# What applicants need to know about technical equivalence and chemical similarity

## Technical equivalence – Tier I

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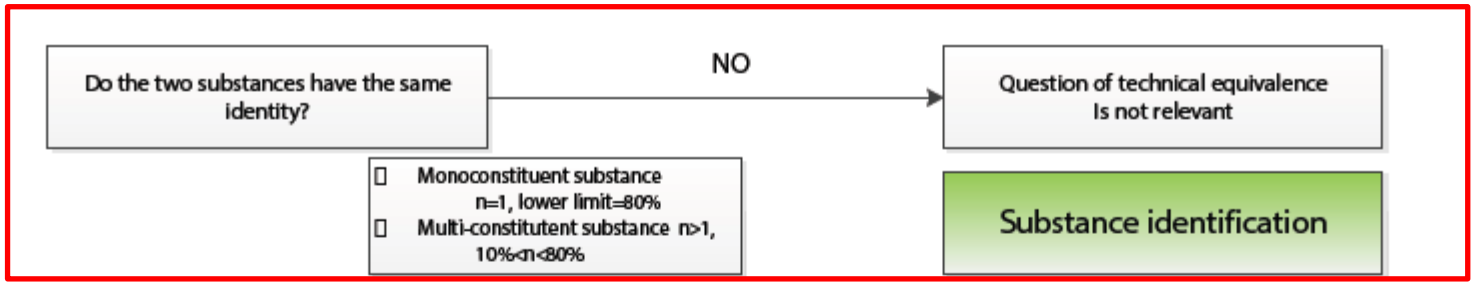
# Outline

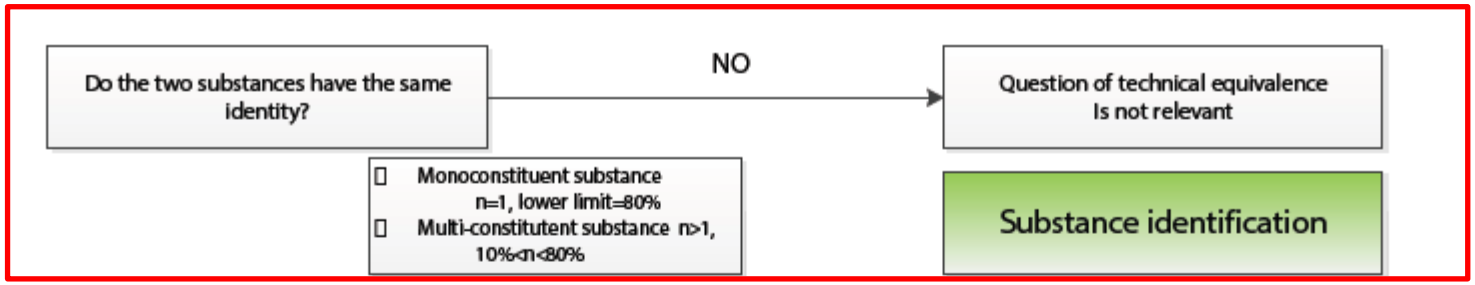
- What Tier I assessment covers
- What information should be provided for Tier I in the technical equivalence application?
- How the assessment is carried out
- Tips to improve the quality of the Tier I-related information in the technical equivalence application
- Key messages

# What Tier I assessment covers

- Tier I consists of the evaluation of:
  - substance identity
  - chemical composition

- The specifications provided for the active substance from an alternative source are compared with the specifications of the reference source included in the approval of the active substance


Do the two substances have the same identity?
NO
Question of technical equivalence Is not relevant
Monoconstituent substance n=1, lower limit=80%
Multi-constitutent substance n>1, 10%<n<80%
Substance identification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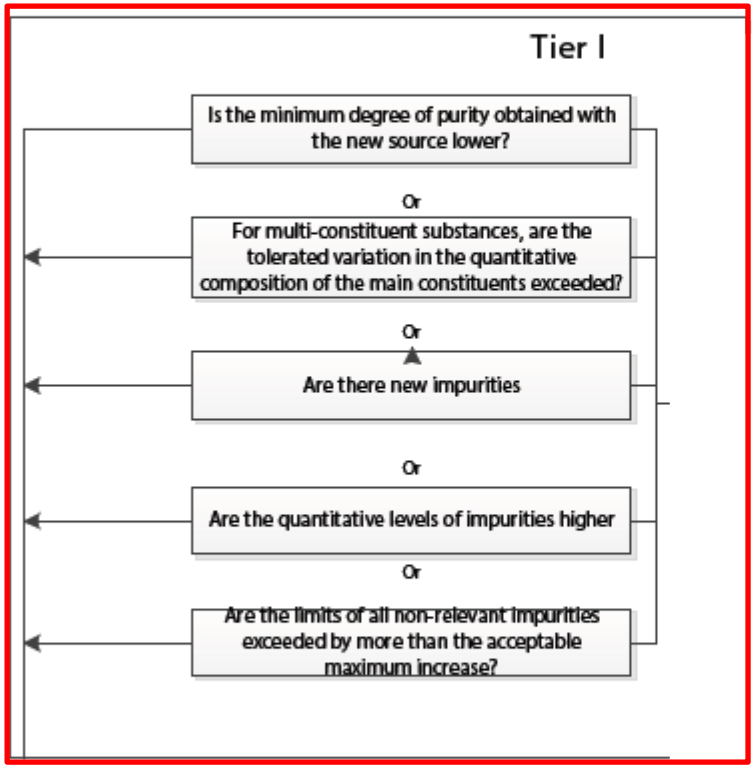
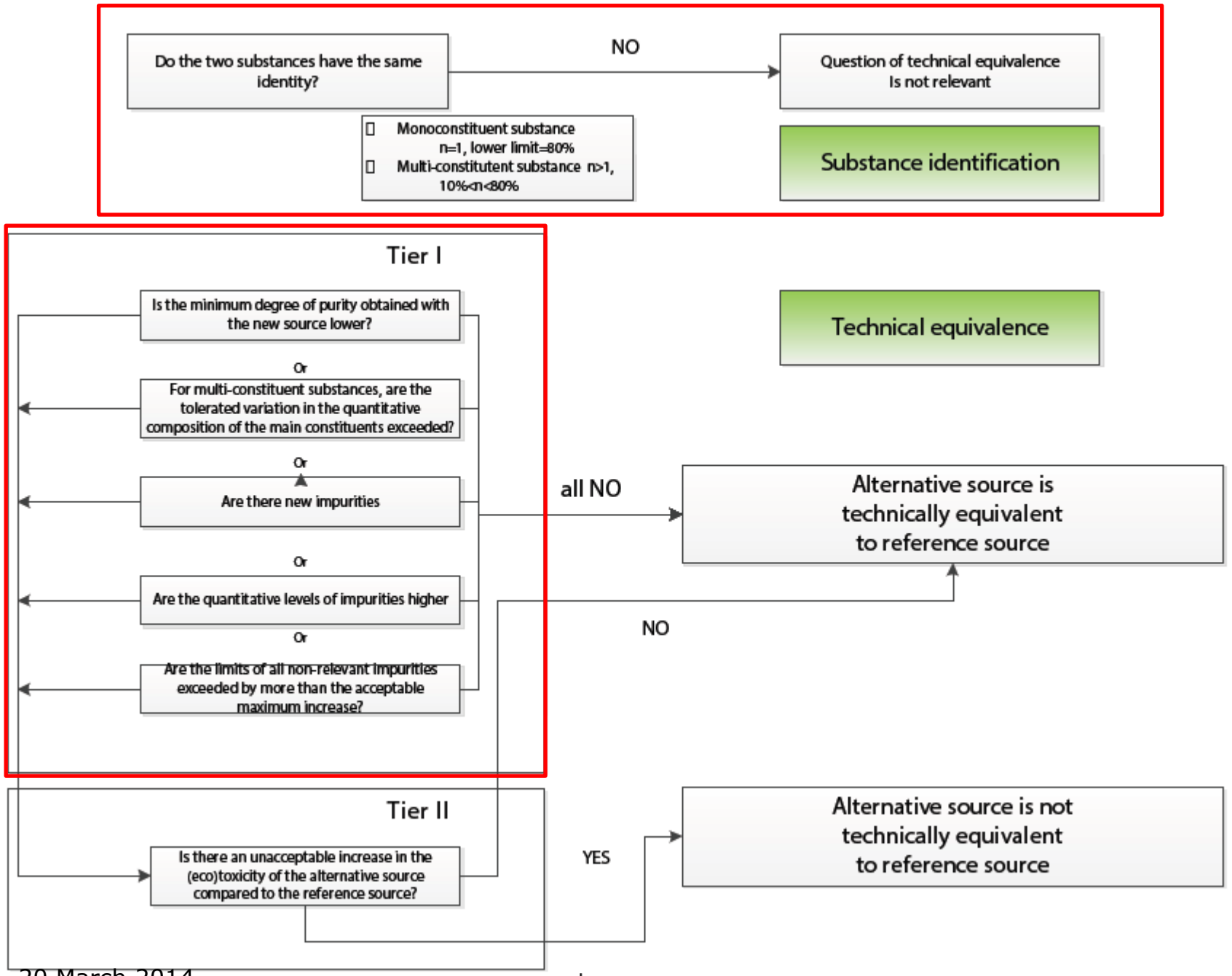

Tier I
Is the minimum degree of purity obtained with the new source lower?
Or
For multi-constituent substances, are the tolerated variation in the quantitative composition of the main constituents exceeded?
Or
Are there new impurities
Or
Are the quantitative levels of impurities higher
Or
Are the limits of all non-relevant impurities exceeded by more than the acceptable maximum increase?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Are the quantitative levels of impurities higher
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Are the limits of all non-relevant impurities exceeded by more than the acceptable maximum increase?
all NO
Alternative source is technically equivalent to reference source
NO
Tier II
Is there an unacceptable increase in the (eco)toxicity of the alternative source compared to the reference source?
YES
Alternative source is not technically equivalent to reference source

# Who should apply for Tier I assessment?

- Example:
  - Technical equivalence applicant that was a participant in the Review Programme and supported the active substance

    - The applicant has detailed knowledge on the composition of the active substance from the reference source

    - The applicant has a reason to believe that the purity and the impurity profile of the active substance from the alternative source is within the accepted limits compared to the specifications for the reference source

# What information should be provided for Tier I?

# Requirements for Tier I applications (1)

- Applicant (name, contact details etc.)
- Manufacturer of the active substance; Method of manufacture
- Identity of the active substance (numerical and other identifiers)
- Information on optical activity and full details of any isomeric composition
- Specification of active substance purity, including the upper and lower limit
- Identity of any impurities and additives including by-products of synthesis, optical isomers, unreacted and end-groups of polymers and unreacted starting materials of UVCB substances

# Requirements for Tier I applications (2)

- Analytical profile of at least five representative batches (…) including information on content of the impurities
- Analytical method used in the five batch analysis
- Absorption spectra data

***For more details, see "Guidance on applications for technical equivalence" and "Guidance on information requirements"***

# Method of manufacture (1)

- Description of the synthesis pathway including:
  - Chemical reactions
  - Starting materials
  - Solvents
  - Substances generated in the synthesis, etc.

- Reaction conditions when relevant, e.g.:
  - Temperature
  - Pressure

# Method of manufacture (2)

- The method of manufacture is important for understanding the active substance composition and impurity profile specifications, e.g.:
  - When active substances are racemates/specific isomers: information on the manufacturing process is important for verifying the isomeric composition (e.g. enantiomeric composition of the starting materials may be relevant to determine the enatiomeric composition, etc.)
  - Impurities: the impurity profile should be in line with the method of manufacture
- Technical equivalence application is specific for the method of manufacture → change in the process may result in the need to have a new technical equivalence assessment

# Composition specifications (1)

- Specification of active substance purity
  - typical concentration, upper and lower limits for concentration
- Isomeric composition
- Impurity specifications:
  - identities
  - typical concentrations and the range of concentrations for each impurity:
    - Impurities ≥0.1% w/w (dry technical material)
    - Relevant impurities even if <0.1% w/w
- Additives

# Composition specifications (2)

- An explanation of how the specification was derived must be provided:
  - e.g. an explanation based on the five-batch analysis, mean ± 3 × std deviation
  - Quality control (QC) data can be submitted e.g. to modify the minimum purity of the active substance or the maximum limit of some impurities from what is shown in the five-batch analysis data (Note: QC data does not replace five-batch analysis)

# Impurities (1)

- **Accurate information on the identities and content of impurities is essential for TE Tier I assessment, therefore remember to:**

  - Provide clear identifiers for the impurities in all parts of the dossier (IUPAC name, possible EC/CAS identifiers, structural formula)
  - Clearly indicate the maximum concentration specification of each impurity
  - Include an explanation on how the specifications were derived

# Impurities (2)

- If you provide analytical information on an impurity which is not actually detected in the representative batches, make sure you clearly indicate whether the impurity should be considered as part of the composition specifications.

# Analytical profile of at least five representative batches and method used in the five-batch analysis (1)

- Report GLP compliant
- Representative batches
- Analytical closure of individual batches covering at least 98% (active substance and fully identified impurities)
- Fully validated methods for
  - Active substance
  - Impurities ≥0.1% w/w (dry technical material)
  - Relevant impurities even if <0.1% w/w
  - Additives
  - Validation parameters: see ”Guidance on information requirements”

# Analytical profile of at least five representative batches and method used in the five batch analysis (2)

- Specific/highly specific methods depending on the substance type

- Isomeric ratios of substances with chiral centers must be investigated using analytical methods such as:
  - chiral chromatography
  - optical activity

# Absorption spectra data (1)

- Absorption spectra data :
  - UV/VIS
  - IR
  - NMR
  - mass spectrum
  - molar extinction coefficient at relevant wavelengths, where relevant for the purified active substance of stated specification

**Spectral data is necessary for confirming the identity of the active substance**

# Absorption spectra data (2)

- The sample used in the measurements should not contain interfering amounts of impurities, additives or other components which might overlap with the signals from the active substance and prevent the verification of the active substance identity

- Technical equivalence cannot be assessed without the spectra data

# How is Tier I application assessed?

# How is Tier I application assessed – what is assessed first?

- Is the identity of the active substance verified?
- Are the impurities clearly identified?
- Are the specifications for the composition profile reasonable (active substance purity, impurity profile, additive(s))?
  - Is there sufficient information to confirm that the batches are representative?
  - Are the specifications in line with the analytical information i.e. five-batch data, with support from QC data?
  - Is it explained how the specifications were derived from the five-batch data?
  - Is there reason to suspect that the specifications do not cover the whole composition?

# How is Tier I application assessed – criteria for concluding on technical equivalence (1)

**Specifications of the alternative source vs. reference specifications for the approved active substance**

**All of the following conditions need to be met:**

- The minimum degree of purity obtained with the alternative source is equal to or higher than the one obtained with the reference source

- For multi-constituent substance, each main constituent remains in the 10-80 % range and the concentration of each main constituent does not deviate by more than 5 % absolute or 10 % relative, whichever is larger

# How is Tier I application assessed – criteria for concluding on technical equivalence (2)

- No new impurity or additive is present
- The limit of each relevant impurity or additive is not exceeded
- The limits of all significant but not relevant impurities as certified on the basis of a five-batch analysis for the reference source are not exceeded by more than the following levels:

| Limits of significant but not relevant impurities in the technical specifications of the reference source | Acceptable maximum increase in the alternative source[4] |
|---|---|
| ≤6 g/kg | 3 g/kg |
| >6 g/kg | 50% of the certified limit |

# Tips and key messages

# Tips on how to improve your application and to ensure smooth assessment (1)

- Include all required information in the first submission
- Ensure that all provided information is clear, consistent and easy to find
- Use analytical methods appropriate for the type of substance (e.g. chiral chromatography)

# Tips on how to improve your application and to ensure smooth assessment (2)

- Indicate clearly what are the composition specifications of your active substance, including the impurities and possible additive(s), and how the specifications were derived
  - Use the IUCLID composition fields in Section 2.9 to report the composition specifications to be considered in the technical equivalence assessment
- **Why? If something is not clear or is missing**
  **→ request for further information from ECHA**
  **→ delay in processing your application**

# Key messages

- Tier I assessment focuses on substance identity and chemical composition

- ECHA checks if
  - the specifications are reasonable and verified by the analytical information → technical equivalence Tier I assessment is possible
  - the specifications comply with the specifications for the AS obtained from the reference source → alternative source is/is not technically equivalent according to Tier I

- To ensure smooth assessment it is recommended to provide all required information in a clear and consistent manner

# Further information on technical equivalence Tier I


- Guidance on applications for technical equivalence http://echa.europa.eu/guidance-documents/guidance-on-biocides-legislation?panel=guidance_applications_technical_equivalence
- Guidance on information requirements http://echa.europa.eu/guidance-documents/guidance-on-biocides-legislation?panel=guidance_information_requirements
- Guidance for identification and naming of substances under REACH and CLP http://echa.europa.eu/guidance-documents/guidance-on-reach

# Thank you

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