EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ICH Q3D elemental impurities & ICH M7 mutagenic impurities recent considerations

EMA SME workshop: Focus on quality for medicines containing chemical substances
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Aim pharmaceutical development

- to design a quality product and its manufacturing process to consistently deliver the intended performance of the product

- studies can be a basis for quality risk management. It is important to recognize that quality cannot be tested into products; i.e. quality should be built in by design

- information and knowledge gained from these studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls

In other words..

- to turn active substance into a medicine that is "fit for continuous & adequate use"

- implies e.g.
  - positive benefit to risk evaluation (B/R+) at time MA
  - commercial batches have same efficacy & safety profile as batches that were considered during MA application
  - medicine is suitable for use in daily practice

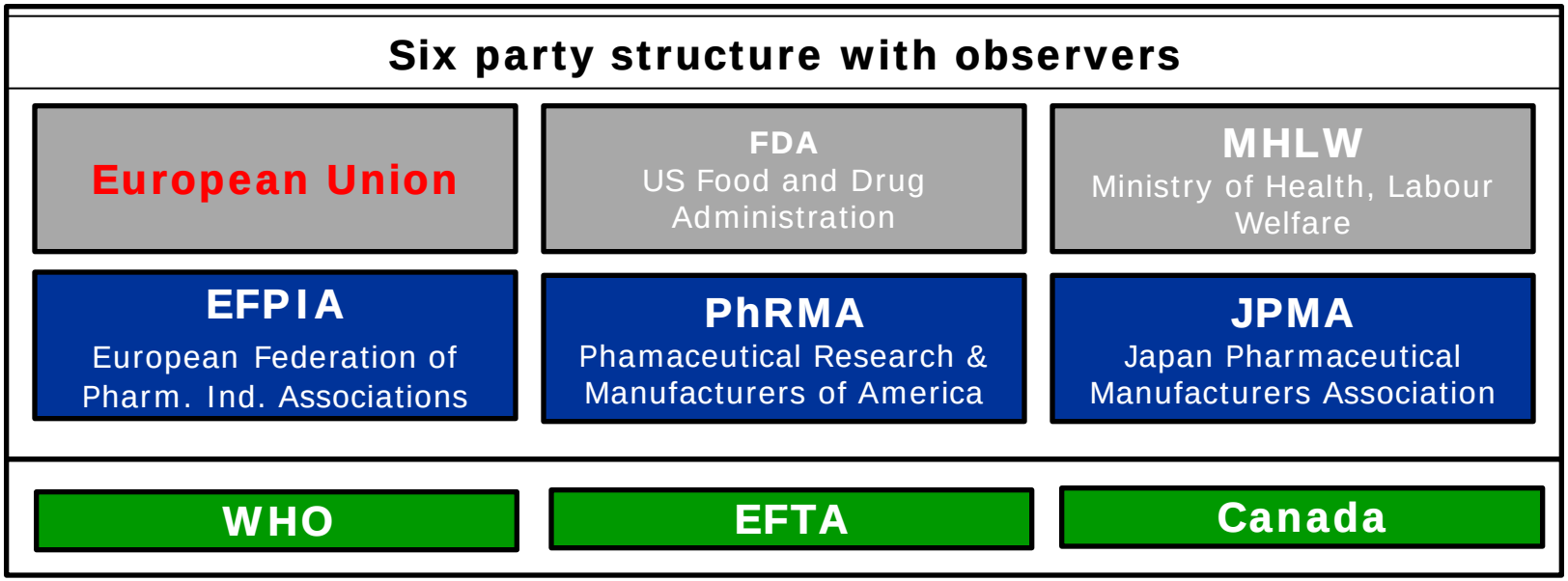
How to assure?

- directives & regulations
- European pharmacopoeia & pharmacopoeia member states
- regulatory jurisprudence & guidelines & Q&As
- reflection papers & regulatory/scientific knowledge asessor

- quality guidelines
  - developed by QWP or multidisciplinairy groups
  - developed by ICH and adopted by CHMP

ICH

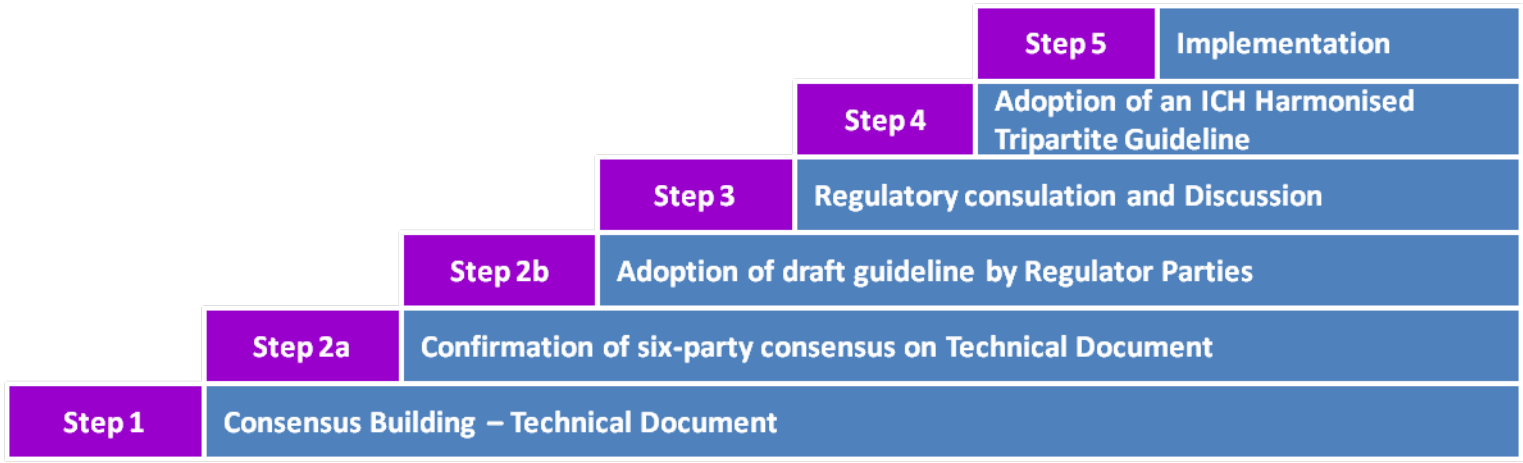
- International Conference of Harmonization of **Technical Requirements** for the Registration of Pharmaceuticals for Human Use



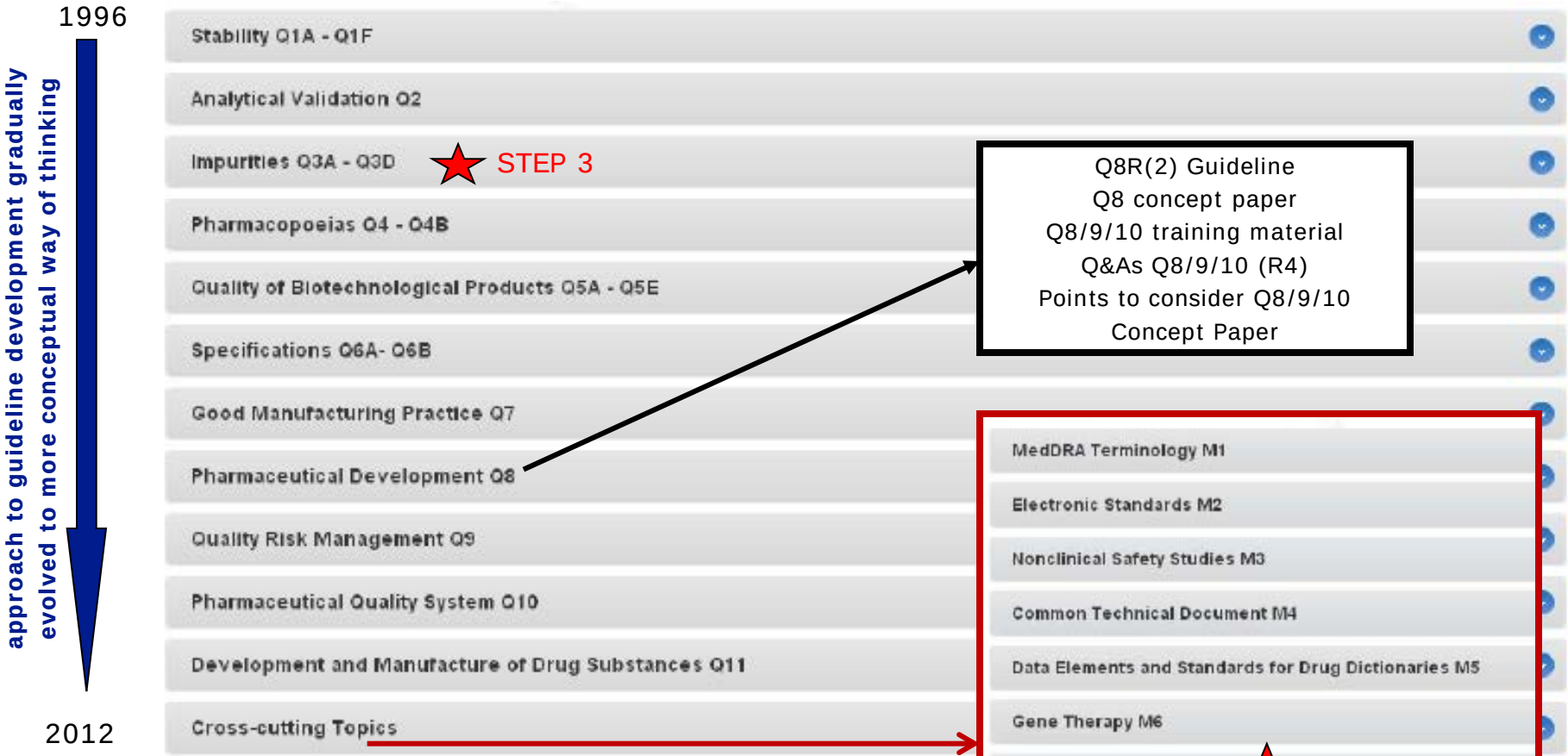
http://www.ich.org/

Steps in drafting ICH guidelines

From June 2012



Quality guidance



ICH focus on impurities

"the synthesis of drug substances involves the use of reactive chemicals, reagents, solvents, catalysts, and other processing aids. As a result of chemical synthesis or subsequent degradation, impurities 3 reside in all drug substances and associated drug products"

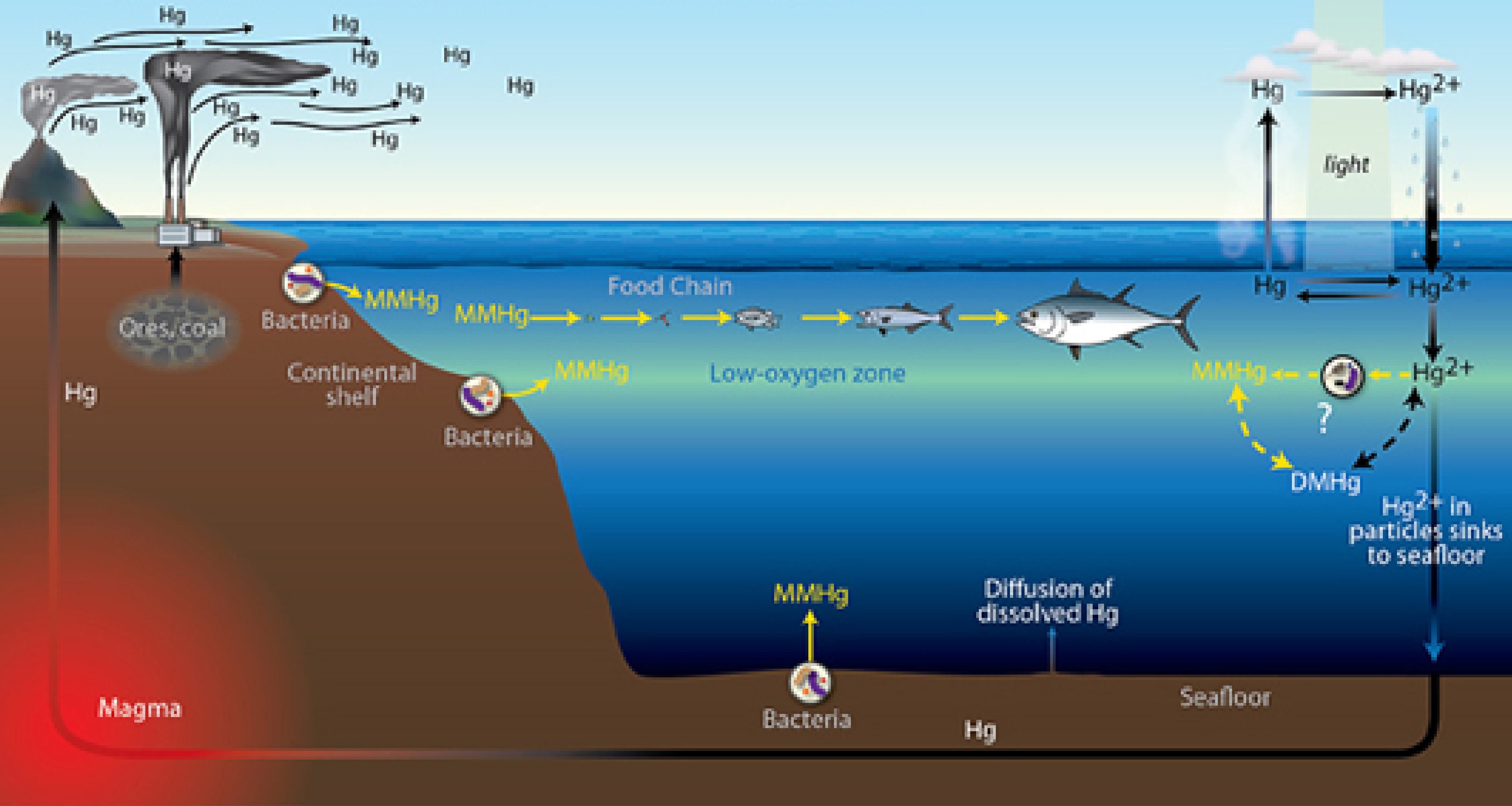
main guidance: ICH Q3A/B

supplemented by ICH Q3C on residual solvents

all incoming materials may contain sources of others…

The Mercury Cycle

Mercury (Hg) cycles from Earth to atmosphere to oceans and back to Earth. In the ocean, mercury is converted to monomethyl mercury (MMHg), a neurotoxin that moves up the food chain and becomes highly concentrated in tuna, swordfish, and other fish that people eat.



Q3D Elemental impurities

current EU Guideline CHMP/SWP/4446/2000

- 14 metals used in synthesis
- limits for metals in drug substance
- extraneous sources not covered (GMP)

Q3D scope

– permitted daily exposure (PDE) for 24 elements, additional 10 assessed

– not limited to reagents and catalysts

– emphasises risk assessment

Permitted Daily Exposure

- in EU currently given for the oral, the parenteral and the inhalation routes of administration

- protective of all patient groups
  - even if 50 kg body weight is used at one point in the calculation, the safety factors used ensure suitability for medicines for e.g. premature children

- principles of ICH Q3C residual solvents used for safety assessment

Drug product

- drug product should comply with PDE

- all contributions should be taken into account
  - e.g. drug substance, excipients, process equipment, container-closure system, environment
  - a risk assessment show which elements may be present and from what source
  - a control strategy is to be set up accordingly

Risk assessment

identify

- known and potential sources

analyze

- determine probability of observance

evaluate

- compare predicted levels with PDE

control

- implement control strategy where needed

Control Threshold

- if total contribution from all sources to the levels in the drug product is consistently below 30% of the PDE
  - no additional controls necessary
  - showing consistency includes full understanding of all variability

Control options

For each element to be controlled

- Option 1
  - all components of DP comply with listed concentration limit based on max. 10 g daily intake of entire DP. Components may be used in any proportion in DP

- Option 2a
  - all components of DP comply with a DP specific calculated concentration limit based on actual max. daily intake of entire DP. Components may be used in any proportion in DP

Options continued

- Option 2b
  - Allows individual components of DP have higher concentration limits than in Option 1 & 2a. This is to be compensated by other components having lower limits. The total amount of an element from the DP does therefore not exceed the PDE

- Option 3
  - The concentration limit is set in the DP specification to ensure compliance with the PDE

ICH M7

M7 guideline control of DNA reactive mutagenic impurities in pharmaceuticals to limit potential carcinogenic risk

- focus principles quality and risk management
- scope different from EU and much more detailed..
  - new drug substances and new drug products during their clinical development and subsequent applications for marketing
  - also applies to new marketing applications and post approval submissions for marketed products, but only in certain cases

Scope….

- not covered (with exceptions), but principles may apply
  - biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation products, herbal products, and crude products of animal or plant origin
- not applicable
  - drug substances and products for advanced cancer indications
- excluded
  - excipients used in existing marketed products and flavoring agents

on purpose: little clarity to applicability new excipients

Guideline outline

- introduction, scope, general principles
- considerations for marketed products
- drug substance & drug product impurity assesment
- hazard assessment elements
- risk characterisation
- control
- documentation
- notes, glossary, references

General concept

- impurities bearing potential to directly cause DNA damage at low levels and therewith potential causing cancer
- mutagen usually detected in bacterial reverse mutation test e.g. Ames
- treshold of toxicological concern (TTC) developed to define acceptable intake for unstudied chemicals that will not pose a risk of carcinogenecity > 10-5 excess lifetime risk
- high potency carcinogens (cohort of concern) identified

New concept: less than lifetime approach

Table 2: Acceptable intakes for an individual impurity

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

Table 3: Acceptable intakes for total impurities

Duration of treatment	< 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	60	10 (30*)	5

*For clinical development up to 3 years. Similar principles could be applied to marketed products with justification.

Table 1: Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions (according to Ref. 17 with modifications)

Class	Definition	Proposed action for control
1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)	Control at or below acceptable limits (generic or adjusted TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data	Control at or below acceptable limits (generic or adjusted TTC) or do bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance which has been tested and is non-mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity	Treat as non-mutagenic impurity

*Or other relevant positive mutagenicity data indicative of DNA-reactivity related induction of gene mutations (e.g. positive findi in *in vivo* gene mutation studies)

Thank you for your attention

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