China and Japan Regional Joint Public Meeting on ICH

Topic 4: Cell Therapy and Regenerative Medicines

Updates on ICH S topics ：

Masakazu Hirata, Jihei Nishimura

(PMDA)

ICH S11 :

Outline of guideline for nonclinical safety testing in support of development of paediatric pharmaceuticals

小児医薬品開発の非臨床安全性試験に関するガイドラインの概略

ICH S1B（R1）:

Addendum to the guideline on testing for carcinogenicity of Pharmaceuticals

医薬品のがん原性試験に関するガイドラインの補遺

Jihei Nishimura
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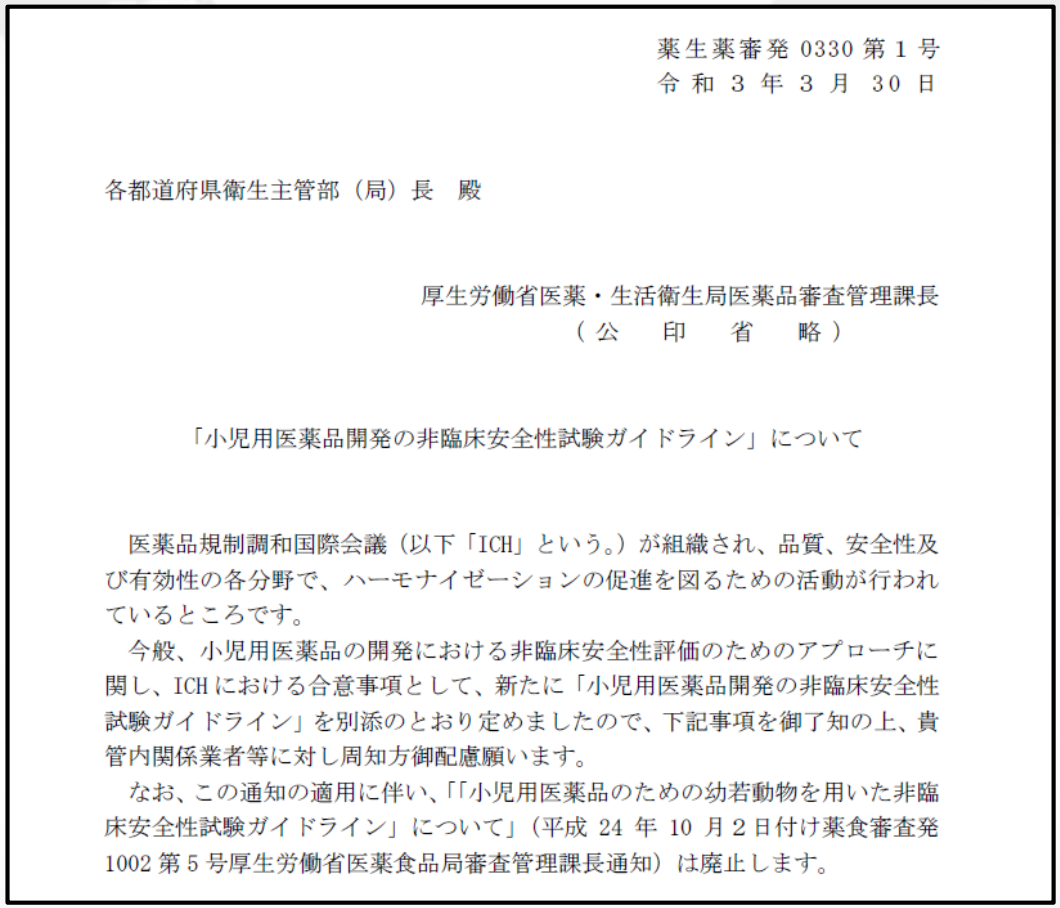
ICH S11: Timeline



薬生薬審発 0330 第 1 号
令 和 3 年 3 月 30 日

各都道府県衛生主管部（局）長　殿

厚生労働省医薬・生活衛生局医薬品審査管理課長
（ 公　印　省　略 ）

「小児用医薬品開発の非臨床安全性試験ガイドライン」について

医薬品規制調和国際会議（以下「ICH」という。）が組織され、品質、安全性及び有効性の各分野で、ハーモナイゼーションの促進を図るための活動が行われているところです。

今般、小児用医薬品の開発における非臨床安全性評価のためのアプローチに関し、ICH における合意事項として、新たに「小児用医薬品開発の非臨床安全性試験ガイドライン」を別添のとおり定めましたので、下記事項を御了知の上、貴管内関係業者等に対し周知方御配慮願います。

なお、この通知の適用に伴い、「「小児用医薬品のための幼若動物を用いた非臨床安全性試験ガイドライン」について」（平成 24 年 10 月 2 日付け薬食審査発 1002 第 5 号厚生労働省医薬食品局審査管理課長通知）は廃止します。

- **This document was developed based on a Concept Paper and Business Plan (approved 2014)**
  2014年にコンセプトペーパー及びプランが承認
- **This document has been signed off as a Step 4 document (April, 2020)**
  2020年4月にStep4到達
- **Training material has been published (August, 2020)**
  2020年8月にTraining materialを作成

- **The Step 5 document was notified by MHLW in March of 2021 in Japan**
  2021年3月にStep5（通知化）

Key Principles of S11 guideline

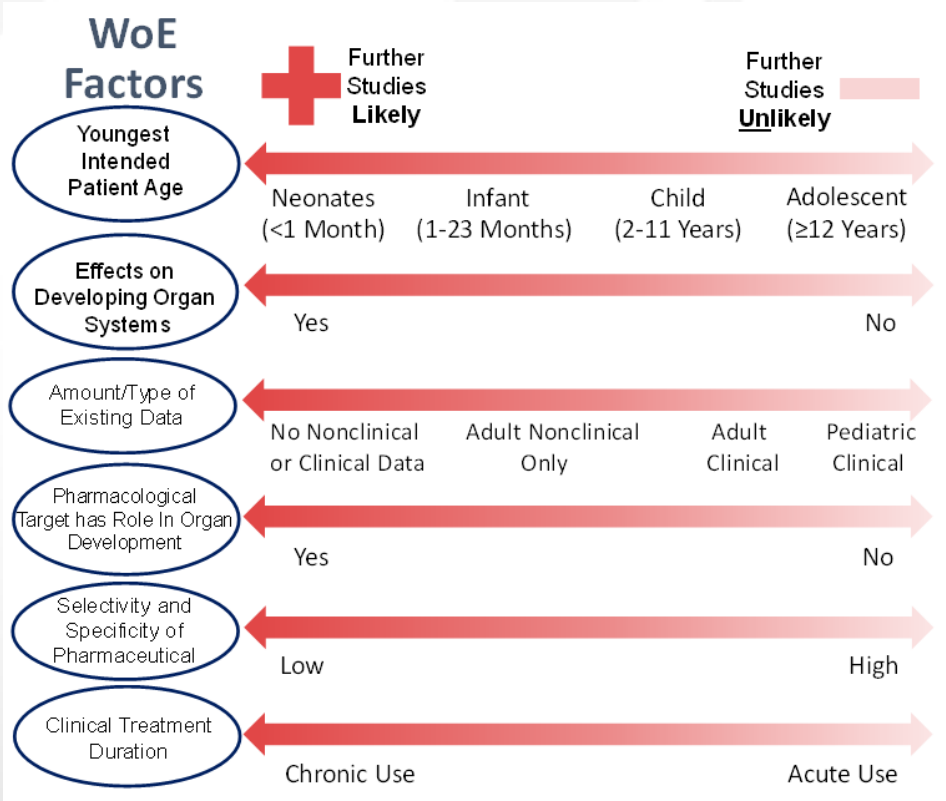
- **Harmonized criteria for need/no need for additional nonclinical investigations** 追加の非臨床試験の要否
  - **Weight of evidence (WoE) based decision** WoEアプローチに基づく決定
  - **Guidance for Paediatric-only development** 小児のみの開発
  - **Early consideration of nonclinical plan** 非臨床試験計画の早期検討

- **Harmonization of design of Juvenile Animal Study (JAS)**
  幼若動物試験のデザイン
  - **Customized JAS, with core and additional endpoint**
    主要エンドポイントと特定の懸念に対するするための追加エンドポイントを含む幼若動物試験

Key Principles of S11 guideline

- **Integrated assessment from several sources, to determine whether additional nonclinical investigations are needed, with emphasis on the factors considered most important to inform the clinical risk assessment**

複数の情報源からの統合的な評価により、小児の臨床におけるリスク評価のために、最も重要となる要因に重点を置いて、追加の非臨床調査が必要かどうかを判断する



Application and Outcome of the Weight of Evidence Evaluation

JAS Study

- **Should be aligned with the WoE outcome and customized with core and additional Endpoint.**
  WoEの結果を踏まえ、主要と追加のエンドポイントをカスタマイズする必要あり
- **Organ systems mature in different ways in different animal. Understanding the relative level of maturity across species is necessary.**
  器官系の成熟は、動物により異なるので、動物種間の成熟度の相対的なレベルを理解することが必要である
- **Generally single species (preferably rodent, the use of NHP is discouraged)**
  原則、単一動物種 （好ましくはげっ歯類、NHPの使用は推奨しない）

Another study

- **e.g., *in vitro* or *ex vivo* investigations**
  例えば、*in vitro*又は *ex vivo*試験

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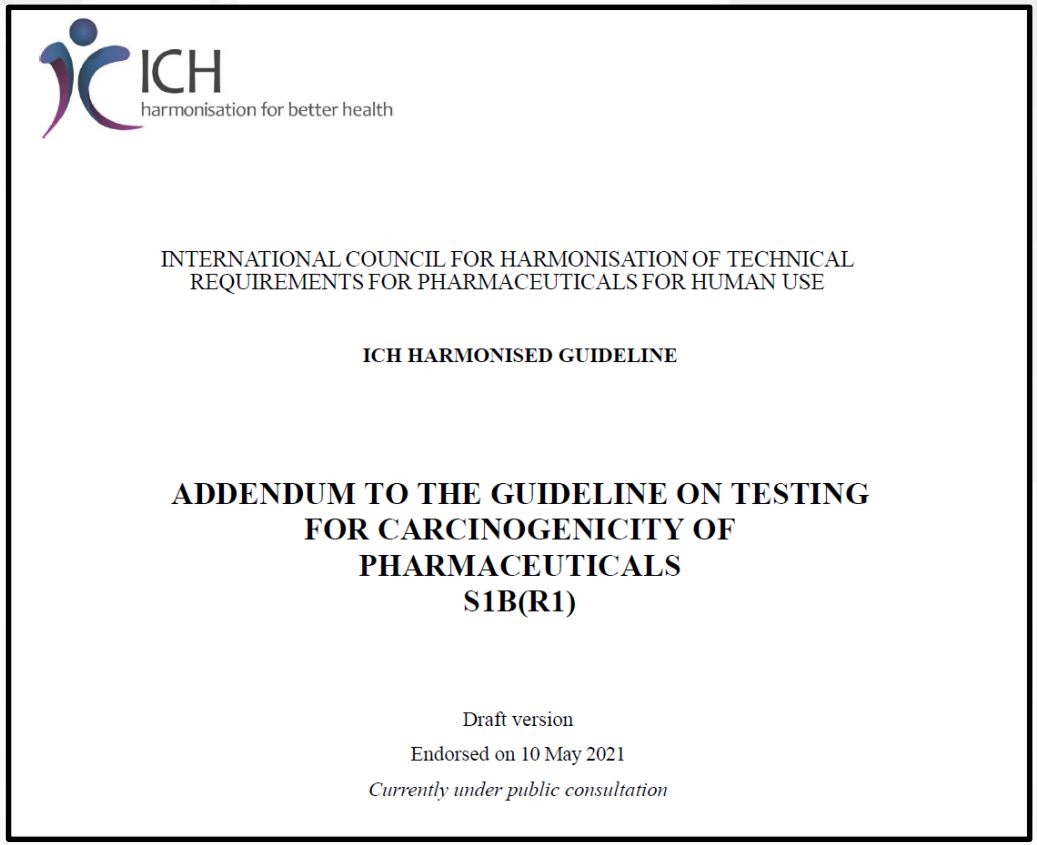
ICH S1B（R1）:

Addendum to the guideline on testing for carcinogenicity of Pharmaceuticals

「医薬品のがん原性試験に関するガイドラインの補遺」の進捗

Jihei Nishimura
(PMDA)

Timeline of S1B(R1)



ICH harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM TO THE GUIDELINE ON TESTING FOR CARCINOGENICITY OF PHARMACEUTICALS
S1B(R1)

Draft version

Endorsed on 10 May 2021

Currently under public consultation

- **This document was developed based on a Concept Paper and Business Plan (approved April 2012)**
  2012年4月から議論を開始
- **ICH S1 Expert Working Group Meeting was launched (June 2012)**
  2012 年6月にEWGが発足
- **This document endorsed as Step 2b document (10 May 2021)**
  2021 年5月10日にStep2b到達

Purpose of S1B(R1)

- **This Addendum demonstrates …**
  - New testing scheme for assessing human carcinogenic risk of small molecule pharmaceuticals by introducing an additional approach

低分子医薬品のヒトへのがん原性リスクを評価するための新しい評価の枠組みの提供

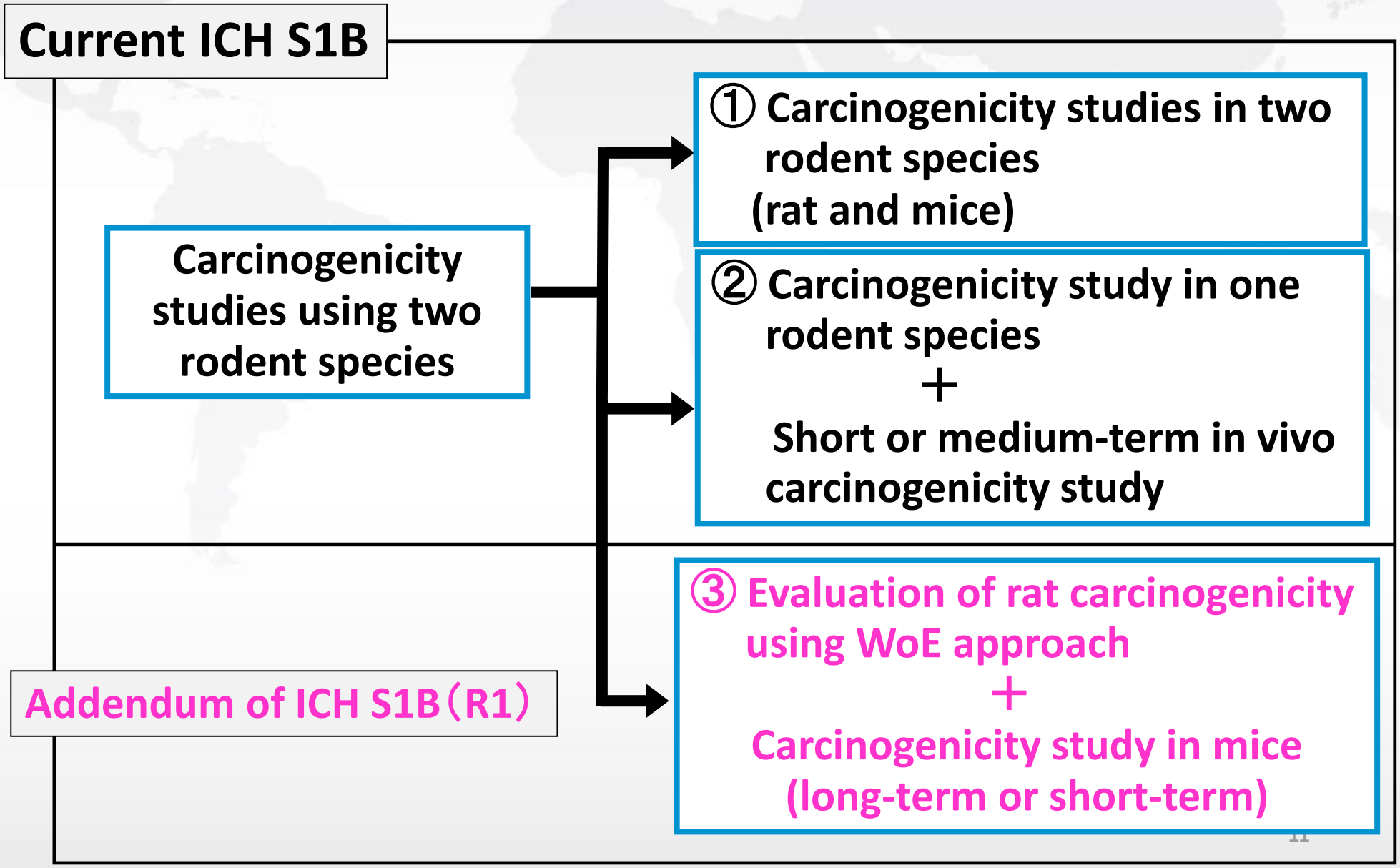
    - Carcinogenicity risk assessment by specific weight of evidence [WoE]) WoEによるがん原性評価
    - Application of this integrative approach may exempt the implementation of a rat 2-year study

ラット2年間がん原性試験の実施を免除できる可能性がある

  - Addition of setting based a plasma exposure ratio as approach for setting the high dose in the rasH2-Tg mouse model

rasH2マウスを用いた発がん性試験の高用量の設定に臨床曝露量比（×50倍）に基づく設定が可能

New scheme of carcinogenicity studies

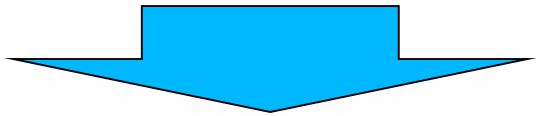


Factors to consider for a WoE assessment

1. **Data that inform carcinogenic potential based on drug target biology and the primary pharmacologic mechanism of the parent compound and active major human metabolites.**
   薬理学的観点からの発がん性に係わるデータ
2. **Results from secondary pharmacology screens for the parent compound and major metabolites that inform off-target potential, especially those that inform carcinogenic risk.**
   副次的薬理学作用からの発がん性に係わるデータ
3. **Histopathology data from repeated-dose toxicity studies completed with the test agent, with particular emphasis on the long term rat study, including exposure margin assessments of parent drug and major metabolites.**
   親及び代謝物の曝露評価を含む反復投与毒性試験の成績、特にラット長期反復投与毒性試験の病理組織成績

Factors to consider for a WoE assessment

4. **Evidence for hormonal perturbation, including knowledge of drug target and compensatory endocrine response mechanisms.**
   ホルモン変動の証拠
5. **Genetic toxicology study data using criteria from ICH S2(R1).**
   遺伝毒性の成績
6. **Evidence of immune modulation in accordance with ICH S8.**
   免疫毒性の証拠



This is an integrative approach that provides specific WoE criteria that inform whether or not a 2-year rat study adds value in completing a human carcinogenicity risk assessment.

2年間ラットがん原性試験を実施する代わりに、WoEアプローチによって、ヒトの発がんリスクを評価する

High dose selection

Current ICH S1B

Carcinogenicity studies in two rodent species (rat and mice)

Toxicity Endpoints (MTD)

Saturation of Absorption

Pharmacodynamic Endpoints

Maximum Feasible Dose

Limit Dose

Additional Endpoints

Pharmacokinetic Endpoints
(human exposure (AUC) × 25)

Short or medium-term in vivo carcinogenicity study

Toxicity Endpoints (MTD)

Saturation of Absorption

Pharmacodynamic Endpoints

Maximum Feasible Dose

Limit Dose

Additional Endpoints

~~Pharmacokinetic Endpoints
(human exposure (AUC) × 25)~~

High dose selection

Current ICH S1B

Carcinogenicity studies in two rodent species (rat and mice)

Toxicity Endpoints (MTD)

Saturation of Absorption

Pharmacodynamic Endpoints

Maximum Feasible Dose

Limit Dose

Additional Endpoints

Pharmacokinetic Endpoints
(human exposure (AUC) × 25)

Short or medium-term in vivo carcinogenicity study

Toxicity Endpoints (MTD)

Saturation of Absorption

Pharmacodynamic Endpoints

Maximum Feasible Dose

Limit Dose

Additional Endpoints

Pharmacokinetic Endpoints
(human exposure (AUC) × 50)
: only rasH2-Tg mouse model

Addendum of ICH S1B (R1)

Work plan:
Expected future Key Milestones

Expected future completion date	Milestone
Around the end of 2021	Step 3 receiving comments during the consultation period
May 2022	Step 4 Guideline

S12

Nonclinical Biodistribution Considerations for Gene Therapy Products

Step 2b

Masakazu Hirata (PMDA)

China and Japan Regional Joint Public Meeting on ICH, June 2021

Background to S12

- **Gene Therapy (GT) Products: legal or regulatory definition may vary by region(s), but scientific basis for consideration is applicable regardless**
- **GT products are designed to exert its effect through gene expression in cell-specific manner often with long duration, requiring specific consideration in nonclinical development**
- **Biodistribution (BD): the *in vivo* distribution, persistence, and clearance profile of the administered GT product**
- **Nonclinical BD data enable optimal design of nonclinical safety and pharmacology studies, supporting administration of GT products in early clinical trials as well as safety monitoring**

S12 Timeline

- Proposal for the topic and IWG establishment endorsed by Assembly at ICH Amsterdam meeting in May 2019
- IWG established in July 2019 with experts from ICH member organisations (ANVISA, Brazil; EC, Europe; FDA, United States; Health Canada, Canada; MFDS, Republic of Korea; MHLW/PMDA, Japan; NMPA, China; Swissmedic, Switzerland; TFDA, Chinese Taipei; BIO; EFPIA; JPMA; PhRMA) and observer organisations (CDSCO, India; IFMPA; WHO; TGA, Australia)
- S12 formally endorsed at ICH Singapore meeting in November 2019
- S12 Step 2 document endorsed at ICH Incheon (virtual) meeting in June 2021

Overview of topic

- **S12 nonclinical BD guideline describes considerations on:**
  - **GT product types that are within the scope of guideline**
  - **Timing of BD studies**
  - **Elements of a BD study design**
  - **Specific considerations**
  - **Application of nonclinical BD data to inform benefit-risk assessment and clinical trial design**
  - **Note: Germline transmission and shedding are not discussed in S12**

    Refer to ICH considerations on these topics: General principles to address the risk of inadvertent germline integration of gene therapy vectors (2006); General Principles to Address Virus and Vector Shedding (2009**);** Oncolytic Viruses (2009);

Outline of S12 Guideline

- **Objectives:**
  - **to provide harmonised recommendation for the component of a nonclinical development programme of GT products that supports clinical trial design, and help reduce the use of animals, in accordance with the 3Rs (reduce/refine/ replace) principles**
- **BD definition**
- **The GT product types that are within the guideline scope**
  - **Viral and non viral vectors, in vivo and ex vivo GT products**
- **Timing of BD studies**
  - **Assessment completed prior to initiation of the clinical trial**

Outline of S12 Guideline cont.

- **Elements of a BD study design**
  - **Test article, dose level(s), route of administration**
  - **Animal species or model selection**
  - **Biofluid and tissue sample collection**
- **Specific considerations**
  - **BD assay methods, GT expression product levels, immunogenicity, gonadal tissue assessment**
- **Application of nonclinical BD data to inform benefit-risk assessment and clinical trial design**

Work Plan: Expected Future Key Milestones

Expected Completion Date	Deliverable
May-Jun 2021	• *Step 1 sign-off and Step 2a/b endorsement*
Jan 2022	• *End of public consultation period expected*
Mar 2023	• *Step 3 sign-off*
Jun 2023	• *Step 4 adoption*

Thank you!

China and Japan Regional Joint Public Meeting on ICH, June 2021