

+++ + Substance identity:
The critical component of both
lead and co-registration dossiers

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Agenda

- + Substance categories
- + Types of analysis
- + Quality advice

Why is further advice needed?

+ Phase 1 and 2:

'Correct and unambiguous substance identification is a frequent shortcoming in registration dossiers'

(ECHA)

Substance categories

Substance categories

Mono-Constituent Substance
≥80% main constituent (guidance)
Remainder are impurities

Multi-Constituent Substance
No single constituent ≥80%
Multiple constituents ≥10% <80%
Impurities possible

UVCB
Undefined, Variable, Complex, Biological
Defined by starting materials and process
No impurities, all are components

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Substance categories

Mono-constituent substance
≥80% main constituent (guidance)
Remainder are impurities



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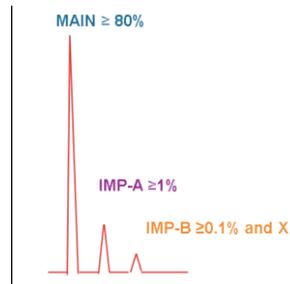
Substance categories

+ Single substance

- + $\geq 80\%$ main constituent (guidance)
- + Remainder are impurities

+ Identify and name all impurities:

- + $\geq 1\%$
- + $\geq 0.1\%$ if hazardous
- + Composition must add to 100%

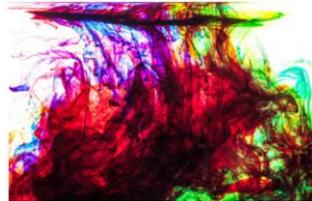


Substance categories

+ Multi-Constituent substance

- + No single constituent $\geq 80\%$
- + Multiple constituents $\geq 10\% < 80\%$
- + Impurities possible

- + When it is physically impossible to create the substances individually and maintain the same properties (not just a formulation)



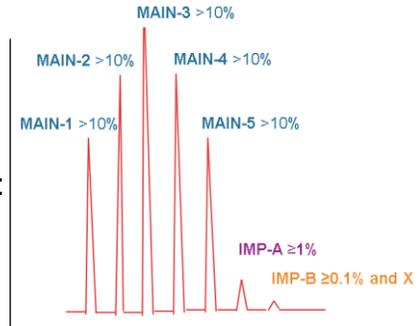
Substance categories

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Substance categories

+ UVCB

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- + Defined by starting materials and process
- + No impurities, all are constituents



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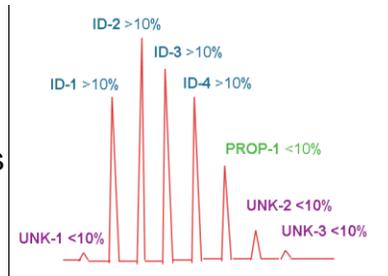
Substance categories

+ UVCB

- + Undefined, Variable, Complex, Biological
- + Defined by starting materials and process
- + No impurities, all are components

+ Identify and name all components $\geq 10\%$

- + $<10\%$ naming is an advantage
- + Make naming proposals
- + Group and categorise unknowns



Types of analysis

Types of analysis (standard methods)

- + Type-1: Basic identity
- + Type-2: Detailed identity
- + Type-3: Purity

Types of analysis (standard methods)

- + Type-1: Basic identity
 - + UV-Vis spectroscopy
 - + IR spectroscopy
- + Type-2: Detailed identity
 - + NMR and/or mass spectrometry
- + Type-3: Purity
 - + GC or HPLC

Types of analysis (standard methods)

MAXIMISE SPECTRAL COVERAGE TO AVOID REPEATS

- + UV-vis
 - + 200-750 nm, consider acid and alkaline environments
- + H-NMR and C-NMR
 - + 0-15 ppm for ^1H , 0-250 ppm for ^{13}C
- + Mass spectrum
 - + 0 to full m/z

Types of analysis (additional methods)

- + Do not consider the list of techniques as exhaustive
- + Perform (additional) tests to suit the substance
- + Aim to **JUSTIFY**, not just **COMPLY**

Types of analysis (additional methods)

+ Inorganics

- + XRD
- + Atomic absorption

+ Organic salts

- + Carbon v Metal balance

+ Oligomers

- + GPC

+ Database comparisons

- + GCMS
- + XRD
- + IR and NMR

+ Organics

- + CHN by combustion
- + GCMS

+ Inorganics

- + Karl Fischer (water)
- + Silver Nitrate (chloride)

+ Chiral substances

- + Optical activity

+ Solid particles

- + BET surface area
- + Electron microscopy

Quality advice

Quality advice (check list)

+ Traceability data essential for high quality reporting

Substance name:	_____
CAS number:	_____
Batch number*:	_____
Manufacture date:	_____
Expiry date:	_____
Purity:	_____
Substance nature:	_____

Laboratory name:	_____
Laboratory address:	_____
Operator name:	_____
Operator signature:	_____
Laboratory head name:	_____
Laboratory head signature:	_____
Analysis date:	_____

*All analyses on the same batch as far as possible

Quality advice (check list)

+ Full technical data and interpretation required

Technique:	_____
Machine details:	_____
Run conditions:	_____

Description of results:
Interpretation of results:
Detailed method:

Full Spectrum:

Role of lead registrant in substance identity

- + The lead registrant is not responsible for certifying the analytics and identity of co-registrant substances
- + Method advice from lead registrants usually only comes in special cases (such as with difficult category justifications)
- + All liability for substance identity rests with the registrant

Conclusions

Conclusions

- + The registrant is fully responsible for the identity of their substance
- + Defined substance categories have been created
- + Analysis selection and quality are vital for identity justification
- + Incomplete identification is not excused