



国立医薬品食品衛生研究所

National Institute of Health Sciences

The 5th International Webinar Conference on
Pharmaceutical Quality Regulatory Sciences
Jointly Organized by NIFDS, PMRJ and RFPQ



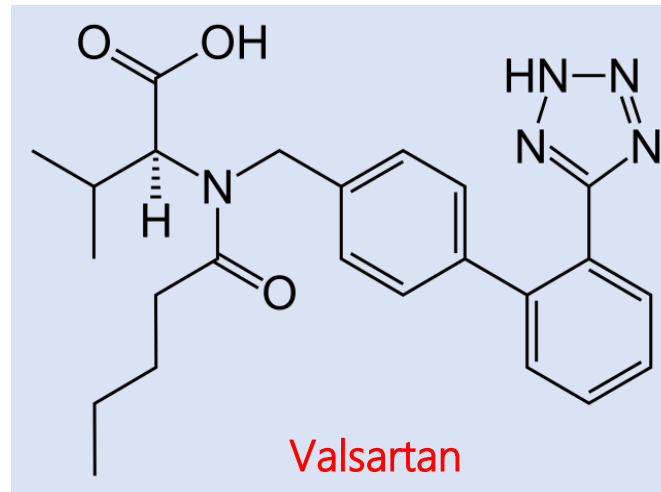
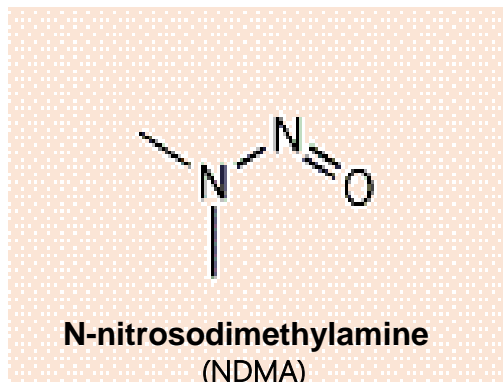
Enhancing safety and quality of life
through scientific research

Assessment and Control of Mutagenic Impurities in Pharmaceuticals

Masamitsu Honma
National Institute of Health Sciences, Japan

Disclaimer

The findings and conclusions in this presentation reflect the views of the authors and should not be construed to represent MHLW or NIHS's views or policies.



報道関係者 各位

医薬品自主回収のお知らせ（クラスI）

（販売名：バルサルタン錠20mg・40mg・80mg・160mg「AA」）

、別添のとおり、あすか製薬株式会社が下記の医薬品の自主回収に着手した旨の情報提供がなされさせていただきます。

記

ン錠20mg・40mg・80mg・160mg「AA」

[る報道発表資料](#) [PDF形式：106KB]

[式会社における報道発表資料](#) [PDF形式：229KB]



▶ 報道・広報	
▶	厚生労働省広報基本指針
▶	大臣記者会見
▶	報道発表資料
▶	広報・出版
▶	行事・会議の予定
▶	広報実施計画
▶	国民参加の場



▶ [情報配信サービスメニューマガ登録](#)



▶ [子どものページ](#)

携帯ホームページ



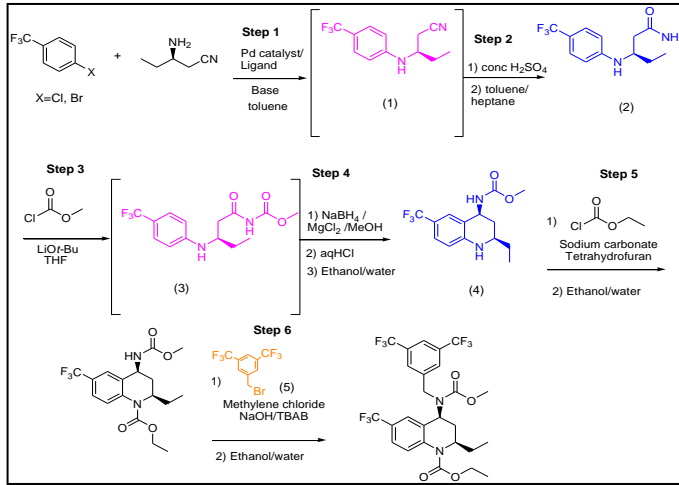
▶ [携帯版ホームページ](#)では、緊急情報や厚生労働省のご案内などを掲載しています。

July 6, 2018 MHLW

Topics

- I. **ICH-M7 Guideline: Assessment and Control of Mutagenic Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk**
- II. **Cancer risk of nitrosamine compounds contained as impurities in pharmaceuticals**

What Is Mutagenic Impurity?



**Synthetic Route of Drug Substances
(Byproducts)**

**Degradation from Drug Substances
(Degradants)**

Impurities

Mutagenic or non-mutagenic?

ICH Quality Guidelines on Pharmaceutical Impurities

- ICH Q3A: Guidelines on impurities of new drug substances
- ICH Q3B: Guidelines on impurities in new drug products

	Maximum daily dose	Qualification Threshold
Drug substance	$\leq 2\text{g}$ $> 2\text{g}$	0.15% or 1 mg, whichever is lower 0.05%
Drug product	$< 10\text{ mg}$ 10 – 100 mg $> 100\text{ mg} - 2\text{ g}$ $> 2\text{g}$	1% or 50 μg , whichever is lower 0.5% or 200 μg , whichever is lower 0.2% or 3 mg, whichever is lower 0.15%

A Problem in ICH Q3A/B (1)

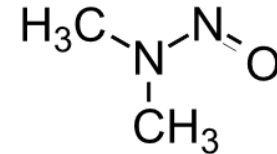
In Q3B;

It is permitted if a drug product (2g/day) contains 0.15% impurity.



In maximum, 3mg/day (0.06mg/kg/day)
of impurity is exposed.

0.1mg/kg/day of NDMA can produce liver tumor in 50% of rats.



N-nitrosodimethylamine
(NDMA)

A Problem in ICH Q3A/B (2)

7. QUALIFICATION OF IMPURITIES (Q3A)

Although **this guideline is not intended to apply during the clinical research stage of development**, in the later stages of development the thresholds in this guideline can be useful in evaluating new impurities observed in drug substance batches prepared by the proposed commercial process.

History of Impurities' Guidelines and Guidances

Before ICH-M7

- **March 1995;** ICH-Q3A guideline
- **November 1996;** ICH-Q3B guideline
- **January 2006;** PhRMA white paper (Muller et al.)
- **July 2006;** EMA-CHMP: Guidelines on the limits of genotoxic impurities
- **December 2008;** US-FDA: Guidance for Industry; Genotoxic and carcinogenic impurities in drug substances and products: Recommended approaches

From ICH-M7

- ◆ **June 2010;** The ICH steering committee approved to develop the ICH mutagenic impurity guideline.
- ◆ **November 2010;** The ICH-M7 EWG initiated the discussion of this topic from Fukuoka meeting.
- ◆ **November 2012;** ICH-M7 draft guideline (Step 1) was developed in San Diego meeting.
- ◆ **June 2014;** ICH-M7 final guideline (Step 4) was completed in Minneapolis meeting.
- ◆ **March 2105;** ICH-M7 (R1) draft guideline (Addendum; Step 1) was developed (without F2F meeting).
- ◆ **March 2017;** ICH-M7 (R1) final guideline (Addendum; Step 4) was completed (without F2F meeting).
- ◆ **July 2018;** ICH-M7 (R2) started. Q&A and 2nd Addendum were discussed.
- ◆ **April 2020;** ICH-M7 (R2) Q&A (Step1) was developed in the Web meeting.

ICH-M7 Guideline



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

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

M7

Current Step 4 version
dated 23 June 2014

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 European Union, Japan and USA.

ICH-M7 (June 2014)

1. INTRODUCTION

2. SCOPE OF GUIDELINE

3. GENERAL PRINCIPLES

4. CONSIDERATIONS FOR MARKETED PRODUCTS

5. DRUG SUBSTANCE AND DRUG PRODUCT IMPURITY

ASSESSMENT

6. HAZARD ASSESSMENT ELEMENTS.

7. RISK CHARACTERIZATION

8. CONTROL

9. DOCUMENTATION

NOTES

GLOSSARY

REFERENCES

APPENDICES

Mainly Quality Issues

Mainly Safety Issues

Major Safety Points in ICH-M7 Guideline for Assessment of Mutagenic Impurities

< Hazard Identification >

- The focus of this guideline is on mutagenic (DNA reactive) substances which can be detected by the Ames assay
- Evaluation of mutagenicity of impurities using the (Quantitative) Structure Activity Relationship

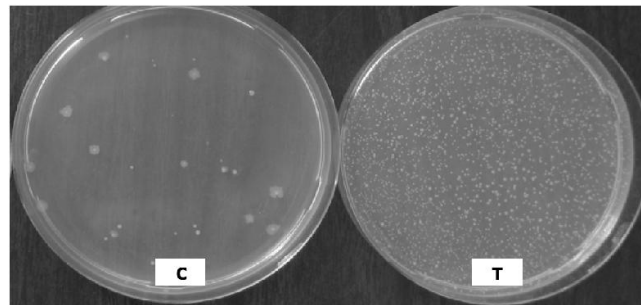
< Risk Assessment >

- Life time cancer risk caused by a mutagenic impurity should be controlled less than 10^{-5}
- Application of a Threshold of Toxicological Concern (TTC) to control mutagenic impurities
- Risk mitigation considering treatment duration and carcinogenic potency of mutagens

Hazard Identification (1)

Ames Test

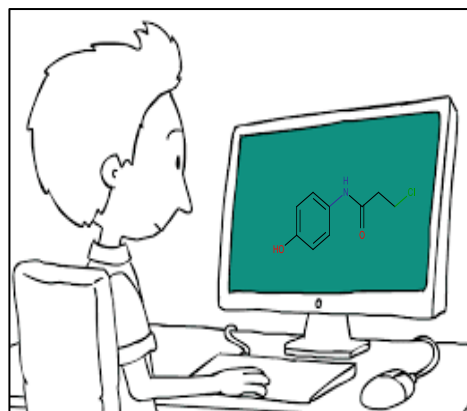
- The focus of this guideline is on **mutagenic substances** that have a potential to directly cause DNA damage when present at low levels, leading to mutations; therefore, potentially causing cancer.
- This type of mutagenic carcinogen is usually detected in a bacterial reverse mutation (mutagenicity) assay (**Ames test**).
- Other types of genotoxicants that are non-mutagenic typically have threshold mechanisms and usually do not pose carcinogenic risk in humans at the level ordinarily present as impurities.



Hazard Identification (2)

Quantitative Structure-Activity Relationships (Q)SAR

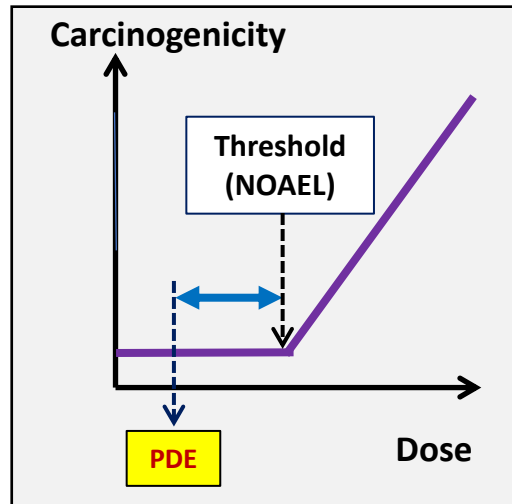
- Structure-based assessments are useful for predicting bacterial mutagenicity outcomes based upon the established knowledge.
- Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be **expert rule based** and the second methodology should be **statistical based**.
- The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule-based and statistical) is sufficient to conclude that the impurity is of no mutagenic concern, and no further testing is recommended.



Risk Assessment (1)

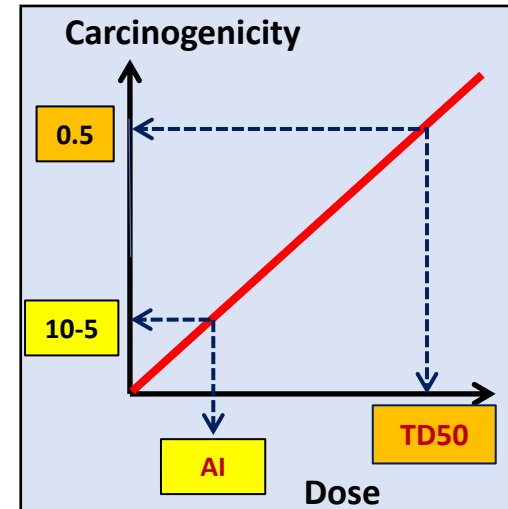
Calculation of Acceptable Level of Carcinogens

Non-Mutagenic Carcinogens



Permissible Daily Exposure (PDE)

Mutagenic Carcinogens



Virtually Safe Dose (VSD), Acceptable Intake (AI)

Lifetime Risk of Cause of Death in Japan (from the report of the Central Environment Council)

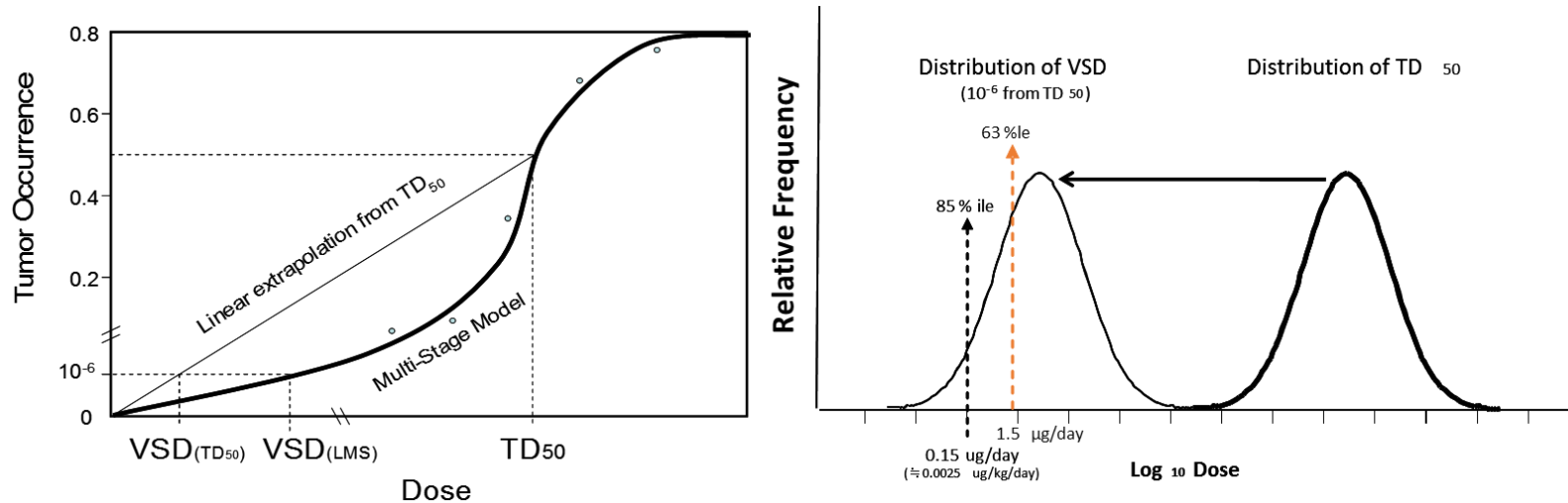
Traffic accident	6×10^{-3}
Water accident	7×10^{-4}
Fire	6×10^{-4}
Natural disaster	3×10^{-5}
Lightning strike	2×10^{-6}

Cancer Mortality and Morbidity Rate in Japanese (National Cancer Center)

- Dying from cancer in a lifetime is 25% for men and 16% for women.
- Getting cancer in a lifetime are 62% for men and 47% for women.

Risk Assessment (2)

Grounds for Calculating TTC



Mutagen, but no Carcinogenic data

**1.5 µg/day
(Threshold of Toxicological Concern; TTC)**

10⁻⁵ carcinogenic risk, if assuming that 10% of unknown chemicals are carcinogens.

Threshold of Toxicological Concern (TTC)

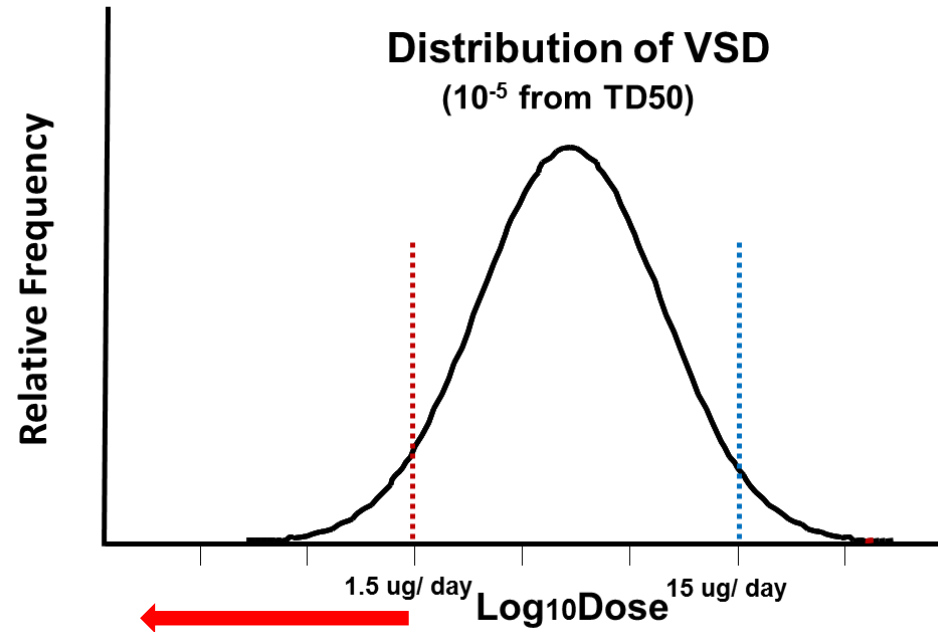
Percentage of carcinogenic substances in unknown compound and percentage of compounds that can control carcinogenic risk by setting threshold

Setting threshold (ug/day)	Estimated Percentage of Carcinogen							
	10 ⁻⁵ Risk				10 ⁻⁶ Risk			
	100%	50%	30%	10%	100%	50%	30%	10%
0.15	86	93	97	99	96	98	99	99
0.3	80	90	96	98	94	97	99	99
0.6	74	87	95	97	91	96	98	99
1.5	63	82	93	96	86	96	97	99
3	55	77	91	95	80	90	96	98
6	46	73	89	95	74	87	95	97

(Munro 1990)

Risk Assessment (2)

Cohort of Concern (COC)



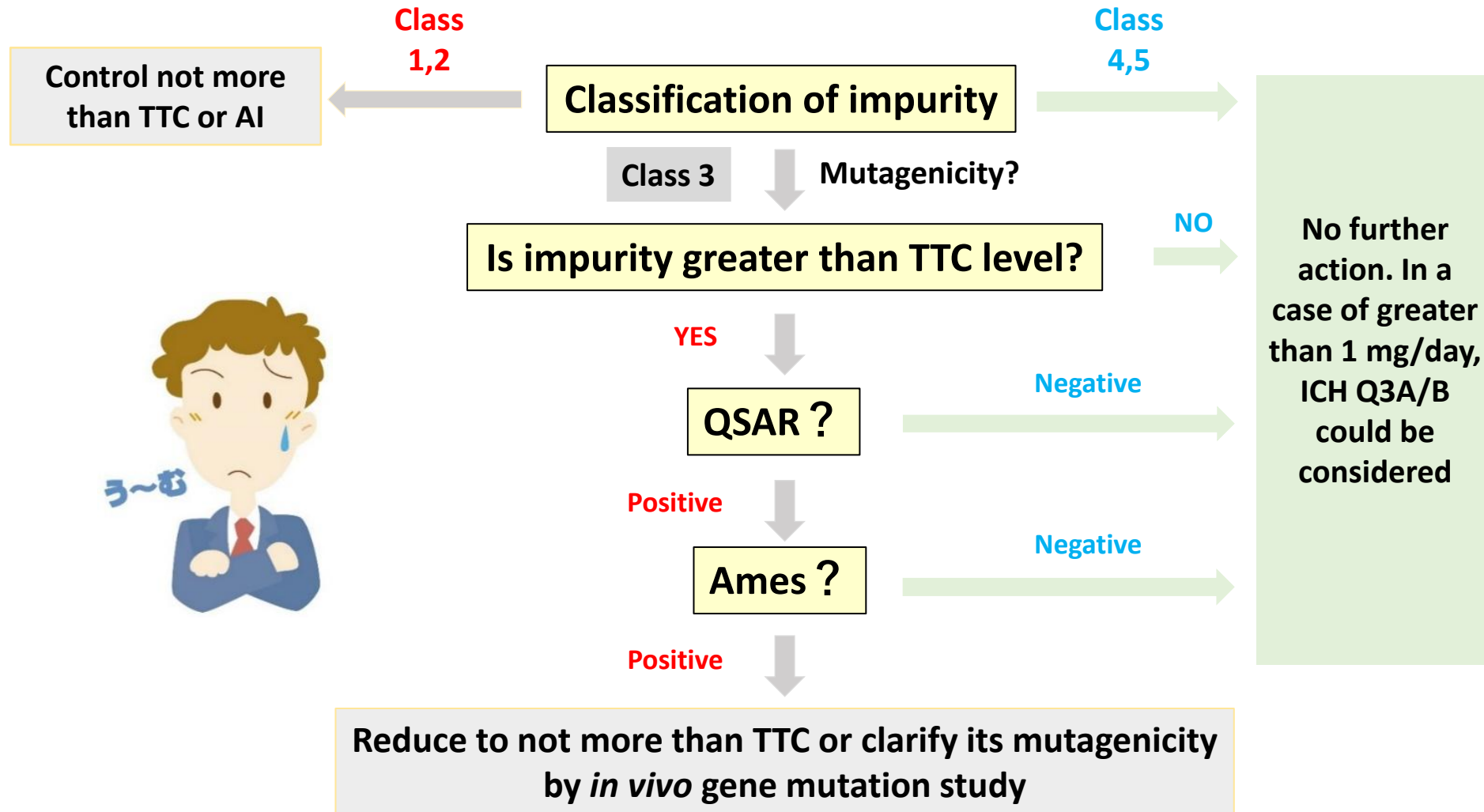
Strong Carcinogens (COC)

- aflatoxin-like-
- N-nitroso-
- alkyl-azoxy-

Classification (1)

Impurity class	Definition	Proposed action for control
Class 1	Known mutagenic carcinogens	VSD, AI
Class 2	Known mutagens with unknown carcinogenic potential	TTC
Class 3	Alerting structure, unrelated to the structure of the drug substance ; no mutagenicity data	
Class 4	Alerting structure, same alert in drug substance or compounds related to the drug substance	Q3A, Q3B
Class 5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	

Classification (2)



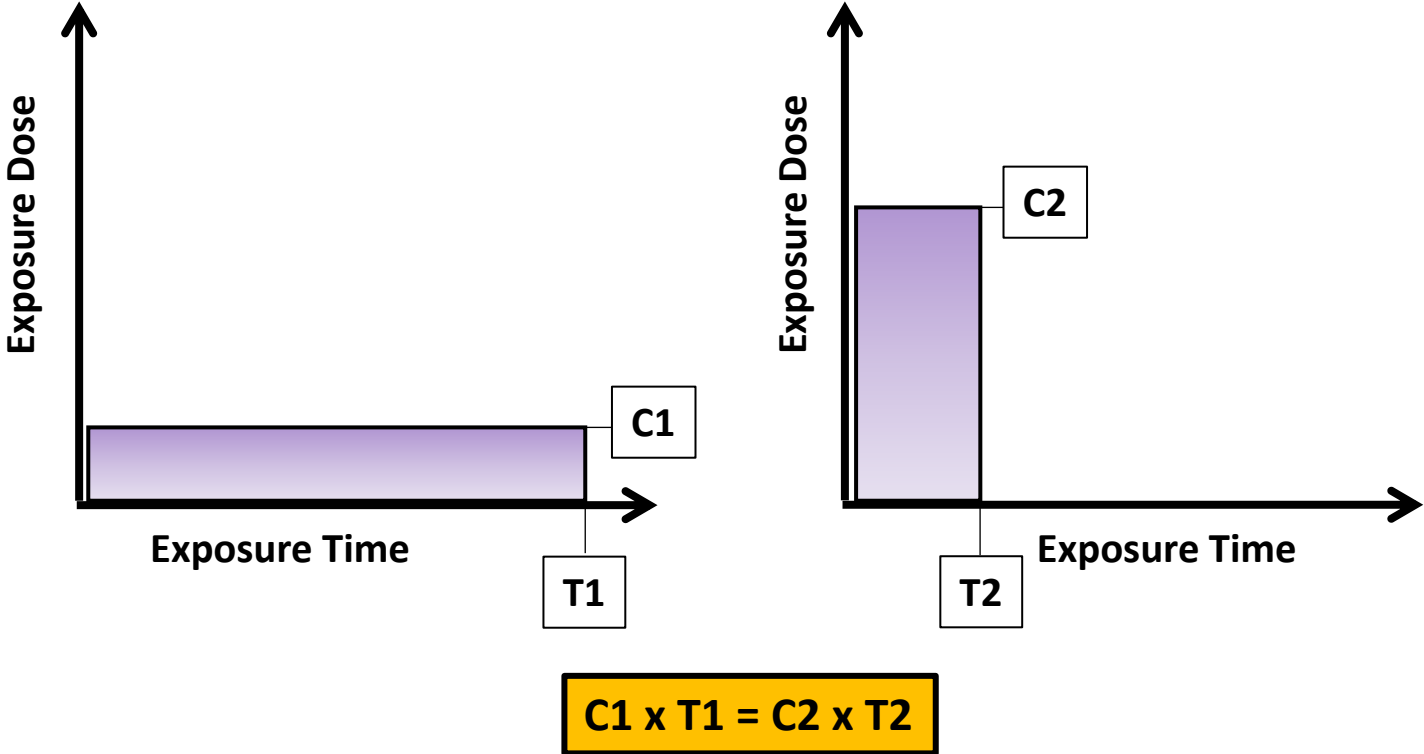
Risk Mitigation

1. Less than Lifetime TTC

2. Compound-specific VSD、 AI

Risk Mitigation (1)

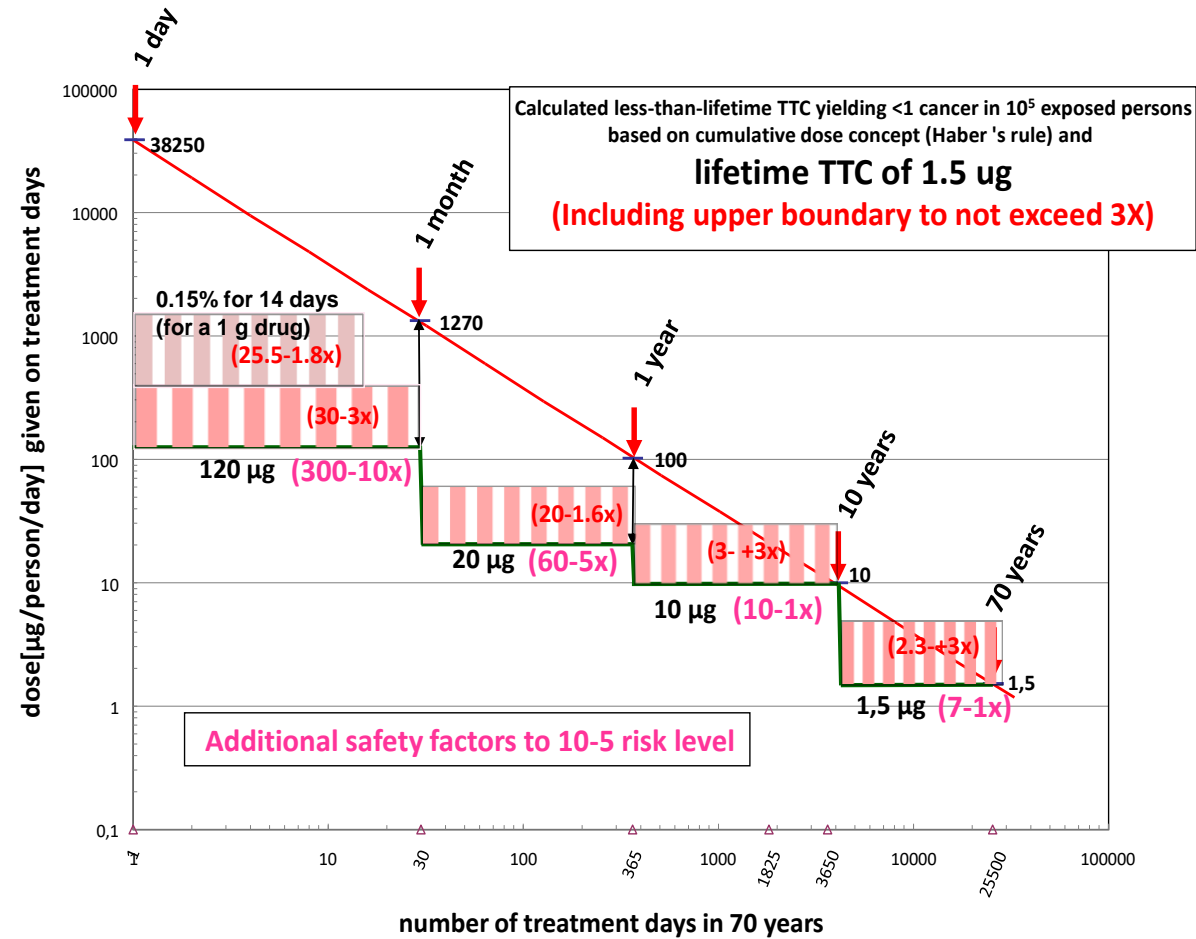
Haber's Rule



Higher exposures for shorter durations are equivalent to lower exposures for longer durations.

Risk Mitigation (2)

Less than Lifetime Risk



Risk Mitigation (3)

ICH-M7; Acceptable daily intakes for LTL exposure

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [$\mu\text{g}/\text{day}$]	120	20	10	1.5

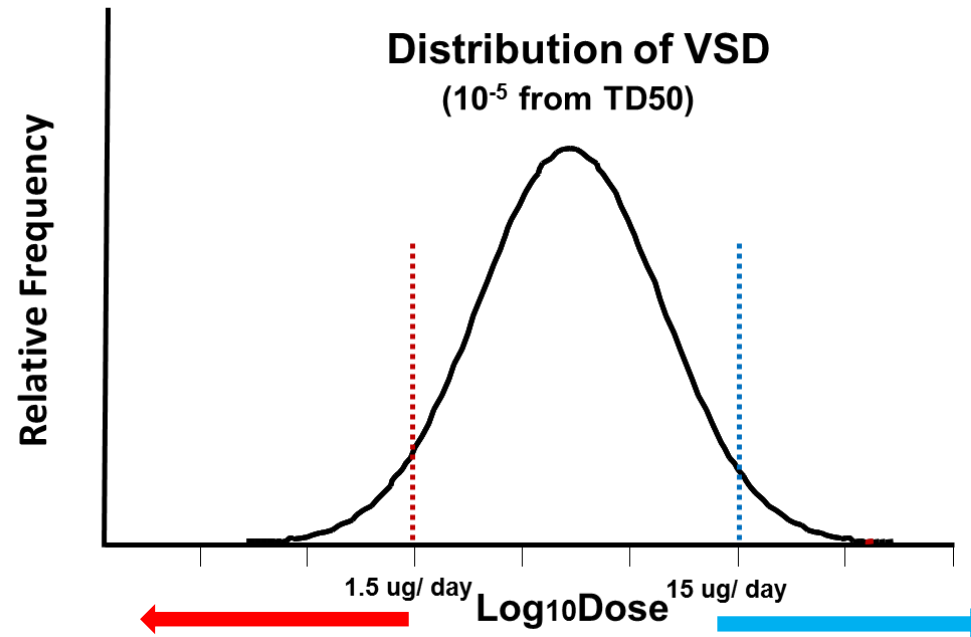


Scenarios with different treatment durations for applying acceptable intakes

Scenario ¹	Acceptable Intake ($\mu\text{g}/\text{day}$)
<p>Treatment duration of ≤ 1 month: e.g., drugs used in emergency procedures (antidotes, anesthesia, acute ischemic stroke), actinic keratosis, treatment of lice</p>	120
<p>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)</p>	20
<p>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 symptoms² (chronic Herpes, gout attacks, substance dependence such as smoking cessation), macular degeneration, HIV³</p>	10
<p>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</p>	1.5

Risk Mitigation (4)

Cohort of Concern (COC) vs Cohort of Less Concern (COLC)



Strong Carcinogens (COC)

- aflatoxin-like-
- N-nitroso-
- alkyl-azoxy-

Weak Carcinogens (COLC)

- monofunctional alkyl chlorides

ICH-M7 (R1) Guideline

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 subject to consultation by the regulatory parties, in accordance with Process the final draft is recommended for adoption to the regulatory

March 2017

Application of the principles of the ICH-M7 Guideline to Calculation of Compound-Specific Acceptable Intakes (14 chemicals)

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

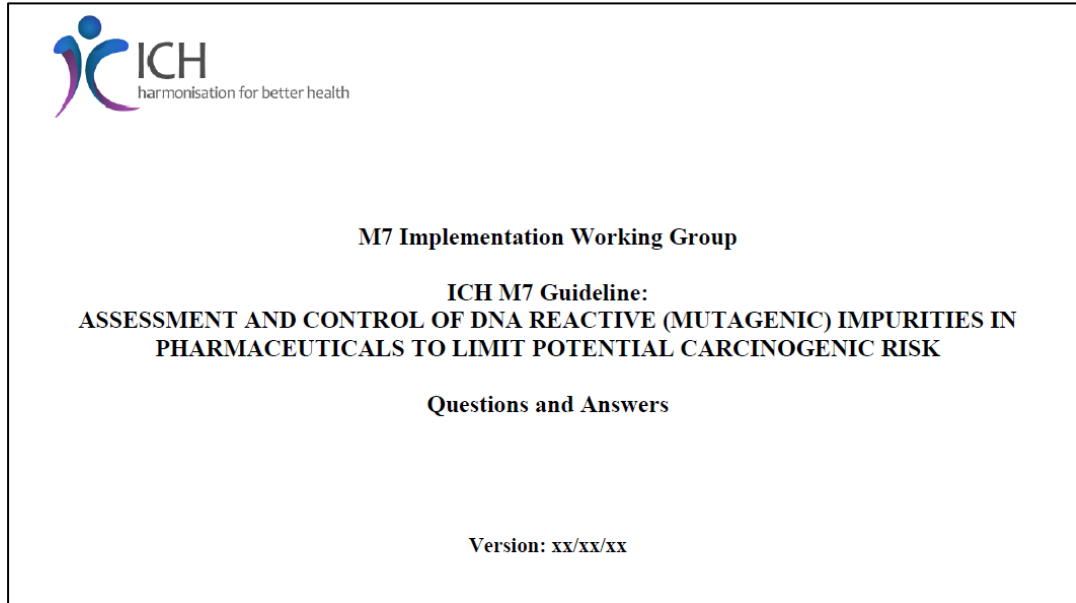
LIST OF ABBREVIATIONS.....	28
Introduction	30
Methods	32
Acceptable Intakes (AIs) or Permissible Daily Exposures (PDEs)	38
Acrylonitrile (CAS# 107-13-1).....	40
Aniline (CAS# 62-53-3) and Aniline Hydrochloride (CAS# 142-04-1).....	46
Benzyl Chloride (o-Chlorotoluene, CAS# 100-44-7).....	54
Bis(chloromethyl)ether (BCME, CAS# 542-88-1)	61
p-Chloroaniline (CAS# 106-47-8) and p-Chloroaniline HCl (CAS# 20265-96-7).....	65
1-Chloro-4-nitrobenzene (para-Chloronitrobenzene, CAS# 100-00-5).....	70
p-Cresidine (2-Methoxy-5-methyl aniline, CAS# 120-71-8)	76
Dimethylcarbonyl chloride (CAS# 79-44-7).....	81
Dimethyl Sulfate (CAS# 77-78-1).....	85
Ethyl chloride (Chloroethane, CAS# 75-00-3)	89
Glycidol (CAS# 556-52-5)	92
Hydrazine (CAS# 302-01-2).....	96
Hydrogen peroxide (CAS# 7722-84-1).....	102
Methyl chloride (Chloromethane, CAS# 74-87-3).....	108
Note 1	112
Note 2	114
Note 3	116

Compound-Specific AI in Addendum of ICH-M7 (R1)

Compound	CAS#	Chemical Structure	AI or PDE (µg/day)	Comment
Acrylonitrile	107-13-1		5	TD ₅₀ linear extrapolation
Benzyl Chloride	100-44-7		41	TD ₅₀ linear extrapolation
1-Chloro-4-nitrobenzene	100-00-05		117	TD ₅₀ linear extrapolation
p-Cresidine	120-71-8		45	TD ₅₀ linear extrapolation
Dimethylcarbonyl chloride	79-44-7		5 0.6 (inhalation)*	TD ₅₀ linear extrapolation
Ethyl chloride	75-00-3		1,810	TD ₅₀ linear extrapolation
Glycidol	556-52-5		4	TD ₅₀ linear extrapolation
Hydrazine	302-01-2		42 Inhalation: 0.2*	TD ₅₀ linear extrapolation

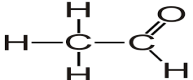

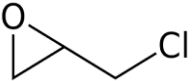
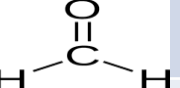
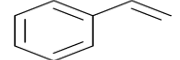
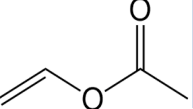

The next step of ICH-M7 (R2)

Q&A Document



Step 3 (under public comments)

2nd Addendum with 7 carcinogens

Compound	CAS#	Chemical Structure		
Acetaldehyde	75-07-0			
Ethyl bromide	74-96-4			
Epichlorohydrin	16-89-8			
Formaldehyde	50-00-0			
Styrene	100-42-5			
Vinyl acetate	188-05-4			
1,2-dibromoethane	106-93-4			

It will be reach to Step 1 within 2020.

ICH-M7 (R2) EWG

Expert list

ANVISA, Brazil

- Dr. Maria Augusta Carvalho Rodrigues

APIC

- Mr. Jacques Van Gompel

EC, Europe

- Dr. Roland Froetschl*
- Dr. Maryam Mehmandoust

EFPIA

- Dr. Andreas Czich
- Dr. Lutz Mueller
- Dr. Oliver Thiel

FDA, United States

- Dr. Aisar Atrakchi
- Dr. Timothy J. McGovern
- Dr. Rajan Pragani
- Ms. Barbara Scott

Global Self-Care Federation

- Dr. Esther Vock

Health Canada, Canada

- Dr. Amirthini Rajkumar
- Dr. Alisa Vespa

HSA, Singapore

- Dr. Looi Yee Hoo

JPMA

- Dr. Kiyohiro Hashimoto
- Dr. Kazusei Komatsu

MFDS, Republic of Korea

- Ms. Ji Youn Nam

MHLW/PMDA, Japan

- Dr. Yosuke Demizu
- Dr. Junichi Fukuchi
- Dr. Keiji Hirabayashi
- Dr. Masamitsu Honma

NMPA, China

- Mr. Hongyuan Da
- Mr. Lei Ma

PhRMA

- Dr. Krista Dobo
- Dr. Christian Wetter

Swissmedic, Switzerland

- Dr. Anja Langenkamp

TFDA, Chinese Taipei

- Dr. Chou Chia-Wei

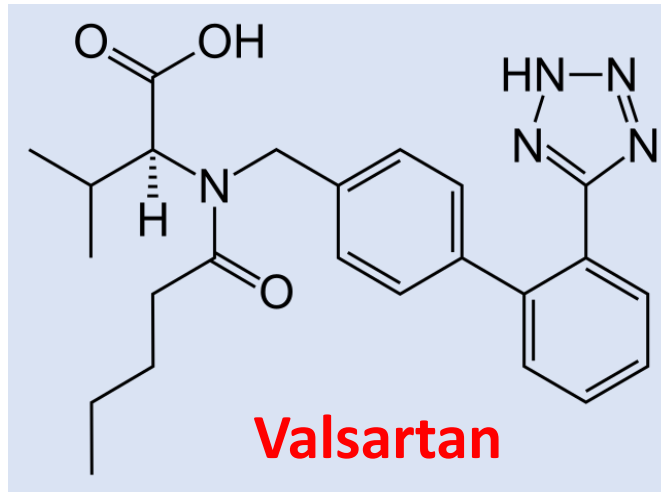
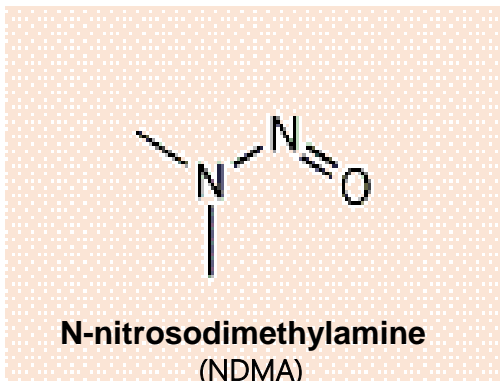


In Charlotte, USA, Nov. 2018

* Rapporteur

Topics

- I. **ICH-M7 Guideline: Assessment and Control of Mutagenic Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk**
- II. **Carcinogenic risk of nitrosamine compounds contained as impurities in pharmaceuticals**



報道関係者 各位

医薬品自主回収のお知らせ（クラスI）

（販売名：バルサルタン錠20mg・40mg・80mg・160mg「AA」）

、別添のとおり、あすか製薬株式会社が下記の医薬品の自主回収に着手した旨の情報提供がなされさせていただきます。

記

ン錠20mg・40mg・80mg・160mg「AA」

[る報道発表資料](#) [PDF形式：106KB]

[式会社における報道発表資料](#) [PDF形式：229KB]



▶ 報道・広報	
▶	厚生労働省広報基本指針
▶	大臣記者会見
▶	報道発表資料
▶	広報・出版
▶	行事・会議の予定
▶	広報実施計画
▶	国民参加の場



▶ [情報配信サービスメールアドレス登録](#)



▶ [子どものページ](#)

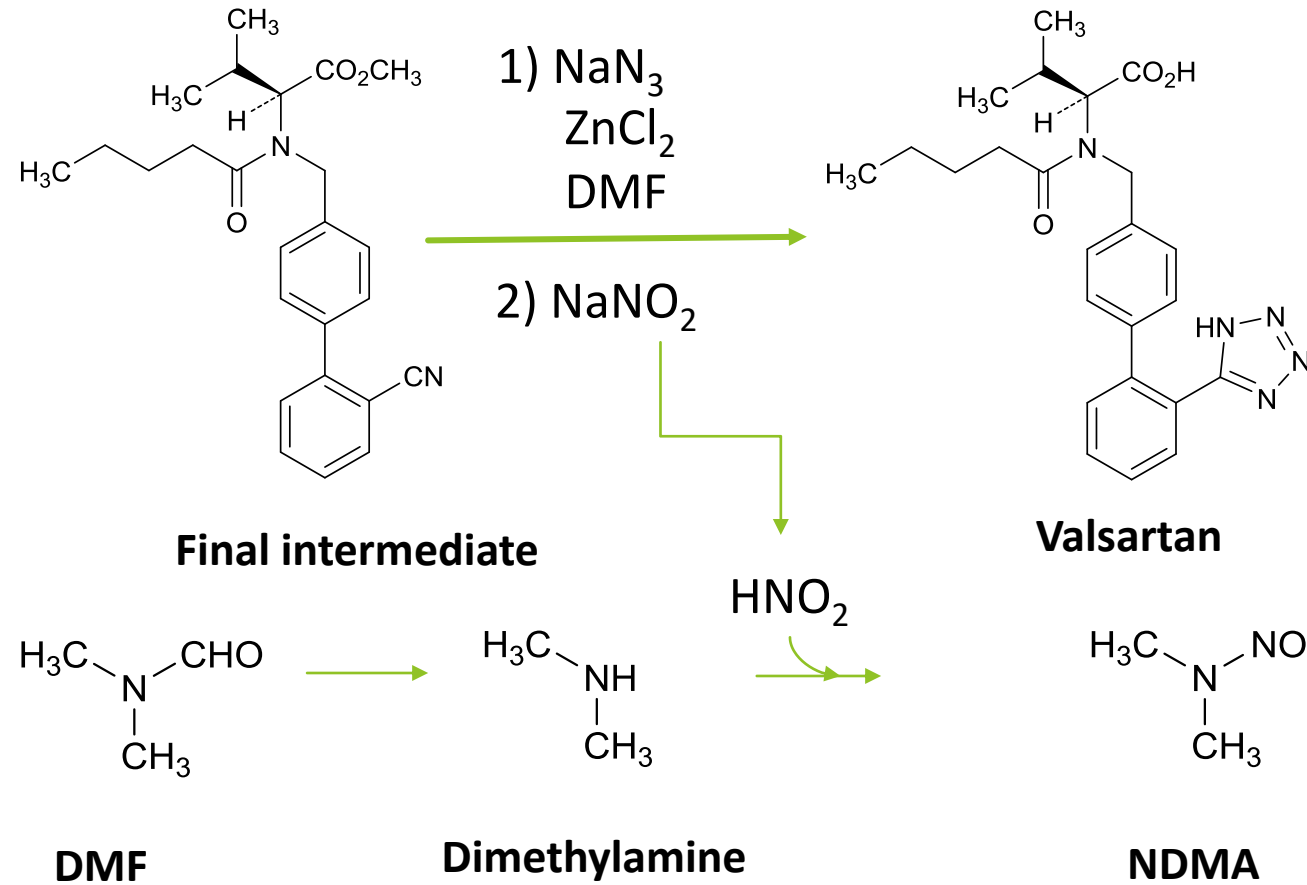
携帯ホームページ



▶ [携帯版ホームページ](#)では、緊急情報や厚生労働省のご案内などを掲載しています。

July 6, 2018 MHLW HP

NDMA by-Product Process in Valsartan Production



Valsartan Contained 2nd impurity: N-Nitrosodiethylamine (NDEA)

FDA NEWS RELEASE

FDA provides update on its ongoing investigation into valsartan products; and reports on the finding of an additional impurity identified in one firm's already recalled products

[Share](#) [Tweet](#) [LinkedIn](#) [Email](#) [Print](#)

[More Press Announcements](#)

[Press Announcements](#)

For Immediate Release: September 13, 2018

The U.S. Food and Drug Administration is updating the public on the agency's ongoing investigation surrounding the recent voluntary recall of several drug products containing the active pharmaceutical ingredient (API) valsartan, used to treat high blood pressure and heart failure.

The FDA's latest testing of products shows an additional unexpected impurity in three lots of [Torrent Pharmaceuticals' recalled valsartan drug products](#). This second impurity, N-Nitrosodiethylamine (NDEA) is a known animal and suspected human carcinogen. These Torrent products were included in the company's recall on August 23, 2018.

The FDA and the European Medicines Agency have learned that Zhejiang Huahai Pharmaceuticals (ZHP) found NDEA in several batches of its valsartan API. The FDA immediately began retesting all valsartan API and products, including both recalled

Content current as of:
09/13/2018

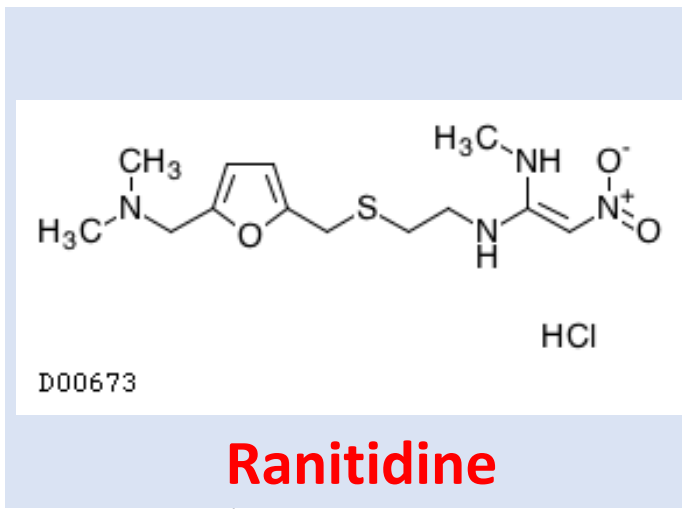
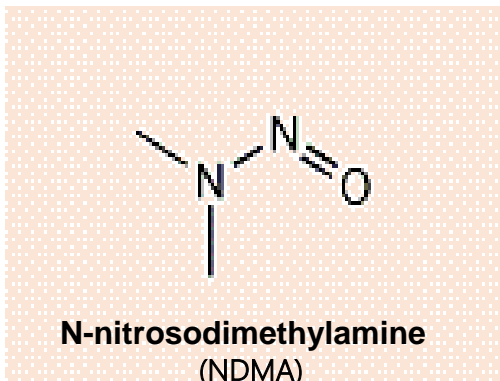
Follow FDA

[Follow @US_FDA](#)

[Follow FDA](#)

[Follow @FDAmedia](#)

September 2018



報道関係者 各位

医薬品自主回収のお知らせ（クラスI）

(販売名: ラニチジン錠75mg・150mg「サワイ」、ラニチジン錠75mg・150mg「ツルハラ」、
・150mg「トーワ」、ラニチジン注50mg・100mg「NP」、ラニチジン錠75
mg・150mg「マイラン」)

係のとおり、大阪府内の医薬品製造販売業者が下記の医薬品の自主回収に着手した旨の情報提
お知らせいたします。

記

75mg「サワイ」、ラニチジン錠150mg「サワイ」
錠75mg「ツルハラ」、ラニチジン錠150mg「ツルハラ」
錠75mg「トーワ」、ラニチジン錠150mg「トーワ」
注50mg「NP」、ラニチジン注100mg「NP」
錠75mg「マイラン」、ラニチジン錠150mg「マイラン」



▶ 報道・広報
▶ 厚生労働省広報基本指針
▶ 大臣記者会見
▶ 報道発表資料
▶ 広報・出版
▶ 行事・会議の予定
▶ 国民参加の場

関連リンク



▶ [情報配信サービスメ
ルマガ登録](#)



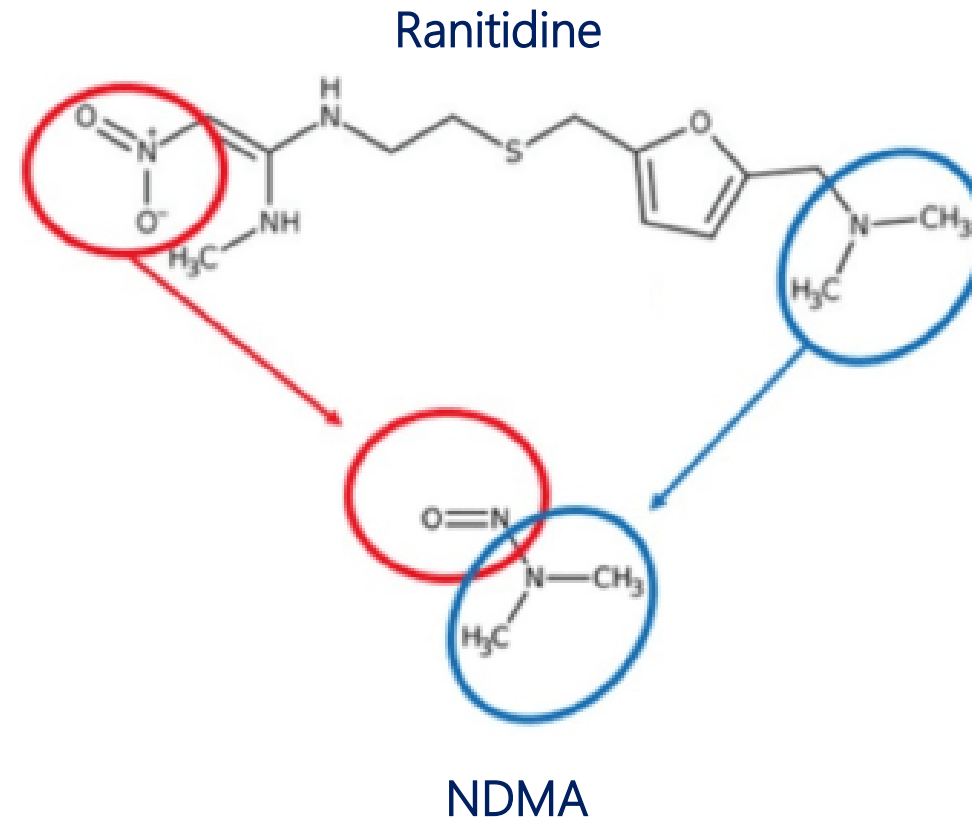
▶ [子どものページ](#)

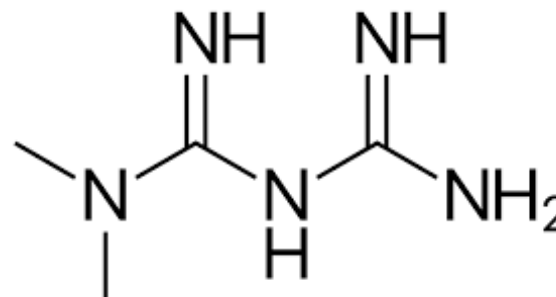
携帯ホームページ



▶ [携帯版ホームページ](#)
では、緊急情報や厚
生労働省のご案内な
どを掲載していま
す。

Generation of NDMA by Decomposition of Ranitidine





Metformin

報道関係者 各位

Unknown cause (A substance derived from nitrocellulose resin contained in the printing ink on the tablet contact surface of PTP aluminum foil reacts with dimethylamine, which is a raw material that remained slightly in the tablet?)

医薬品自主回収のお知らせ(クラスI)

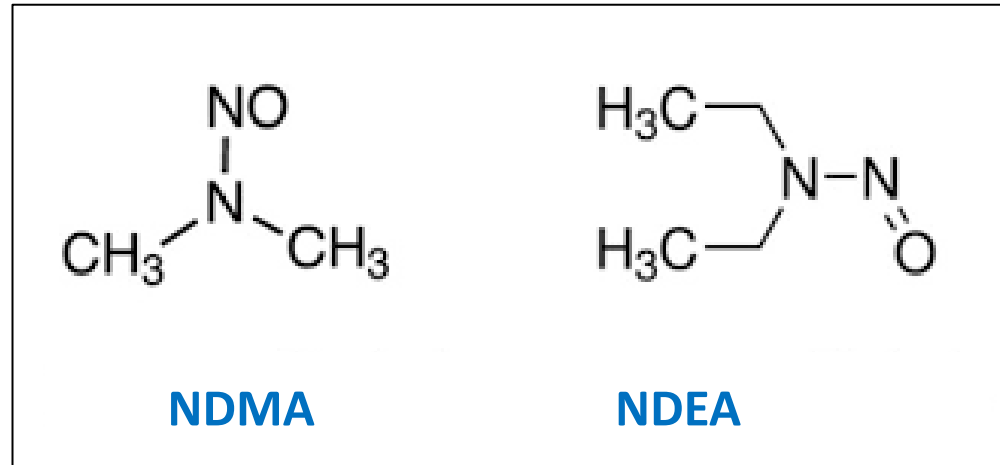
(販売名：メトホルミン塩酸塩錠 500mg MT「JG」)



、東京都より、別添のとおり、日本ジェネリック株式会社が下記の医薬品の自
に着手した旨の情報提供がなされましたので、お知らせいたします。

April 2020 MHLW

AI (Control limit) of NDMA and NDEA



NDMA : 0.0959 $\mu\text{g}/\text{day}$

(Rational data : $\text{TD}_{50} = 0.0959 \text{ mg}/\text{kg}/\text{day}$ (Rat))

NDEA : 0.0265 $\mu\text{g}/\text{day}$

(Rational data : $\text{TD}_{50} = 0.0265 \text{ mg}/\text{kg}/\text{day}$ (Rat))

Cancer Risk Assessment of NDMA Impurities in Drugs

Drug	Assumed usage	Maximum daily intake of NDMA	Cancer Risk
Valsartan	Take 160mg/day for 4 years	10.7 µg/day	6.4×10^{-5}
Ranitidine	Take 300 mg/day for 2 years	1.773 µg/day	5.3×10^{-6}
Metformin	Take 1500mg/day for 10 years	0.1226 µg/day	1.8×10^{-6}

Other Nitrosamine Compounds as Impurities in Drugs

NEWS

FDA finds another carcinogenic impurity in ARB blood pressure drug

By Nikki Withers (European Pharmaceutical Review)

4 March 2019

No comments yet

SHARES

25

f t in

RELATED TOPICS

Drug Safety, Impurities, Regulation & Legislation

RELATED ORGANISATIONS

Food and Drug Administration (FDA)

RELATED DRUGS

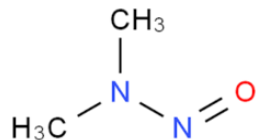
losartan

RELATED PEOPLE

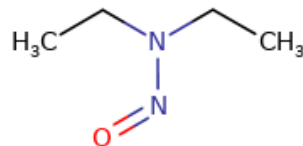


March 2019

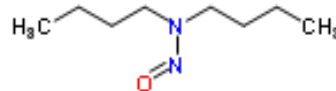
NDMA
(62-75-9)



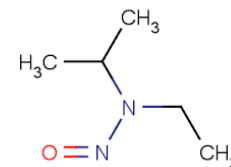
NDEA
(55-18-5)



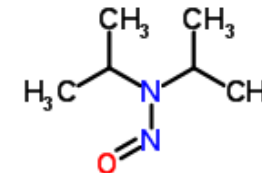
NDBA
(924-16-3)



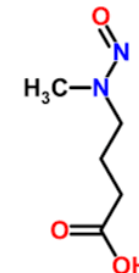
NEIPA
(16339-04-1)



NDIPA
(601-77-4)



NMBA
(61445-55-4)



Summary

- ◆ If mutagenicity is found in pharmaceutical impurities, strict control is required.
- ◆ Mutagenicity of impurities is assessed by QSAR → Ames test → *in vivo* gene mutation assay. If negative results are obtained in higher assessment, the strict control is not necessary.
- ◆ Mutagenic impurities that have not been tested for carcinogenicity should be controlled by TTC (1.5 µg/day), which is corresponding to a lifetime cancer risk level of 1 in 100,000.
- ◆ TTC levels can be mitigated by duration of exposure and characteristics of mutagenic substances.
- ◆ Nitrosamine compounds are extremely strong carcinogens (COCs) and require stricter control.
- ◆ ICH guidelines is originally intended for new pharmaceuticals, but the ICH-M7 guideline will be applied to generic drugs in the future from the viewpoint of ensuring quality and safety.