CBG MEB MEDICINES EVALUATION BOARD

Draft Reflection Paper Non-genotoxic impurities

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Disclaimer

- **The views expressed in this presentation are those of the presenter and do not necessarily reflect those of the MEB, the EMA or any other regulatory body or authority.**

Impurity qualification

- **Impurities in medicinal products need to be qualified (i.e. the safety should be evaluated)**
- **Specific guidance in Quality and Multidisciplinary ICH guidelines**
  - ICH M7: genotoxic impurities
  - ICH Q3C: solvents
  - ICH Q3D: metal impurities
- **Other impurities: ICH Q3A and ICH Q3B**

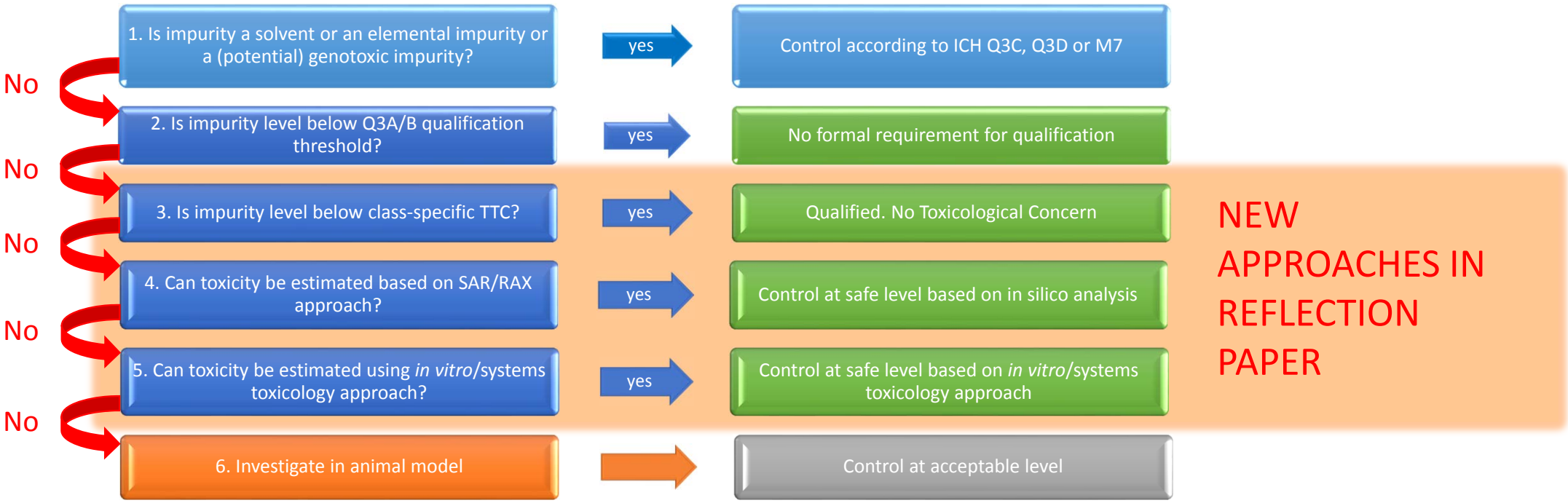
Problem statement

- Impurities are usually qualified through non-clinical safety studies and clinical studies with active substance/product
- Data gap emerges for new impurities that have not been qualified previously
- **ICH Q3A/B guidelines ask for (comparative) animal studies**
- **Animal studies provide limited information**
  - Administered dose of impurities in studies is low
  - Background toxicity of active substance
  - Studies do not discriminate between toxicity by active substance and impurity
- **Animal studies should not be performed if information can be obtained otherwise** (Directive 2010/63/EU)

Draft Reflection Paper on the qualification of non-genotoxic impurities

- **EMA/CHMP/SWP/545588/2017**
- **Released for consultation on 23 November 2018 until 30 September 2019**
- **The RP has regard to the non-clinical aspects of qualification of non-genotoxic impurities**
- **The RP does not change the ICH Q3A/B guidance but rather extends on it and provides an alternative approach to qualify non-genotoxic impurities**
- **The RP tries to establish a conceptual framework to facilitate discussions among stakeholders.**
- **The RP may contribute to the ongoing efforts to reduce, refine and replace animal experiments**

Alternative strategy for impurity qualification



1. Is impurity a solvent or an elemental impurity or a (potential) genotoxic impurity?

Control according to Q3C, Q3D or M7

- M7: If a potential mutagenic impurity turns out to be class 4 or 5 → treat as non-genotoxic impurity → RP

2. Is impurity level below Q3A/B qualification threshold?

No formal requirement for qualification

- The RP does not intend to change current ICH Q3A/B qualification thresholds

- What if daily exposure > TTC and impurity level is < qualification threshold?
  - To further reduce any remaining concern the principles of the RP can be considered.

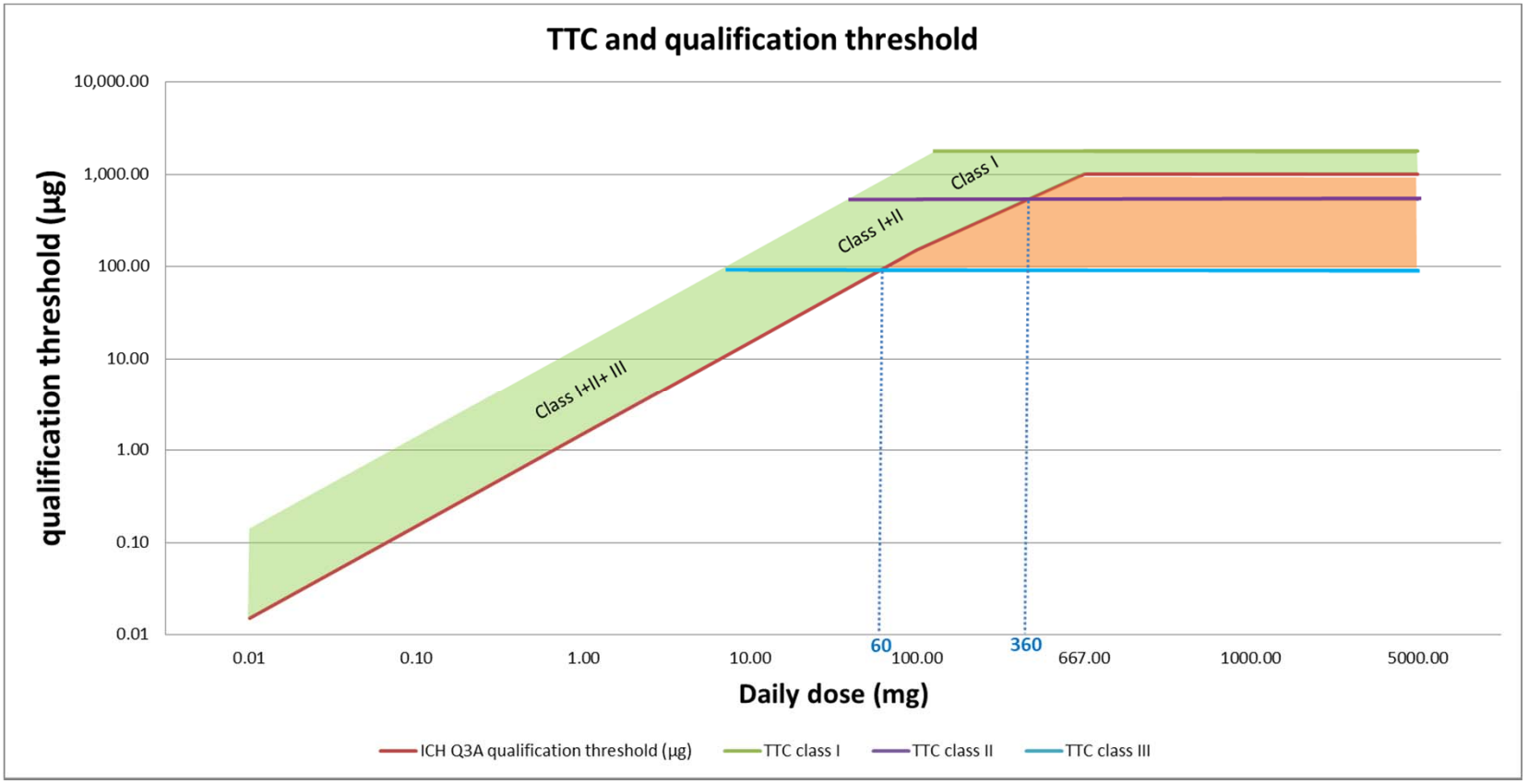
- Impurity level > qualification threshold, but daily exposure < TTC
  - No need for further studies: qualified.

3. Is impurity level below class-specific TTC?

Qualified. No Toxicological Concern

- TTC is a scientifically valid methodology to assess the safety of substances of unknown toxicity
- Originally developed by Munro et al. (1996).
- 5th percentile of distribution of (most conservative) NOAELs in oral toxicity studies; 100-fold safety factor
- Class-specific TTC values for Cramer Class I, II and III: 1800, 540 and 90 µg/person per day
- Exemptions for organic phosphates and carbamates (18 µg/person).
- Modified values with different datasets: Tluczkiewicz et al. (2011): 1930, 1478 and 63 µg/person/d for classes I, II and III.
- Modified values with different exposure routes: Tluczkiewicz et al. (2017): 2 and 4260 µg/person/d for toxic and low toxic compounds after inhalatory exposure

3. Is impurity level below class-specific TTC?



4. Can toxicity be estimated based on SAR/RAX approach?

Control at safe level based on in silico analysis

- Read across (RAX) for compounds structurally similar to known compounds
- Impurity closely related to API: does difference alert for toxicity?
- (Quantitative) Structure Activity Relationships (Q)SAR
- No signal indicating risk → qualified
- In case of alert → quantify risk → control a safe level
  - Additional data needed (next step)

4. Can toxicity be estimated based on SAR/RAX approach?

Control at safe level based on in silico analysis

- Which tools to use?
  - OECD QSAR toolbox

- Validity, reliability and relevance of results?
  - OECD principles:
    - ✓ defined endpoint
    - ✓ unambiguous algorithm
    - ✓ applicability domain
    - ✓ measures of goodness-of–fit, robustness and predictivity
    - ✓ mechanistic interpretation of the model used.

- Further discussion on use of QSAR for qualification of drug impurities needed
  - Workshops

5. Can toxicity be estimated using *in vitro*/systems toxicology approach?

Control at safe level based on *in vitro*/systems toxicology approach

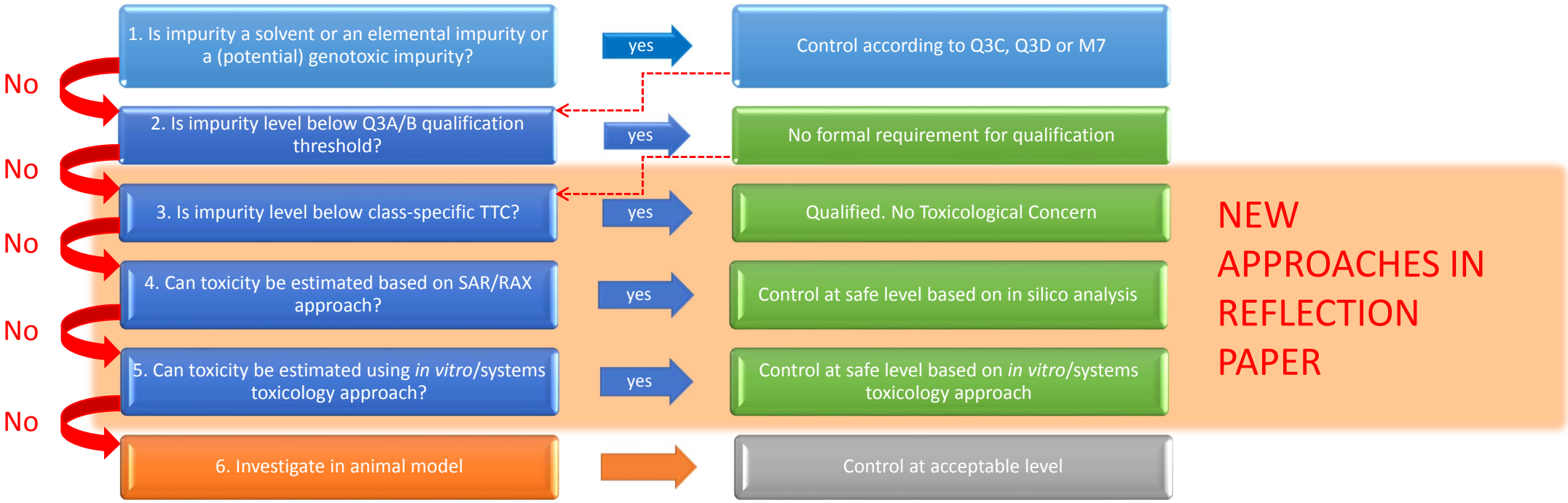
- In case of specific alert: targeted *in vitro* assay(s)
- In case of insufficient information from *in silico* analysis: hazard identification based on *in vitro* analysis
  - New Approach Methodologies under development
    - E.g. EUToxrisk, TOX21
- Show that the method is suitable for its intended purpose
  - Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)
  - OECD Guidance document for describing non-guideline in vitro test methods
- Testing of impurities alone

6. Investigate in animal model

Control at acceptable level

- Only when other options have run out
- Design should be comparative (old *vs.* new; pre *vs.* post).
- Testing of impurity alone

Alternative strategy for impurity qualification



Conclusion

- New approaches provide alternative options for qualification of non-genotoxic impurities
- Impurity-specific data is more informative
- Full risk characterisation is not necessary. Only ascertain that at proposed level there is no safety concern.
- Non-animal methodologies advance 3Rs
- Further discussion necessary on choice of appropriate tools

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Comments or questions?