will provide valuable input.

An ICH Expert Working Group (EWG) is called upon to achieve the intended goals. The EWG will require broad expertise in the non-clinical development of ONTs (e.g., general toxicity, genotoxicity, carcinogenicity, safety pharmacology, reproductive & developmental toxicity, juvenile toxicity, immunotoxicity, pharmacokinetics/ADME and *in silico* and *in vitro* approaches to minimize off-target effects).

The aim is to complete the guideline within 3 years from the appointment of the working group (approximately 18–24 months to reach *Steps 2a* and *2b*).

Key milestones:

• High-level outline of guideline: June 2025;

• Expected start of regulatory consultation and discussion: June 2026;

• *Step 1* and *2a/b* Sign-Off and Step 3 Public consultation: October 2026;

• *Step 3* Sign-off and *Step 4* Adoption of the harmonised guideline: November 2027

Consultation with other existing ICH Working groups: engagement with ICH E14/S7B working group to discuss QTc/cardiac safety aspects is envisioned.

5. Impacts of the project and post-hoc evaluation

The new guidance will benefit key stakeholders by harmonising non-clinical testing approaches considering the special characteristics of ONTs, which will accelerate the development of ONTs. The possibility to refer to well-established ONTs containing precedented chemical modifications may also avoid redundant non-clinical safety assessments, including animal studies.

The guideline will complement existing safety guidelines (ICH S1A, S2(R1), S7A/B, S5(R3), S6(R1), S9, M3(R2)) and dependencies with the ongoing efforts around ICH E14/S7B are foreseen.

The activation of this ICH project is likely to amplify momentum and benefit to the field especially at the time of publication of the Step 2a/b document (foreseen after 18–24 months from initiation of EWG activities). The major health and financial benefits would likely be realised shortly after *Step 5* (foreseen after 3 years from the initiation of activities). Post hoc evaluation of the impact of the project by the EWG might be necessary at which time the value of further follow up could be considered.