ICH
harmonisation for better health

ICH-M7 (R2)

「潜在的発がんリスクを低減するための医薬品中DNA 反応性（変異原性）不純物の評価及び管理ガイドライン」の改定

国立医薬品食品衛生研究所・変異遺伝部
本間　正充

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

M7(R2) EWG Membership List

EC, Europe
NEW Dr. Roland Froetschl
Dr. Diana van Riet-Nales

FDA, US
Dr. Aisar Atrakchi
Dr. Stephen Miller
NEW Ms. Barbara Scott
NEW Dr. Timothy J. McGovern

HSA, Singapore
Dr. Looi Yee Hoo

MFDS, Republic of Korea
NEW Dr. Hyun-Kyung Kim

NMPA, China
NEW Mr. Lei Ma
NEW Mr. Hongyuan Da

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Dr. Lutz Mueller*
NEW Dr. Oliver Thiel

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NEW Dr. Amirthini Rajkumar
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Dr. Naoto Fukutsu
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MHLW/PMDA, Japan
Dr. Masamitsu Honma（Rapporteur）
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Dr. Junichi Fukuchi
NEW Dr. Keiji Hirabayashi

PhRMA
NEW Dr. Krista Dobo
NEW Dr. Christian Wetter

WSMI

＊:シャーロット会議欠席

History of ICH-M7

- ICH steering committee approved to develop the ICH-M7 guideline on June 2010
- ICH-M7 EWG initiated the discussion from Fukuoka meeting on November 2010
- ICH-M7 draft guideline (Step 2) was developed in San Diego meeting on November 2012
- ICH-M7 final guideline (Step 4) was completed in Minneapolis meeting during June 2014
- ICH-M7 (R1) draft guideline (Addendum; Step 2) was developed on March 2015 (without F2F meeting)
- ICH-M7 (R1) final guideline (Addendum; Step 4) was completed on March 2017 (without F2F meeting)
- ICH-M7 (R2) maintenance EWG started from June 2017
- ICH-M7 (R2) had F2F meeting in Charlotte on November 2018

Topics in the Charlotte meeting

- **Development of the 2nd addendum for compound specific acceptable intakes (AIs) or permitted daily exposures (PDEs) for new DNA reactive (mutagenic) impurities**
  - New data become available.
- **Update M7 text on HIV**
- **Development of Question & Answer document to clarify and address Quality and Safety issues**
  - Based on the experience gained from the application of M7-based control strategies for mutagenic impurities from 2014, the M7(R2) EWG intends to provide clarity and additional explanation to encourage proper implementation of the M7 concepts.

Status before the Charlotte meeting

Charlotte meeting is the 1st F2F meeting (Step 0)

- **The M7guideline reached step 4 in Minneapolis meeting in 2014 after several F2F meetings, and the M7(R1) guideline with addendum was finalized in 2017 without F2F meetings.**
- **The M7(R2) EWG is currently undertaking maintenance of the guideline to expand the addendum. The M7(R2) EWG has discussed candidate chemicals as impurities for the second addendum.**
- **The M7(R2) EWG also requested approval from MC to update M7 text and develop Questions and Answers for safety and quality topics in the concept paper. After approval, M7(R2) EWG members compiled information identified by their regions before the F2F meeting.**

Progress made at the Charlotte meeting

Development of the 2nd Addendum

- **A number of compounds are identified and selected for which a monograph will be prepared.**
- **Other compounds are more appropriately discussed under Q&A.**
- **Remaining compounds are agreed they are outside the scope of M7.**
- **Additional Qs and/or compounds may be submitted by mid of January 2019.**

ICH-M7 (R1) 1st Addendum

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH)

ICH HARMONISED GUIDELINE

ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK

M7(R1)

Current *Step 4* version

dated 31 March 2017

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 the ICH regions.

Appendix 3: Addendum to ICH M7

Application of the Principles of the ICH M7 Guideline to Calculation of Compound-Specific Acceptable Intakes

TABLE OF CONTENTS

14 chemicals

Proposed Chemicals

PhRMA, EFPIA

Regulatory Toxicology and Pharmacology 94 (2018) 172–182

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Potential impurities in drug substances: Compound-specific toxicology limits for 20 synthetic reagents and by-products, and a class-specific toxicology limit for alkyl bromides

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[m] Sanofi, Vitry-sur-Seine, France

JPMA, FDA, MHLW

- **Ethyl Bromide CAS# 74-96-4**
- **Isopropyl chloride CAS# 75-29-6**
- **2-bromoethanol CAS# 540-51-2**
- **EMS**
- **NDMA**
- **NDEA**

Candidate Chemicals from PhRMA and EFPIA

Consider for Inclusion in the Addendum

- **Acetaldehyde** – Mammalian cell mutagen and rodent carcinogen – Class 1 (Addendum)
- **Vinyl acetate** – Mammalian mutagen, and rodent carcinogen, Class 1 (Addendum)
- **Formaldehyde** - Mutagenic in Ames, Not a carcinogen via oral route, Carcinogen via the inhalation route – Class 1
- **Epichlorohydrin**- Mutagen and Carcinogen – Class 1
- **Styrene** – Mutagen and carcinogen – Class 1

Does Not Belong

- **Triphenylphosphine** – Not a mutagen, not tested in carci - Class 5
- **Triphenylphosphine oxide** - Not a mutagen, not tested in carci - Class 5
- **HATU** – Not a mutagen, not tested in carci - Class 5

Helpful for Q & A

- **Acrolein** – Mutagen, but not a rodent carcinogen - Class 5
- **P-aminophenol** – Mutagen, but not a carcinogen – Class 5
- **Methyl Bromide** - Mutagen, but not carcinogenic - Class 5
- **Mesityl oxide** – Not a mutagen, not tested in carci, structural alert- Class 5
- **P-Nitrophenol** – Not a mutagen, not a carcinogen, structural alert – Class 5
- **t-butyl chloride** – conflicting Ames data, not tested in carci – Class 5
- **HOAt** – conflicting Ames data, not tested in carci - Class 5
- **EMS** – Mutagenic, carcinogenic – Class 1
- **EDAC** – Mutagen, negative in vivo genotoxicity testing, not tested in Carci – Class 5
- **Acetamide** – Not a mutagen, but is a rodent carcinogen – Class 5
- **Hydroxylamine** - Not a mutagen, but is a rodent carcinogen – Class 5
- **Methyl iodide**

Revisit (after Charlotte meeting)

- **Monofunctional alkyl bromides** –Class 1 (mitigation of TTC)

Progress made at the Charlotte meeting

Update M7 Text on HIV

General agreement reached and final confirmation pending.

- **Treatment for HIV has advanced.**
- **Change in the treatment duration from 1-10 years to >10 years to lifetime is appropriate.**
- **Implement change in the guideline by moving "HIV" in the one table on treatment duration and adjust the footnote.**
- **Draft Q&A to explain the reason for the change and how the change would affect future regulatory submissions (initial version agreed).**

Note 7 **Table 4**: Examples of clinical use scenarios with different treatment durations for applying acceptable intakes

Scenario[1]	Acceptable Intake (µg/day)
Treatment duration of ≤ 1 month: e.g., drugs used in emergency procedures (antidotes, anesthesia, acute ischemic stroke), actinic keratosis, treatment of lice	120
Treatment duration of > 1-12 months: e.g., anti-infective therapy with maximum up to 12 months treatment (HCV), parenteral nutrients, prophylactic flu drugs (~ 5 months), peptic ulcer, Assisted Reproductive Technology (ART), pre-term labor, preeclampsia, pre-surgical (hysterectomy) treatment, fracture healing (these are acute use but with long half-lives)	20
Treatment duration of >1-10 years: e.g., stage of disease with short life expectancy (severe Alzheimer's), non-genotoxic anticancer treatment being used in a patient population with longer term survival (breast cancer, chronic myelogenous leukemia), drugs specifically labeled for less than 10 years of use, drugs administered intermittently to treat acute recurring symptoms[2] (chronic Herpes, gout attacks, substance dependence such as smoking cessation), macular degeneration, HIV[3]	10
Treatment duration of >10 years to lifetime: e.g., chronic use indications with high likelihood for lifetime use across broader age range (hypertension, dyslipidemia, asthma, Alzheimer's (except severe Alzheimer disease), hormone therapy (e.g., growth hormone, thyroid hormone, parathyroid hormone), lipodystrophy, schizophrenia, depression, psoriasis, atopic dermatitis, Chronic Obstructive Pulmonary Disease (COPD), cystic fibrosis, seasonal and perennial allergic rhinitis	1.5

[1] This table shows general examples; each example should be examined on a case-by-case basis. For example, 10 µg/day may be acceptable in cases where the life expectancy of the patient may be limited e.g., severe Alzheimer's disease, even though the drug use could exceed 10 year duration.

[2] Intermittent use over a period >10 years but based on calculated cumulative dose it falls under the >1-10 year category.

[3] HIV is considered a chronic indication but resistance develops to the drugs after 5-10 years and the therapy is changed to other HIV drugs.

HIVを>10 yearsに移動

Foot Noteの変更

"Changed in M7(R2) from 1-10 years to lifetime because of clinical treatment advances. See Q&A."

Progress made at the Charlotte meeting

Development of the Q&A

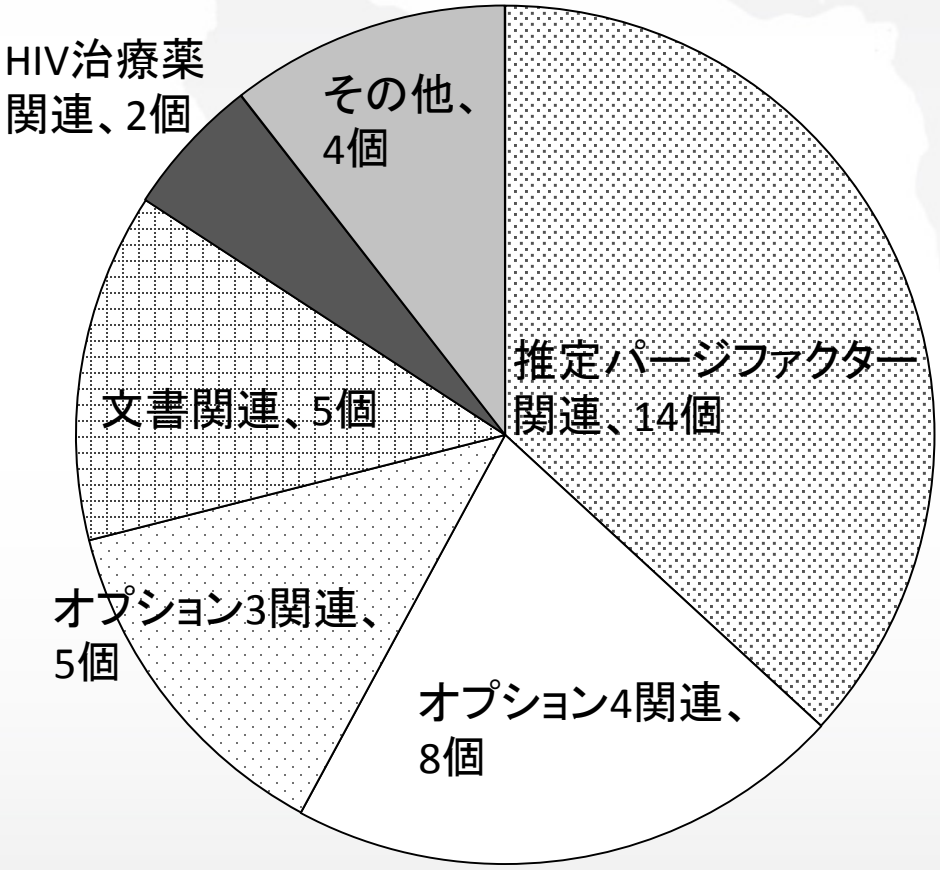
- **Started to evaluate 38 quality and 65 safety related questions submitted to the EWG.**
- **Identifying the overlapping questions and combining**
  - **The EWG will focus on the most relevant topics that need to be addressed.**
- **Intention to condense to approximately 20 for the Q&A**
- **Additional questions may be submitted by mid January 2019.**

Quality関連のQ&Aに関して
～起点～

- M7が導入されて以来、変異原性不純物の管理戦略の妥当性を示す上で、推定パージファクター利用の重要性は高まってきた。しかしながら、その際に留意すべき具体的な点はM7に明示されていない。
- M7の導入後に得られた経験を踏まえ、推定パージファクターに関する留意事項も含め、Q&Aとして明示する期待と需要が高まってきた。

Quality関連のQ&Aに関して ～議論の結果～

会議開始時（合計38個）

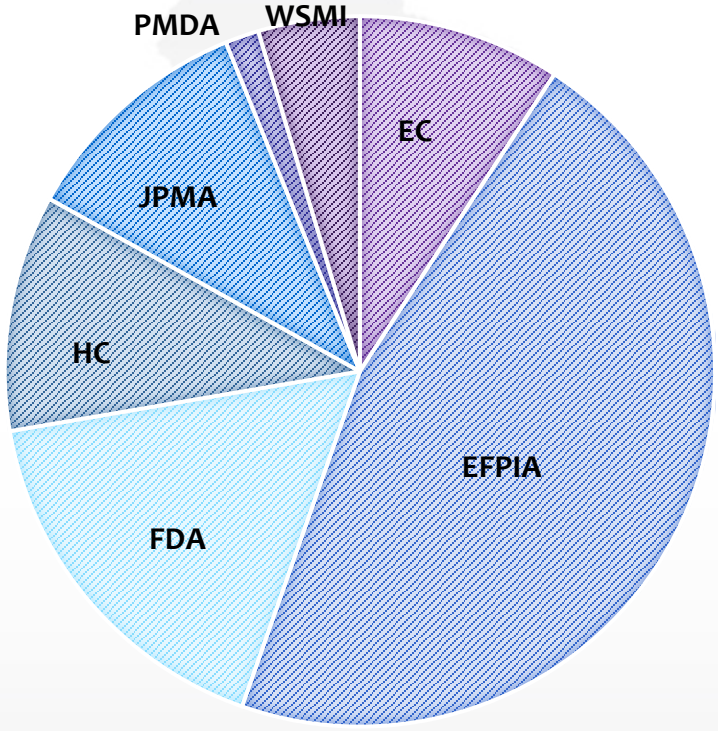


会議後（10個程度）

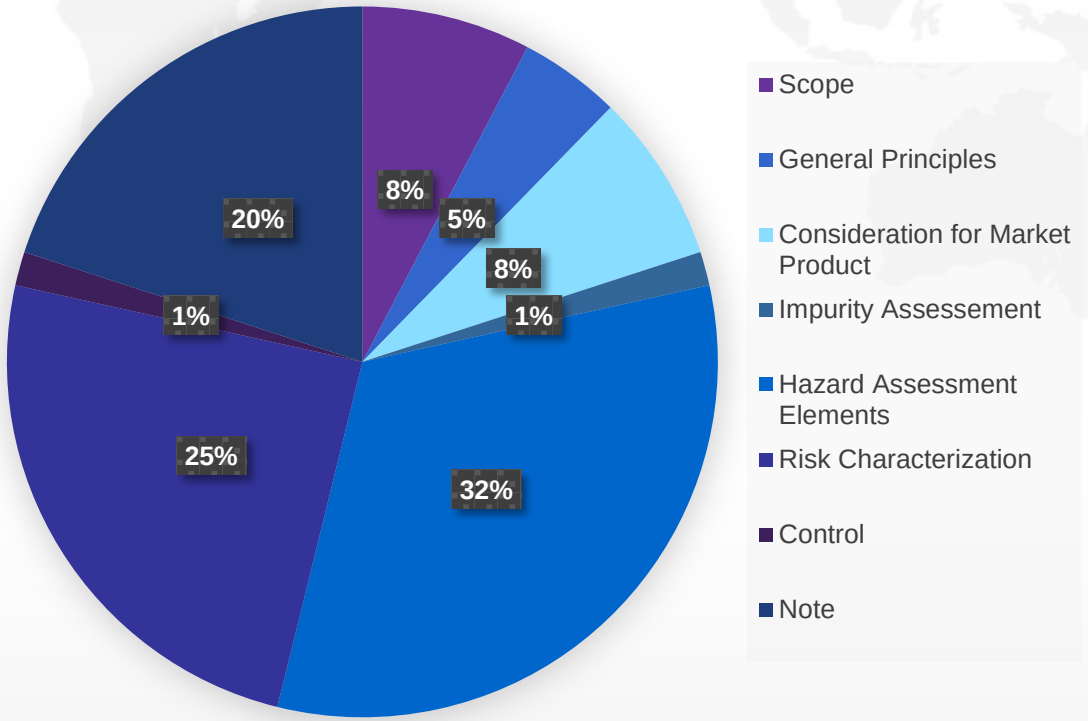
- 主な議論・作業：
  - 内容に重複のあるものを一纏めに。
  - Answerがガイドライン本文の繰り返しになるQuestionを回避。
- 整理・集約の主な結果：
  - 適用に関連するもの
  - オプション2に関連するもの
  - オプション3に関連するもの
  - オプション4に関連するもの
  - CTD等の文書に関連するもの
  - HIV治療薬に関する本文の修正に関連するもの

Safety関連のQ&Aに関して

65のQ&Aの提案機関



65のQ&Aの内容



＊Safetyで10程度、QualityとSafetyで合計20程度のQ&Aを目指す（Q11）

Conclusions

- **M7(R2) EWG worked for updating M7 text with small changes according to the concept paper. The work was completed, and all EWG members agreed.**
- **M7(R2) EWG identified chemicals which can be considered for the 2nd addendum. EWG will accept additional chemicals for the addendum by mid-Jan 2019.**
- **M7(R2) EWG collected and is discussing Q&As received from various regions. EWG will accept additional Q&As for consideration by mid-Jan 2019.**

Work plan: Expected future Key Milestones

Expected Completion date	Deliverable
Jan. 2019	• Regions submit any additional compounds for the addendum list and Q&A proposals
Jun. 2019	• Plan to meet F2F and continuing working on the draft of the 2nd addendum and the Q&A document
Nov. 2019	• *Step 1*, updating M7 text, draft of the 2nd addendum and Q&A document

- Endorsement to nominate a new Rapporteur
  - Masamitsu Honma will be rapporteur until June 2019 (2 years).

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