ICH S1B(R1) ガイドラインの概要
Outline of the ICH S1B (R1) Guideline

小川久美子[1]、西村次平[2]、西川秋佳[1]
[1]国立医薬品食品衛生研究所、[2]（独）医薬品医療機器総合機構

Kumiko Ogawa[1], Jihei Nishimura[2], Akiyoshi Nishikawa[1]
1) NIHS, Kanagawa, 210-9501, Japan, 2) PMDA, Tokyo, 100-0013, Japan

Introduction

ICH S1B(R1)ガイドラインが、10年を超える国際共同前向き研究の末、令和4年8月に成立し、ICHウェブサイト公開された。本改定は、証拠の重み付け（weight of evidence：WoE）に基づいて、2年間ラットがん原性試験の実施がヒト発がんリスク評価に価値を付与すると考えられるか否かを判断する統合的なアプローチを導入し、2年間ラットがん原性試験を実施することなく、ヒトへの発がんリスクを評価することに道を開くものである。

ICH S1B(R1) guideline was published in August 2022 after over 10 years of international joint prospective study. In the addendum, a comprehensive approach based on a weight of evidence (WoE) is introduced to determine whether conducting a 2-year rat carcinogenicity study is considered to add value to human carcinogenicity risk assessment. Thus, it opens the way to assess carcinogenicity risk to humans without conducting a 2-year rat

Mission of the ICH

1990 年の創設以来、ICH は、医薬品開発のグローバル化に対応するために、徐々に進化してきた。ICH の使命は、安全で効果的、高品質の医薬品が、最も資源効率の高い方法で開発および登録されることを保証するために、世界中でより良い調和を達成することである。調和は、規制当局と業界の専門家が協力して科学的合意のプロセスを経て ICH ガイドラインを開発することによって達成される。このプロセスを成功させる鍵となるのは、ICH 規制当局の取り組みによる、最終ガイドラインの実装である。

Since its inception in 1990, ICH has gradually evolved, to respond to the increasingly global face of drug development. ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner. Harmonisation is achieved through the development of ICH Guidelines via a process of scientific consensus with regulatory and industry experts working side-by-side. Key to the success of this process is the commitment of the ICH regulators to implement the final Guidelines.

History of ICH S1B revision

Time line	Meeting	Activity
2011, Feb		S1A guideline revision proposal based on PhRMA's research paper
2011, Nov	Seville meeting	Formation of EWG, but not adopted as an official topic
2012, Feb	EWG TEL meeting 2	6 organizations agreed to become official topics
2013, Aug		Regulatory notice document (RND) (International prospective study was started)
2017, Dec		End of call for Carcinogenicity Assessment Document (CAD; 4-years)
2020, Mar	Amsterdam meeting (web)	Start drafting S1 addendum
2020, Dec		End of call for carcinogenicity Final Study Report (FSR; 7-years)
2021, May		ICH S1B(R1) draft, step 2 document
2021, Dec		End of public comment period
2022, May	Athens meeting	ICH S1B(R1) approved by the assembly
2022, June	EWG TEL meeting 59	Final agreement within EWG
2022, July		Step 3 document sign off
2022, Aug		Step 4 document

Prospective study conducted by DRAs

Part 1: Sponsor submits CAD and DRAs review data (August 2013-December 2017)

Submitted CAD, include prediction of tumor outcome and value category, no later than 14-18 months from start of in-life phase of 2-year rat study to 1 participating DRA

→ Distribute blinded CAD to other DRAs

→ DRAs independently review and categorize blinded CAD

→ DRAs periodically convene to discuss CAD and record concordance among DRAs and with sponsor regarding predicted tumor outcome and value category from CAD

→ Evaluate dataset

Part 2: Sponsor submit Summary of FSR and DRAs review data (November 2015 – December 2020)

Submit summary of FSR to same DRA

→ Distribute blinded FSR to other DRAs

→ DRAs independently review and conclude on outcome of 2-year rat study

→ DRAs periodically convene to discuss FSR and record concordance among DRAs and with sponsor regarding actual tumor outcome from FSR – following unblinding, assess value and concordance with CAD

WoE factors for consideration in a Carcinogenicity Assessment Document (CAD；がん原性評価文書) and requested contents

- 医薬品の標的及び投与経路の主薬理作用、副次的及び標的外の薬理作用、それらのラット及びヒトにおける知見
  (当該医薬品クラスの他の化合物に関する既知の情報)
- 遺伝毒性試験の成績
- ラット反復投与毒性試験 (6ヵ月) の病理組織学的評価
- ラット慢性毒性試験における曝露マージン
- ラットとヒトの代謝プロファイル
- ホルモンかく乱作用の証拠
- 免疫抑制作用
- 特殊な試験及びエンドポイント
- 非げっ歯類長期試験の成績
- トランスジェニックマウス試験

→

- 予測される試験結果
  (陽性/標的臓器又は陰性)
- ヒトのリスク評価における2年間ラットがん原性試験の実施意義
- 2年間ラットがん原性試験の免除に対するカテゴリー分類

↓

各規制当局も個別に内容を検討後、DRA間で協議

Number of cases evaluated in the prospective study

DRAs	FDA	EU	PMDA	Total
No. of FSR/No. of CAD	36/38	2/2	7/8	45/48

1 category 3 (split)
2 category 2 (unanimous)
cases were withdrawn

Category	1	2	3a	3b	Total
Definition	*highly likely to be tumorigenic in humans*	*tumorigenic potential for humans is uncertain*	*highly likely to be tumorigenic in rats but not in humans*	*highly likely not to be tumorigenic in both rats or humans*	
2-year rat study	Would not add value = Can be waived with labeling	Likely to add value = Need to be conducted	Would not add value = Can be waived	Would not add value = Can be waived	
Sponsor	3	11	14	17	45
DRA (Unanimous)	3	18	7	5	45
DRA (Split)			5	7	

24/45=53% was predicted as "not add value for conducting 2-year rat study"
Half of that, 12/45=27% was unanimously agreed in the DRAs.

ICH S1B(R1) : Step 4 Document

- **2022, August 4th, up loaded on ICH website (Step 4)** https://database.ich.org/sites/default/files/S1B-R1_FinalGuideline_2022_0719.pdf

ICH harmonisation for better health

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

ICH HARMONISED GUIDELINE

TESTING FOR CARCINOGENICITY OF PHARMACEUTICALS

S1B(R1)

Final version

Adopted on 4 August 2022

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

TESTING FOR CARCINOGENICITY OF PHARMACEUTICALS

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Japanese version and answers for public comments are up loaded on 2023, March 10th

https://www.pmda.go.jp/int-activities/int-harmony/ich/0051.html

https://public-comment.e-gov.go.jp/servlet/PcmFileDownload?seqNo=0000249843

ICH S1B(R1) : 1. 緒言 -Outline of Introduction

1.1 本補遺の適用範囲

- 本補遺は、ICH S1Aに記載のとおり、がん原性試験を必要とするすべての医薬品に適用される。

1.2 本補遺の目的

- これは、2 年間ラット試験が、ヒト発がんリスク評価に価値を付与する可能性が高いか否かを示す 特定の証拠の重み付け(weight of evidence: WoE)の基準を提供する統合的なアプロー チである。
- 本補遺では、rasH2−Tg マウスモデルにおける血漿中曝露量比に基づく 高用量設定のためのアプローチも追加されているが、ICH S1C(R2)における高用量選択 のための、その他のすべての推奨事項は継続して適用される。

1.1 Scope of the Addendum

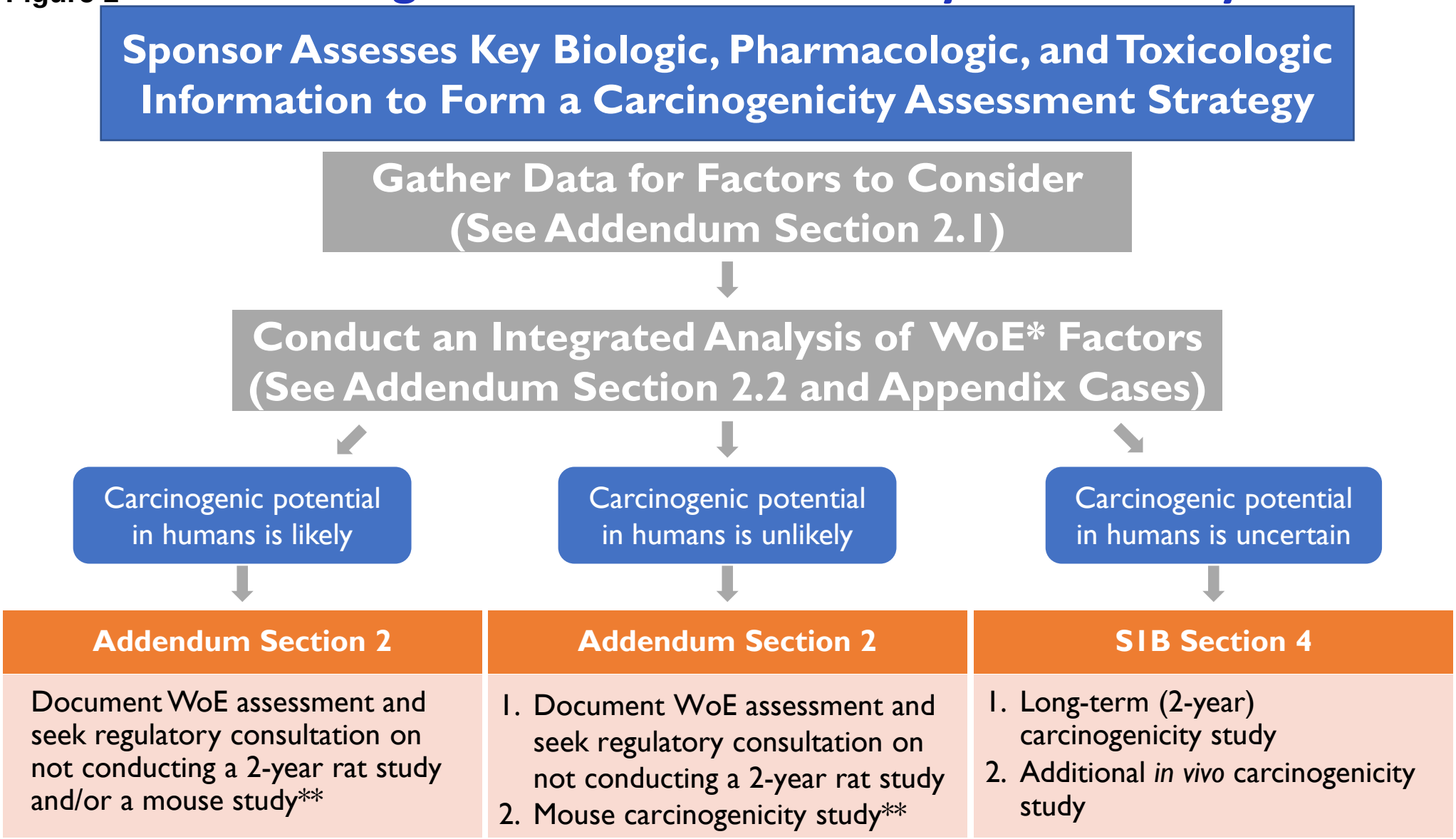
- This Addendum applies to all pharmaceuticals that need carcinogenicity testing as described in Guideline S1A.

1.2 Purpose of the Addendum

- This is an integrative approach that provides specific weight of evidence (WoE) criteria that inform whether or not a 2-year rat study is likely to add value to a human carcinogenicity risk assessment.
- The Addendum also adds a plasma exposure ratio-based approach for setting the high dose in the rasH2-Tg mouse model, while all other aspects of the recommendations for high dose selection in S1C(R2) Guideline still apply.

ICH S1B (R1) : Flow Scheme outlining key steps and options in developing a carcinogenicity assessment strategy and determining the added value of a 2-year rat study

Figure 1



***WoE=Weight of Evidence, **In some cases a mouse study may not be appropriate (see Section 2.3)**

ICH S1B (R1) : 2.1 Factors to Consider for a WoE Assessment

1) 薬理学的機序からの発がん性に関するデータ
2) 副次的薬理作用からの発がん性に関するデータ
   (オフターゲット作用の検討)
3) ラット反復投与毒性試験 (特に6ヵ月)の病理組織学的データ
4) ホルモンかく乱に関するエビデンス
5) 遺伝毒性に関するデータ (ICH S2(R1)参照)
6) 免疫調節に関するエビデンス (ICH S8参照)

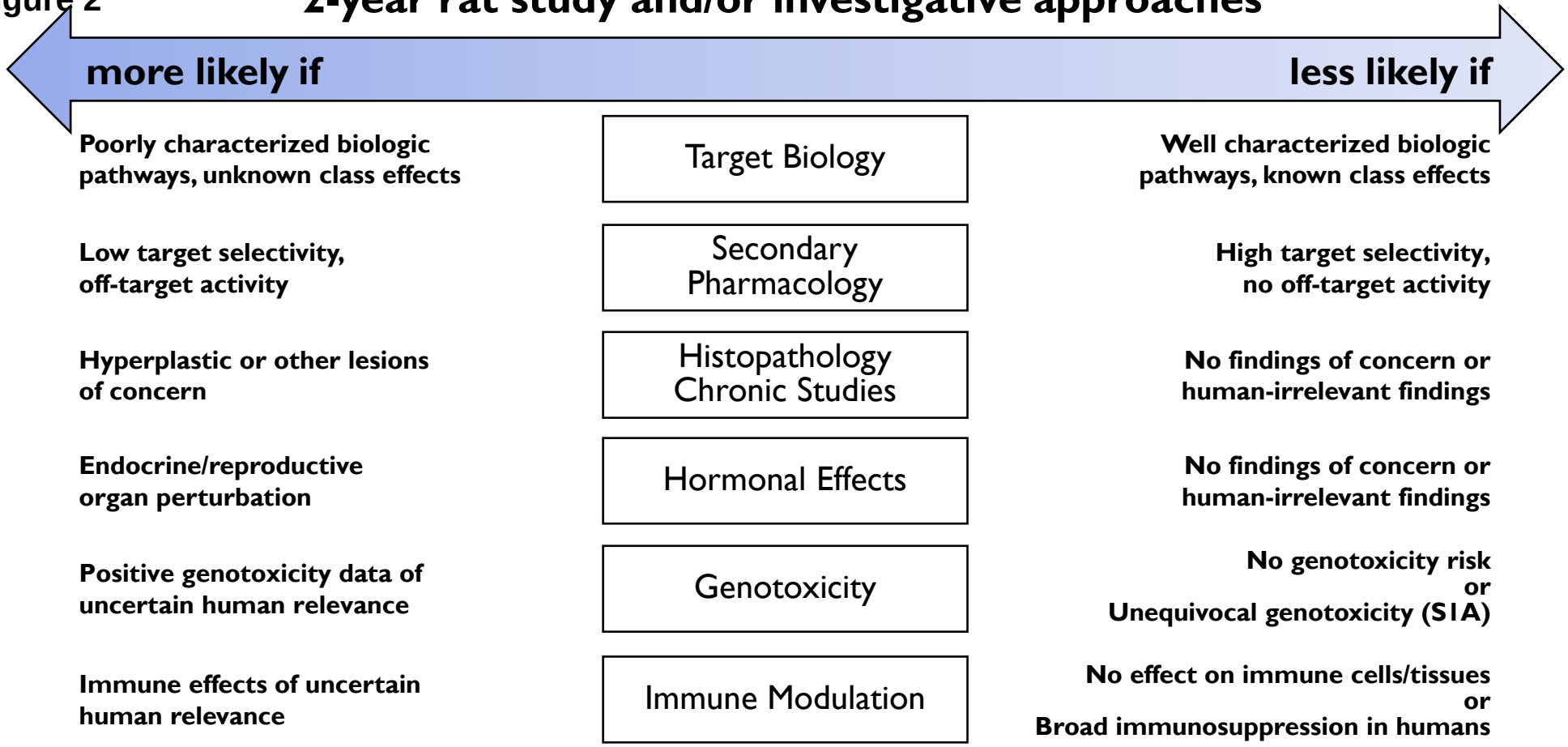
懸念がないことを、該当薬物又は類薬のデータあるいは文献等で示す

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

ICH S1B (R1) : 2.2 Integration of WoE Factors for Assessing Human Carcinogenic Risk

Figure 2

2-year rat study and/or investigative approaches



Potential Investigative Approaches to Further Inform Concerns Identified by WoE (see Section 2.1)

Nonclinical Approaches: Including but not limited to special histochemical stains, molecular biomarkers, serum hormone levels, immune cell function, *in vitro* or *in vivo* test systems, data from emerging technologies.

Clinical Data Approaches: Generated to inform human mechanistic relevance at therapeutic doses and exposures (e.g., urine drug concentrations and evidence of crystal formation; targeted measurements of clinical plasma hormonal alterations; human imaging data).

ICH S1B (R1)：2.3 Mouse Carcinogenicity Studies

WoE評価により2年間ラット試験が有意な価値をもたらさないことが示された化合物についても、ICH S1Bにある標準系統のマウスを用いた2年間試験、またはトランスジェニックモデルを用いた短期試験のいずれかのマウスのがん原性試験は、依然として発がん性評価計画の一部として推奨される。トランスジェニックモデルの使用は3R（reduce/refine/replace）の原則と一致しており、マウスで2年間試験を実施する科学的根拠がある場合を除き、このモデルを優先すべきである。

A carcinogenicity study in mice, either a 2-year study in a standard strain of mice or a short-term study in a transgenic model as in ICH S1B, remains a recommended component of a carcinogenicity assessment plan, even for those compounds for which the WoE assessment indicates a 2-year rat study would not contribute significant value.

Use of a transgenic model is consistent with the 3R (reduce/refine/replace) principles and this model should be prioritized unless there is a scientific rationale for conducting a 2-year study in mice.

Status of implementation

Region	Date	Status
FDA, United States	2022, August 4	Implemented
Swissmedic, Switzerland	2022, August 4	Implemented
MHLW/PMDA, Japan	2023, March 10	Implemented
EC, Europe	2023, March 16	Implemented
NMPA, China	2023, March 22	Implemented
TFDA, Chinese Taipei	2023, May 30	Implemented
Health Canada, Canada	2023, July 21	Implemented
MFDS, Republic of Korea	2023, December 31	In the process of implementation
ANVISA, Brazil		In the process of implementation
SFDA, Saudi Arabia COFEPRIS, Mexico TITCK, Turkey		Not yet implemented

Checked on November 24th

Aim of this information session

本説明会では、承認申請時の留意事項などを情報提供し、適切なS1B(R1)の実装に関する理解を図る機会としたい。

At this information session, we would like to provide information on points to be consider when applying for approval, and use this as an opportunity to gain understanding of appropriate S1B(R1) implementation.

Thank you!

S1B(R1) EWG に対する国際調和評議会の継続的な支援、S1B(R1) EWG の業界メンバーの本取り組みへの貴重な貢献、さらにCAD と試験報告書の提出による前向き評価研究に御協力いただきました製薬企業各社に感謝いたします。

We would like to acknowledge the International Council for Harmonisation for their persistent support of the S1B(R1) EWG, the industry members of the S1B(R1) EWG for their valuable contributions to this effort, and would like to thank the pharmaceutical companies that participated in the Prospective Evaluation Study with submission of CADs and study outcome reports.