



# ICH M7: Assessment and Control of Mutagenic Impurities

(Step 4: 23 June 2014)

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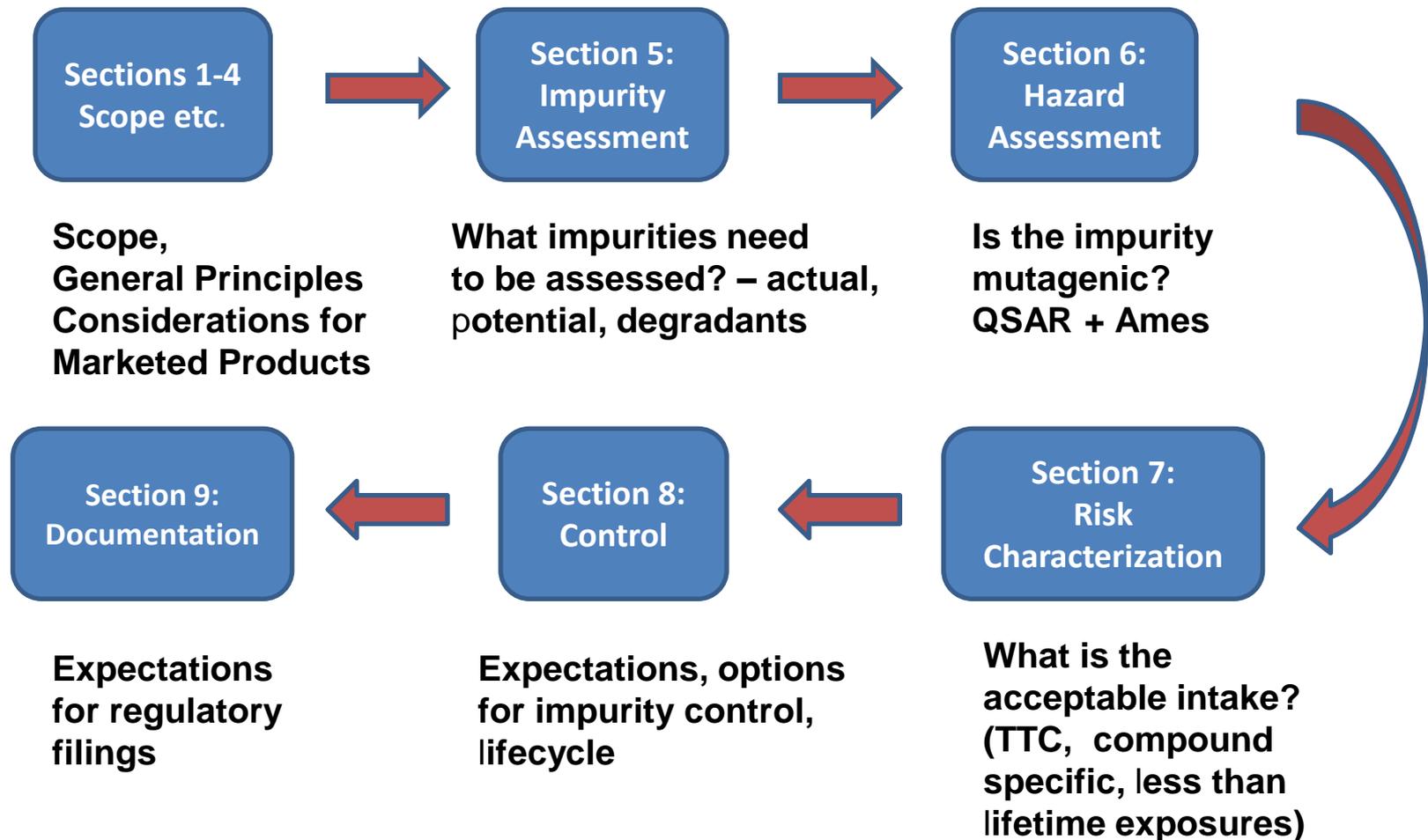
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# Disclaimer

- This talk is based upon my personal views of the ICH M7 guidance document, and does not necessarily represent the views of other members of the M7 Expert Working Group or of the FDA.
- **ICH M7: Assessment And Control Of DNA Reactive (Mutagenic) Impurities In Pharmaceuticals To Limit Potential Carcinogenic Risk**

# Guideline General Framework



# General Principles

- Focus on DNA-reactive impurities, i.e. mutagenic impurities typically positive in the bacterial mutagenicity assay
- Threshold of Toxicological Concern (TTC) concept applies –  $1 \times 10^{-5}$  lifetime risk
- Less than Lifetime (LTL) principle applies
  - Clinical development and marketed products with shorter treatment durations have higher acceptable levels
- Evaluate actual impurities plus risk-based subset of potential impurities

# Scope

- New drug substances and new drug products in clinical development and subsequent application for marketing
- **Certain** post approval submissions of marketed products and to new marketing applications (drug substance previously approved):
  - Changes to the drug substance
  - Changes to the drug product
  - Changes in clinical use

# Synthetic Impurities and Degradation Products

Category (Section)	Guidance for Assessment
<b>Synthetic Impurities in DS (5.1) – From Starting Material (SM) to DS</b>	<ul style="list-style-type: none"> <li>• <b>Actual impurities where the structures are known (e.g., above ICH Q3A identification threshold)</b></li> <li>• <b>Potential impurities can include SMs, reagents and intermediates</b></li> <li>• <b>Assess risk of carryover into DS of identified impurities in SMs and intermediates, and impurities that are reasonably expected by-products in synthesis route</b></li> <li>• <b>For SMs introduced late in synthesis, where the route of synthesis of SM is known, evaluate the final steps of SM synthesis</b></li> </ul>
<b>Degradation Products in DS and DP (5.2)</b>	<ul style="list-style-type: none"> <li>• <b>Actual degradation products identified in DS and DP under long-term storage conditions (e.g., above ICH Q3A/B identification thresholds)</b></li> <li>• <b>Potential degradation products in DS and DP reasonably expected to form under long term storage conditions (e.g., above ICH Q3A/B identification thresholds at accelerated or confirmatory photo-stability studies)</b></li> </ul>

## Hazard Assessment

- Actual and potential impurities are assessed for mutagenic hazards
- **Known mutagen** - evaluate literature and databases
- **Structure of unknown mutagenicity** - perform a computational toxicology assessment using (Q)SAR methodologies that predict bacterial mutagenicity
  - Employ **two** complementary (Q)SAR systems (expert rule-based and statistical based)
  - Apply expert knowledge to review outcomes if warranted
  - Absence of structural alert is sufficient to conclude that impurity is of no concern, and no further testing is recommended

**Table 2: Acceptable Total Daily Intakes for an Individual Impurity (during clinical development and at marketing)**

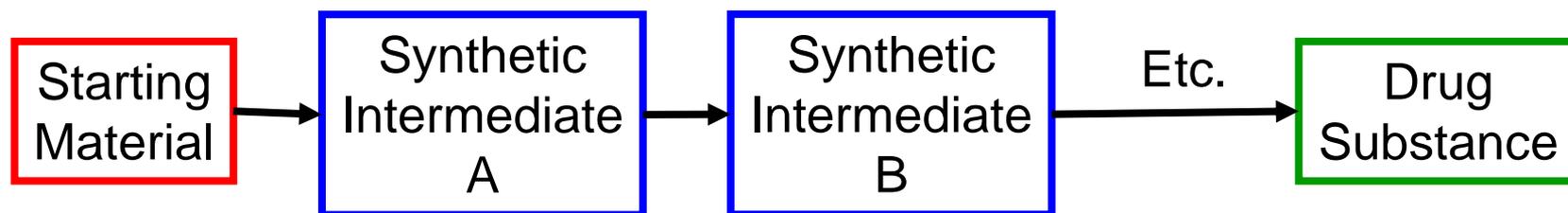
<b>Duration of treatment</b>	<b>≤ 1 month</b>	<b>&gt;1 - 12 months</b>	<b>&gt;1 - 10 years</b>	<b>&gt;10 years to lifetime</b>
<b>Daily intake [µg/day]</b>	<b>120</b>	<b>20</b>	<b>10</b>	<b>1.5</b>

**Table 3: Acceptable Total Daily Intakes for Multiple Impurities\***

<b>Duration of treatment</b>	<b>≤ 1 month</b>	<b>&gt;1 - 12 months</b>	<b>&gt;1 - 10 years</b>	<b>&gt;10 years to lifetime</b>
<b>Total Daily Intake [µg/day]</b>	<b>120</b>	<b>60</b>	<b>30</b>	<b>5</b>

\*For 3 or more Class 2 and 3 impurities specified on the drug substance specification (during clinical development and at marketing).

# Options for Control of Impurities



- Starting Materials and isolated Intermediates each will generally have a specification
  - Synthesis prior to SM will generally be managed under the applicant's quality system
- Removal of impurity can be monitored through any of these specifications, or assured by the manufacturing process controls themselves

# Control Options (8.1)

**Option 1: Monitor the impurity in the drug substance**

Acceptance criterion below the TTC

**Option 2: Monitor the impurity in intermediate, starting material or in-process control**

Acceptance criterion below the TTC

**Option 3: Monitor the impurity in intermediate, starting material or in-process control**

Acceptance criterion above the TTC, with demonstrated understanding of fate and purge and associated process controls

**Option 4: Design robust process controls to reduce the risk of impurity level above the TTC to negligible**

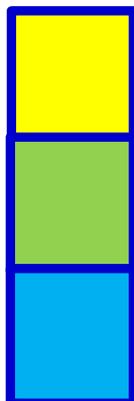
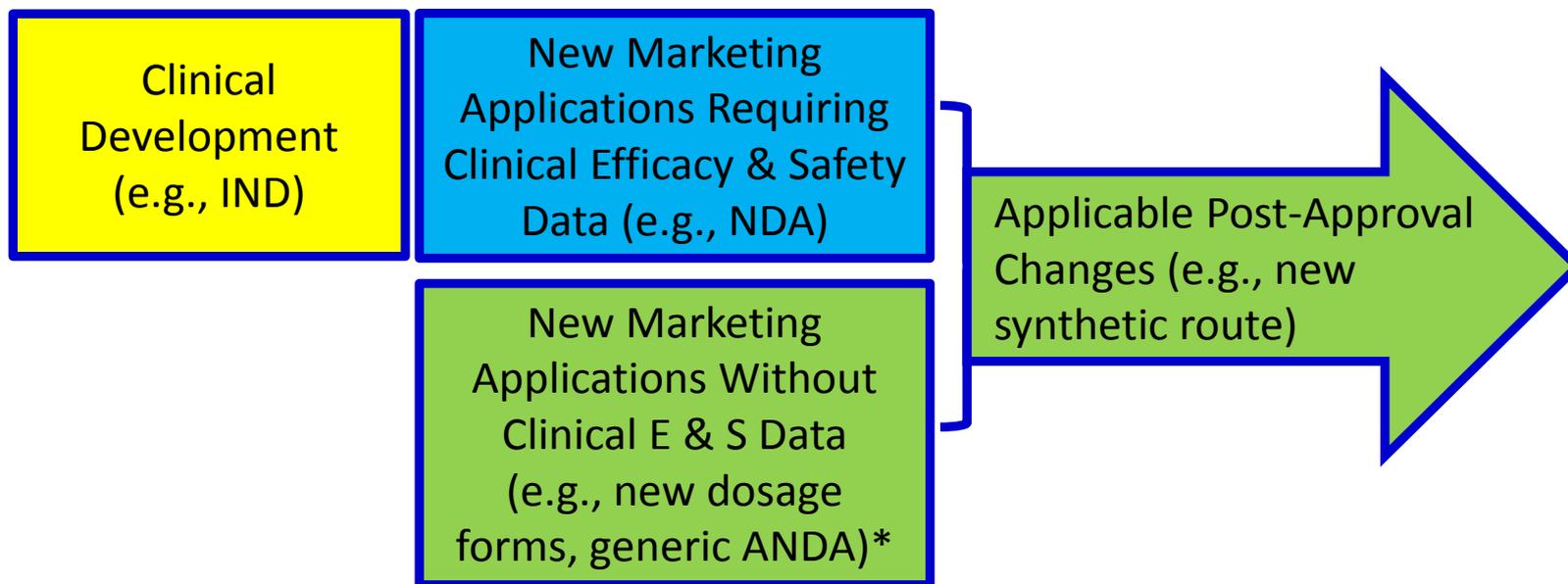
## Control Options (8.2-8.6)

- Considerations for periodic testing (re: ICHQ6A)
- Control of potential degradation products
  - Understand degradation pathway in DS and DP (e.g. from accelerated stability studies)
  - Efforts to control formation of the degradation product under proposed packaging and storage conditions
- Lifecycle management
  - Encouraged to use science-based and risk-based approach for quality systems and management elements as described in ICH Q10

# Implementation of M7 Guideline

- The final (Step 4) version of M7 was published on the ICH website in July 2014.
- Because of the complexity of the guideline, implementation of M7 is not expected until 18 months after ICH publication (i.e., January 2016).
- Applicants may adopt all or portions of the M7 guideline at any time (e.g., less-than-lifetime limits, approaches to control, class-specific limits), until January 2016 when full implementation is expected .
- The following slide shows exceptions to 18 month timeline

# M7 Implementation Timeline



Full implementation of M7 not expected until January 2016

Full implementation of M7 not expected until July 2017

\* This will be addressed by regional regulatory processes

Programs in Phase 2b or 3 before July 2014 may continue to follow Pre-M7 guidance until the marketing application is submitted and approved

# Conclusion

- M7 provides recommendations on how to assess and control mutagenic impurities
- Recommends selecting potential impurities based on the risk of presence at relevant levels in the drug substance or drug product
- Utilizes Structure Activity Relationship to assess and predict mutagenicity potential (Hazard Identification) and if warranted, control or determine risk (Risk Assessment)
- Applies the concept of TTC (Threshold of Toxicological Concern) and classifies impurities into 5 classes based on mutagenicity and carcinogenicity
- Applies LTL (Less-Than-Lifetime) limits based on duration of use providing a flexible and practical approach during clinical development and marketing
- Outlines flexible ways to control mutagenic impurities, and a staged approach to documentation during development

## Acknowledgement:

### ICH M7 Expert Working Group (June 2014)

Party	Topic Leader	Deputy Topic Leader	Expert	Observer	Interested Party
EU	Peter Kasper	Diana van Riet-Nales			
EFPIA	Steven Spanhaak	Lutz Muller	Kevin McKiernan		
MHLW	Masamitsu Honma	Yukio Aso	Junichi Fukuchi Hisami Hiragi		
JPMA	Tsuneo Hashizume	Nobukazu Igoshi	Naoto Fukutsu Kazusei Komatsu		
FDA	Aisar Atrakchi (David Jacobson-Kram)	Stephen Miller	Timothy McGovern Paul Brown		
PhRMA	Warren Ku	David De Antonis	Joseph DeGeorge		
EFTA				Elisabeth Klenke	
HC				Alisa Vespa	
WSMI					Esther Vock
IGPA					Jack Lipman
DRA of China			Sun Tao		
DRA of Singapore			Looi Yee Hoo		
DRA of Korea			Young Mi Song Kwang Moon Lee (Alternate)		

Plus many other colleagues!



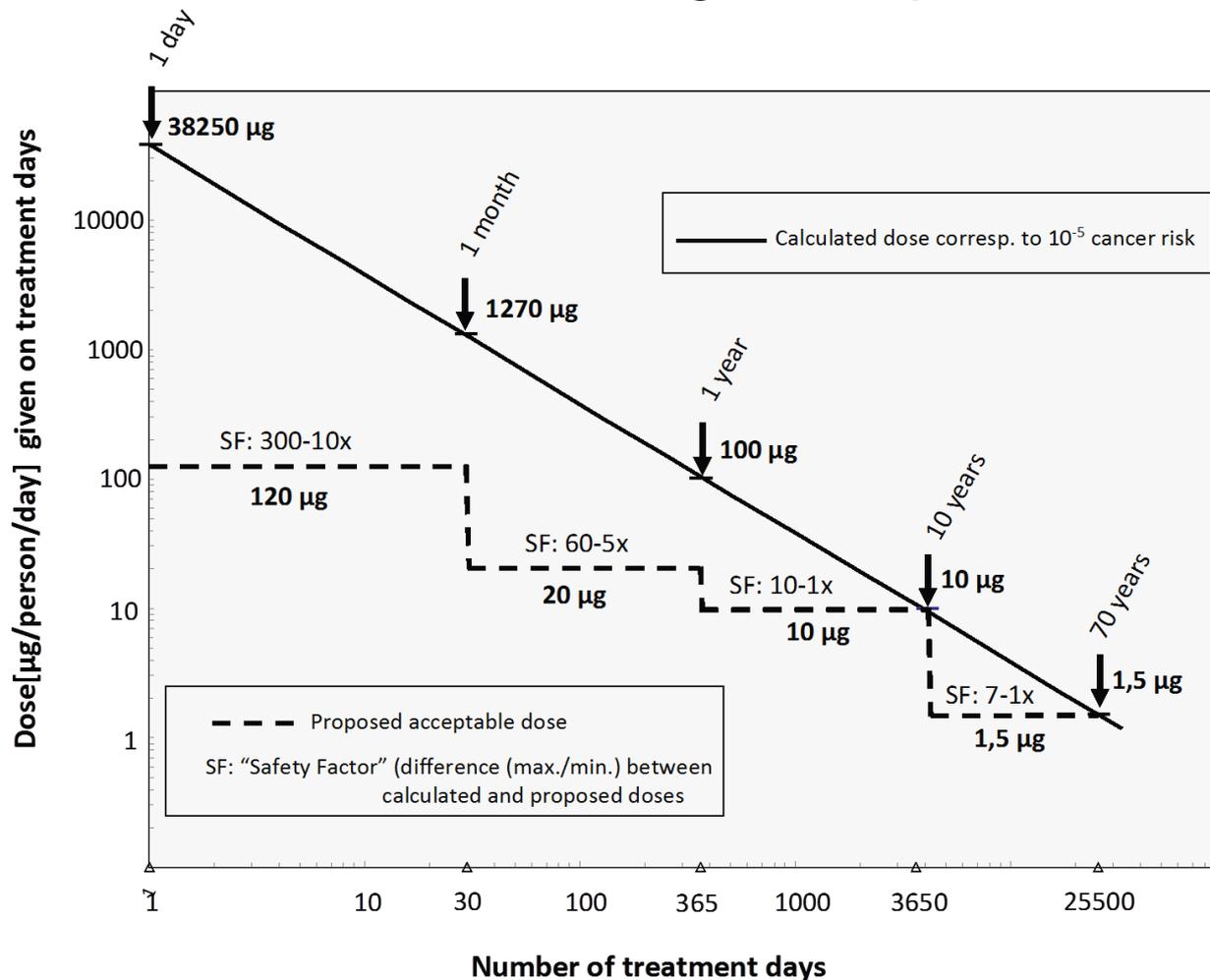
**Thank You!!**

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## Exceptions and flexibility in approaches

- Higher acceptable intakes may be justified:
  - when human exposure to the impurity is much greater from other sources e.g., food, or endogenous metabolism (e.g., formaldehyde)
  - in cases of severe disease, reduced life expectancy, late onset but chronic disease, or with limited therapeutic alternatives
  - based on a risk/benefit analysis when control efforts cannot reduce levels below the acceptable limit
- Lower acceptable intake may be justified for some structural classes of mutagens, i.e. aflatoxin-like-, N-nitroso-, and alkyl-azoxy structures which display extremely high carcinogenic potency.

# Note 6, Figure 1: Establishing less-than-lifetime acceptable intakes for mutagenic impurities



**Table 1: Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions**

<b>Class</b>	<b>Definition</b>	<b>Proposed action for control</b>
Class 1	Known mutagenic carcinogens	≤ compound-specific limit
Class 2	Known mutagens with unknown carcinogenic potential	≤ appropriate TTC
Class 3	Alerting structure, unrelated to structure of DS, no mutagenicity data	≤ appropriate TTC or conduct Ames test (non-mutagenic = Class 5; mutagenic = Class 2)
Class 4	Alerting structure, same alert in DS or compounds related to DS which have been tested and are non-mutagenic	Non-mutagenic impurity (ICH Q3A/B)
Class 5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Non-mutagenic impurity (ICH Q3A/B)

## Implementation (cont.)

- Ames tests should be conducted according to M7 irrespective of the stage of development of the Application. However, Ames tests conducted prior to publication of M7 need not be repeated.
- When development programs have started phase 2B/3 clinical trials **BEFORE** publication of M7, these programs can be completed up to and including marketing application submission and approval without following M7 (i.e., M7 does not apply; may follow pre-M7 guidance).
- When development programs have started phase 2B/3 clinical trials **AFTER** publication of M7, these programs have the option to implement M7 or chose to follow the 18 month grace period (full implementation in January 2016).

## Implementation (cont.)

- Given the complexity and lead-time for development of a commercial manufacturing process, application of M7 to new marketing applications that do not include Phase 2B/3 clinical trials is not expected until 36 months after ICH publication of M7 (e.g., new dosage forms, or new DMFs supporting generic drug applications, may follow pre-M7 guidance until July 2017).
- The 36 month implementation period is also appropriate for applicable post-approval changes (i.e., may follow pre-M7 guidance until July 2017).