Substance Identity: The Critical Component of Both Lead and Co-registration Dossiers

The Lessons from Phase 1 and 2 in Preparation for an Efficient Phase 3

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Agenda

- Why Must We Maximise Efficiency?
- Why is Further Advice Needed?

- Substance Categories
- Types of Analysis
- Quality Advice

- Analytics Sharing and Identity Comparison
- Substances from Multiple Sources
- Analytics Dictate Timing

- Liability and Proof

Why Must We Maximise Efficiency?

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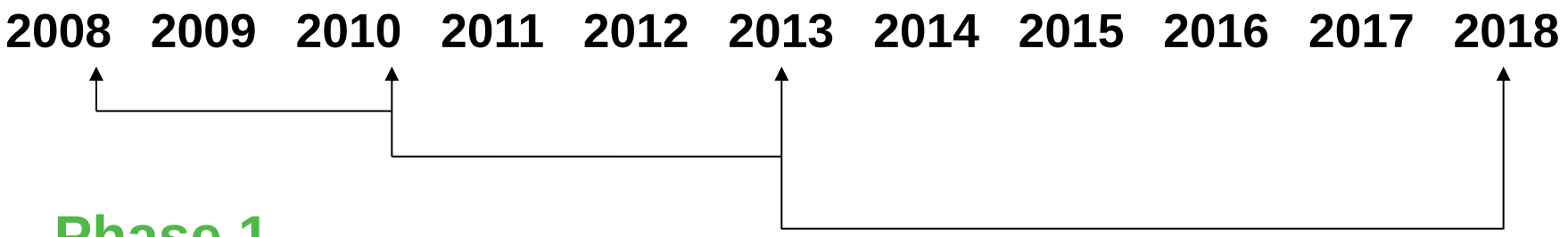
Why Must We Maximise Efficiency?



Phase 1

2 years

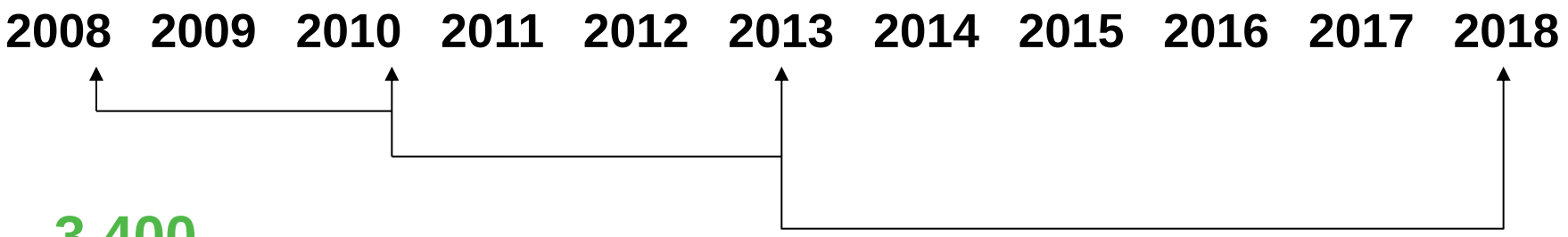
Phase 2

2.5 years

Phase 3

5 years

Why Must We Maximise Efficiency?



3,400 Substances

20,000 Dossiers

3,000 Substances

9,000 Dossiers

25,000 Substances

70,000 Dossiers

No reduction in identity data requirements

Why is Further Advice Needed?

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Why is Further Advice Needed?

ECHA QUOTE

Phase 1 and 2:

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

Substance Categories

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Substance Categories

Single Substance

≥80% main component (guidance)

Remainder are impurities

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

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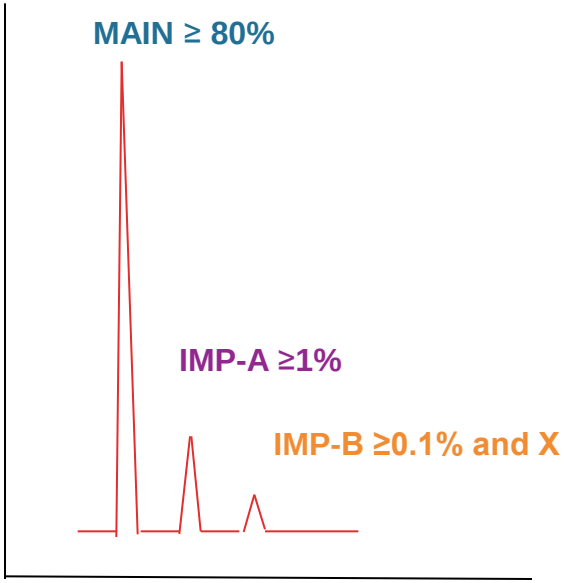
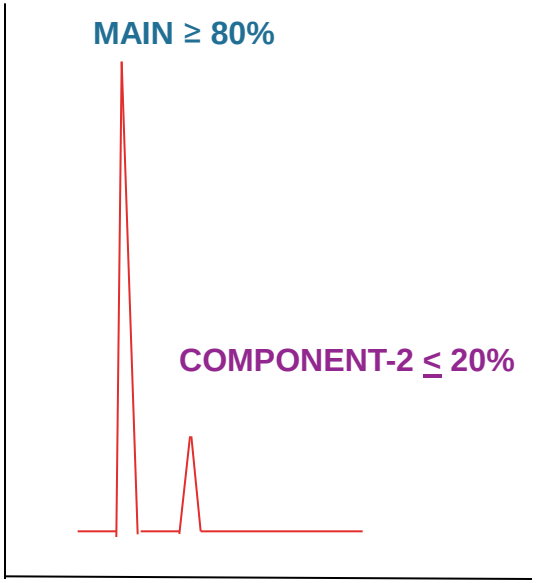


Identify and name all impurities:
≥1%
≥0.1% if hazardous
Composition must add to 100%

Substance Categories

SINGLE SUBSTANCE DEVIATION

Single Substance
≥80% main component (guidance)
Remainder are impurities

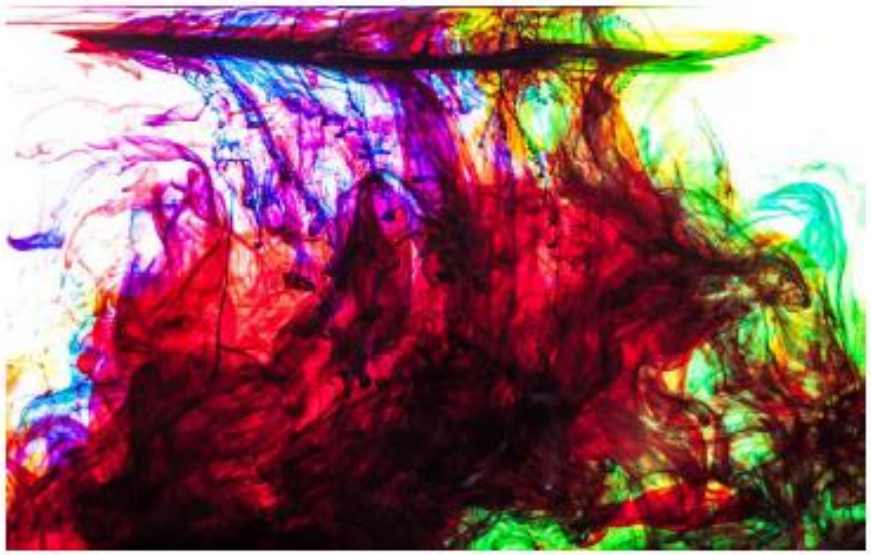


Deviation from 80/20 rule is possible

When component-2 results from an unintentional impurity then **Single**

When component-2 results from a deliberately added starting material consider **Multi-Constituent** or **Two Singles**

Substance Categories



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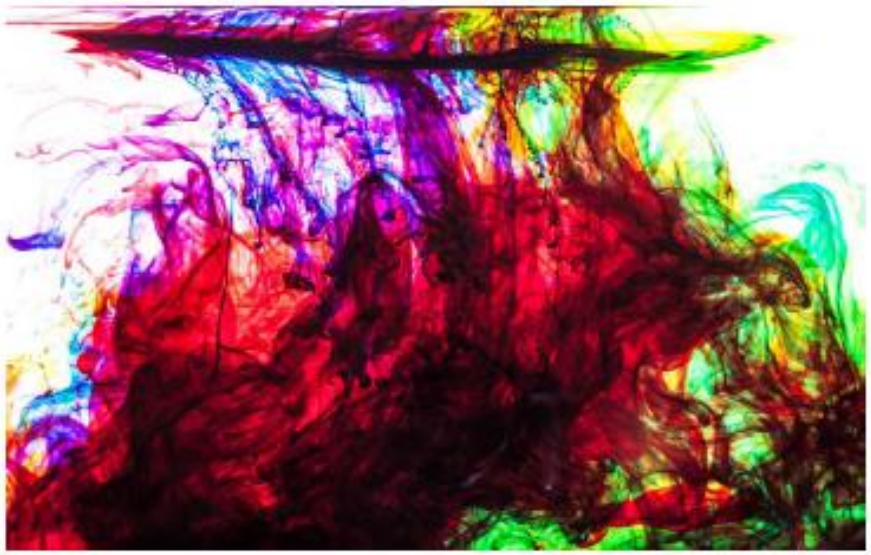

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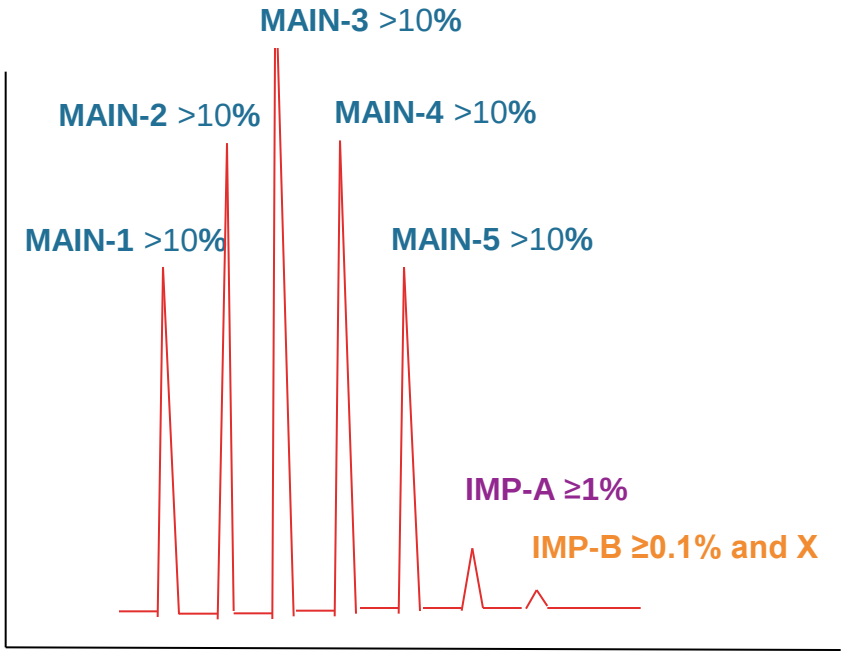
Impurities possible

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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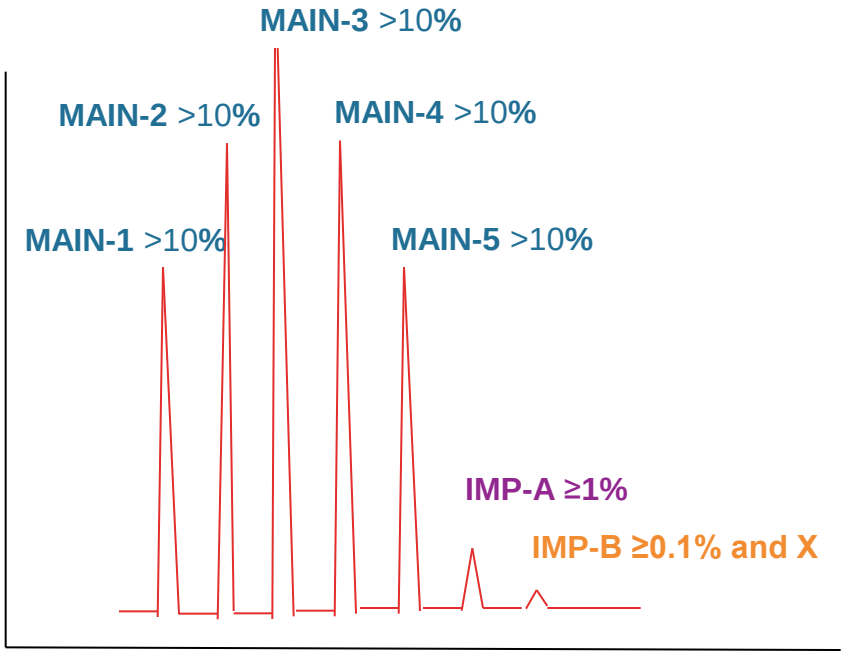

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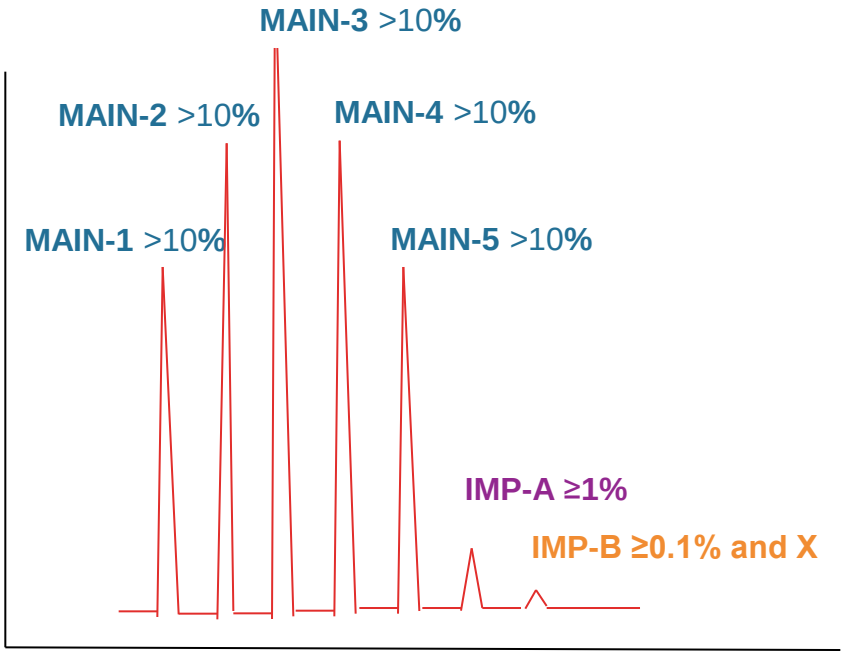
MULTI-CONSTITUENT DEVIATION

Mains 1,2,3,4 and 5 can be registered as single substances when;



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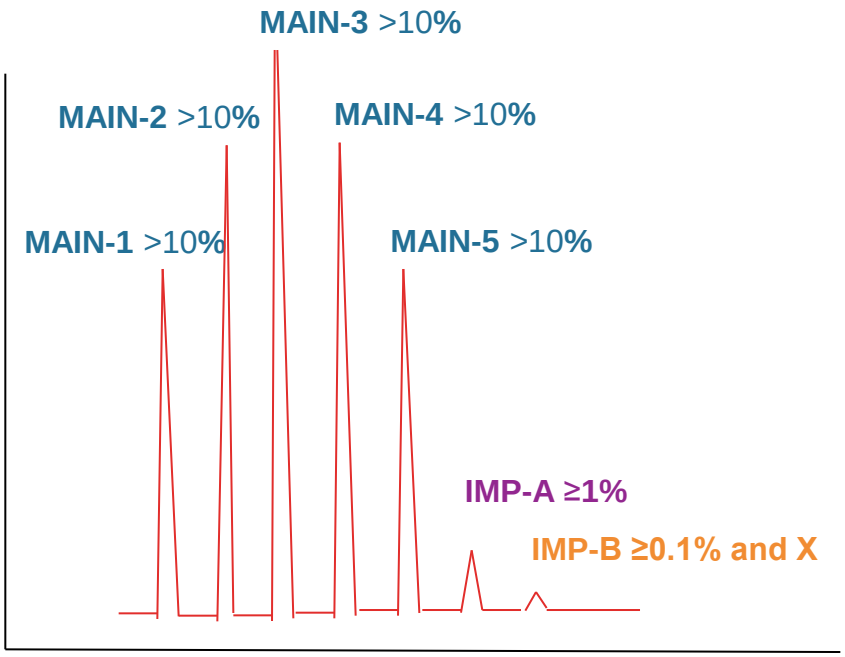


Multi-Constituent Substance
No single component ≥80%
Multiple components ≥10% <80%
Impurities possible

- It creates a more efficient situation
- Sufficient data exists to justify the approach
- There is no reduction in data requirement
- No need for new vertebrate testing

Substance Categories

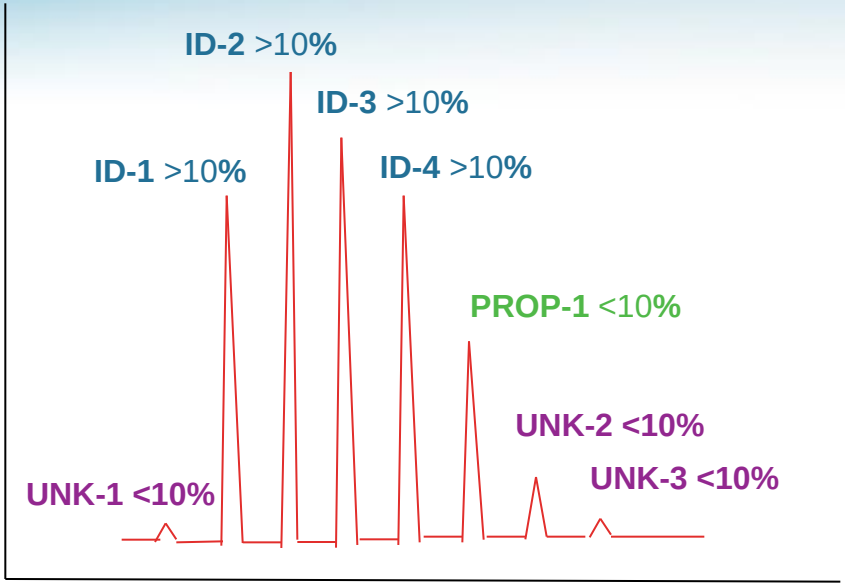
UVCB

Undefined, Variable, Complex, Biological

Defined by starting materials and process

No impurities, all are components

Substance Categories



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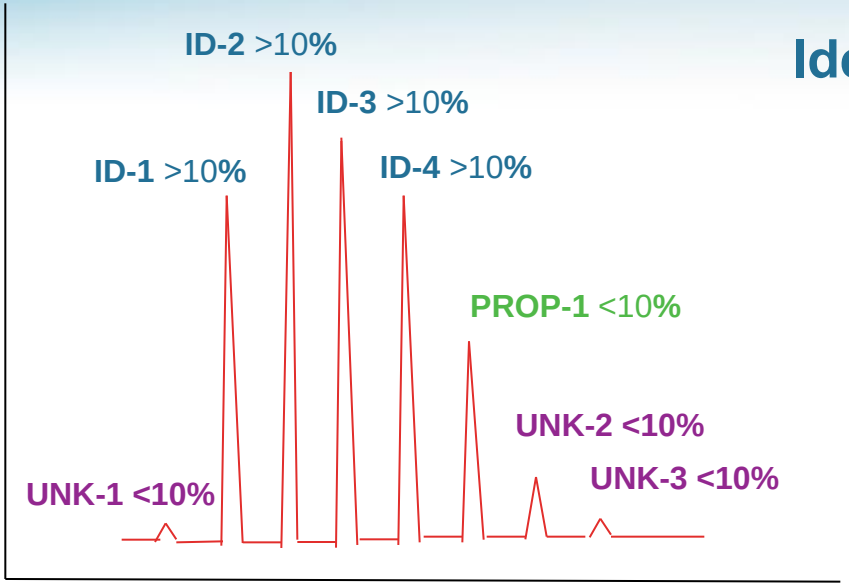

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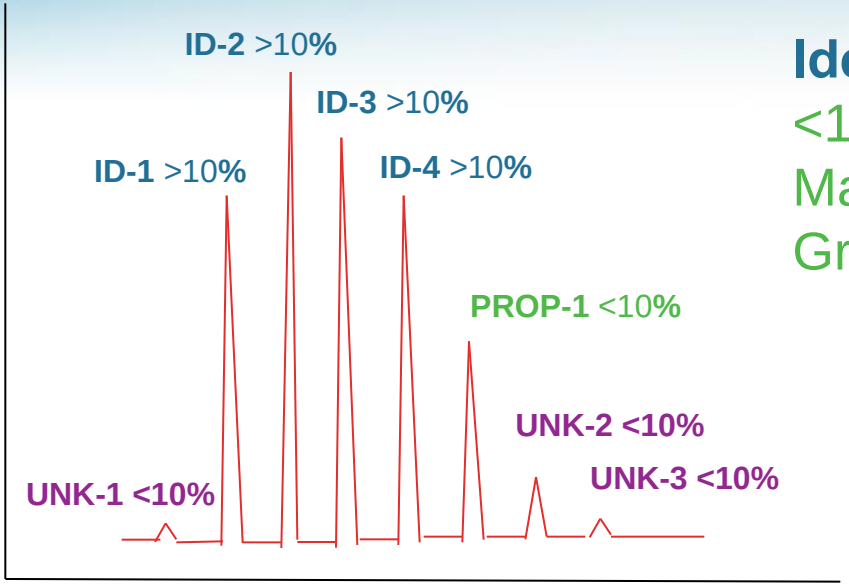

Identify and name all components ≥10%

<10% naming is an advantage

Make naming proposals

Group and categorise unknowns

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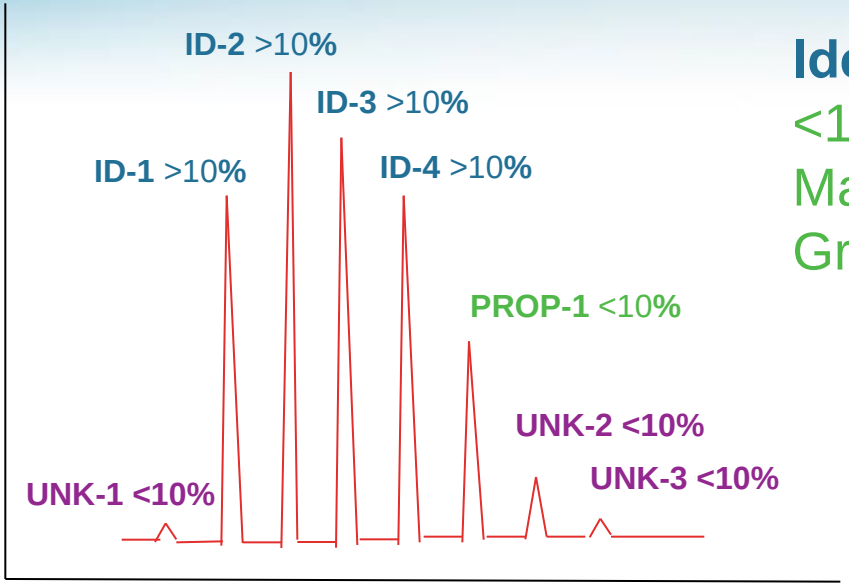

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<10% naming is an advantage

Make naming proposals

Group and categorise unknowns

Average m.wt 200

Identified m.wts 180-220

Unknowns:

- 10 substances in total
- All under 5%
- Total contribution 20%
- M.wts 170-230
- GCMS breakdowns show key main component similarities

UVCB

Undefined, Variable, Complex, Biological

Defined by starting materials and process

No impurities, all are components

Substance Categories

IDENTIFY WELL !!!

- Sameness is very difficult to justify
- Category justifcation can be extremely complex
- Read-across is even more problematic
- "*All under 10% so no naming*" is a proven failure

UVCB
Undefined, Variable, Complex, Biological
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Types of Analysis

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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
- Infra-Red
  - 600 - 4000 cm^{-1}
- H-NMR and C-NMR
  - 0 – 15 ppm for ^{1}H, 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
- Add further 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
  - Electon microscopy

Quality Advice

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Quality Advice

TICK LIST

- Traceability data essential for high quality reporting
  (consider also full GLP if material is to be used for studies)

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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

TICK LIST

- Full technical data and interpretation required

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TICK LIST

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Technique: _____
Machine details: _____
Run conditions: _____

Description of results:

Interpretation of results:

Detailed method:

Full Spectrum:

Analytics Sharing and Identity Comparison

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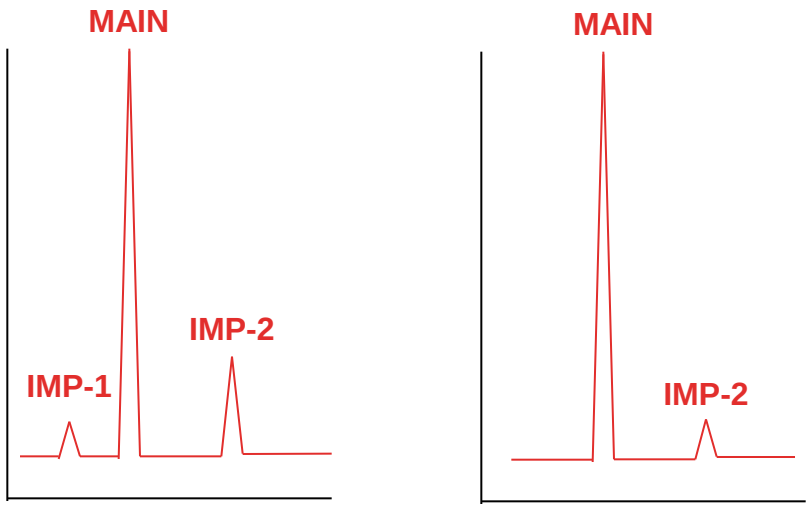
Analytics Sharing and Identity Comparison

- Sharing can reveal business sensitive information



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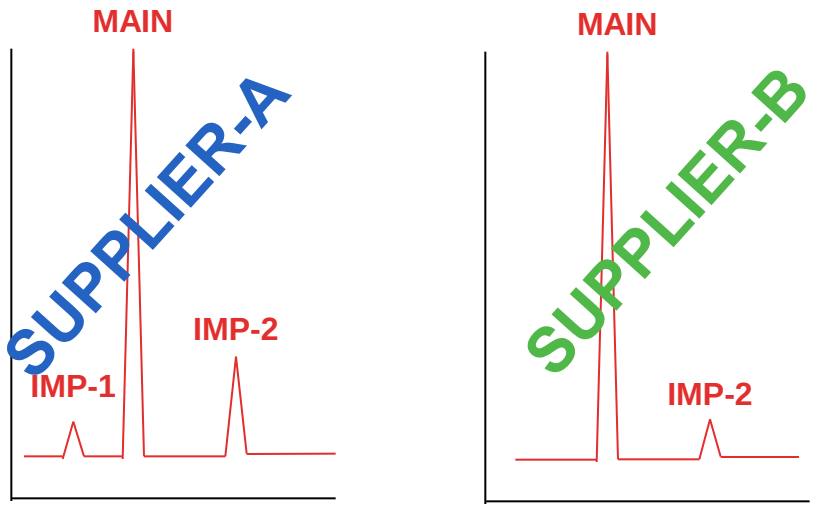
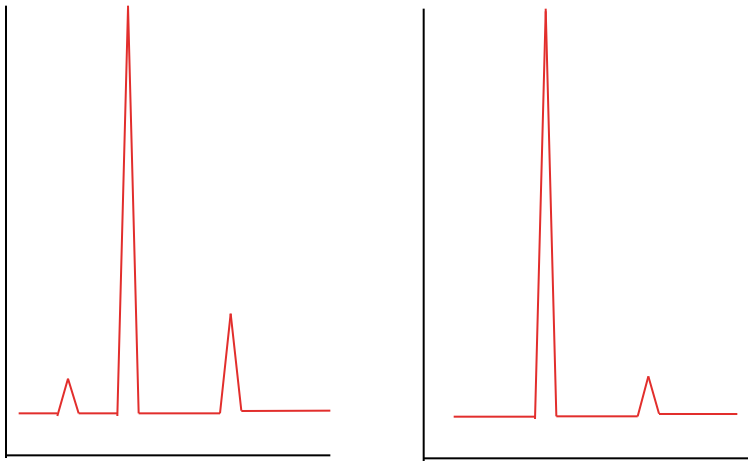


- Do you want your competitors to know your sources ?

Analytics Sharing and Identity Comparison

- Analytical **methods** can also be the market advantage



OWN METHOD

Analytics Sharing and Identity Comparison

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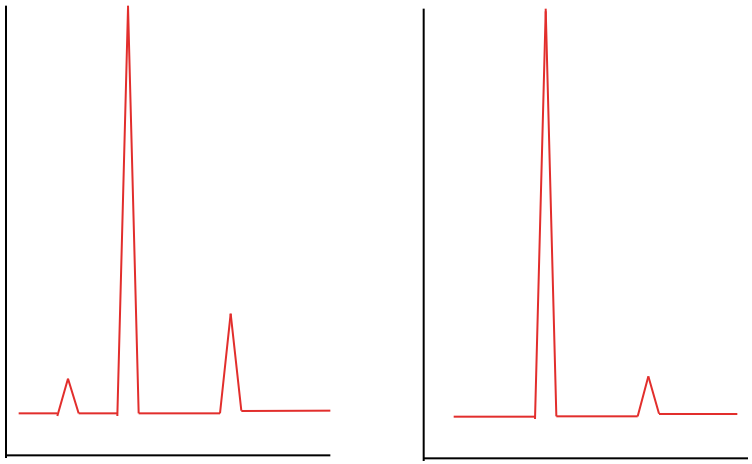
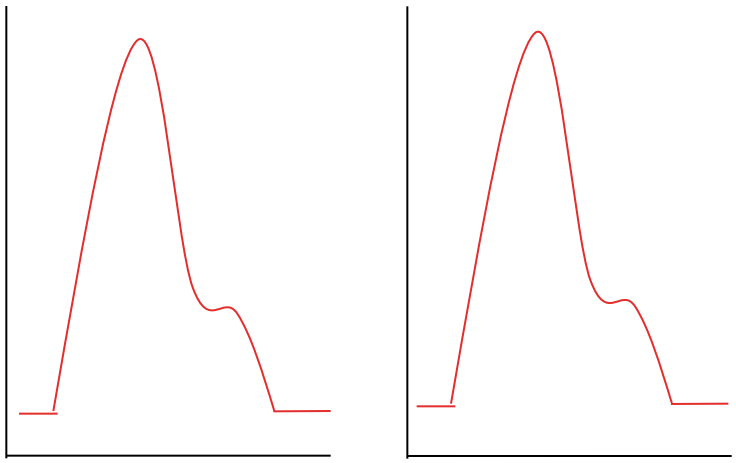


OWN METHOD



COMPETITOR METHOD

- Do you want to train your competitors?

Analytics Sharing and Identity Comparison

- 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)
- Comparisons (if needed) should be done via a trustee
- UVCB and Reaction Product comparisons may be essential

Substances from Multiple Sources

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Substances from Multiple Sources

- Submitted dossier must cover all sources

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- Submitted dossier must cover all sources
  - Declare multiple compositions

COMPOSITION-1
Main Component 95%
Impurity-A 5%

COMPOSITION-2
Main Component 95%
Impurity-B 5%

Substances from Multiple Sources

- Submitted dossier must cover all sources
  - Declare multiple compositions
  - Declare one composition with all possible impurities

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COMPOSITION
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  - As a minimum, have a purity trace for every source

Analytics Dictate Timing

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Analytics Dictate Timing

- Main substance identity is not what you thought
- New impurity found which affects classification
- Non-compliance with lead SIP or SIEF sameness

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BETTER TO FIND THIS NOW RATHER THAN LATER ?

LEAD REGISTRANTS ARE NOT RESPONSIBLE FOR YOUR LATE PROBLEMS !

Liability and Proof

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Liability and Proof

- All liability rests with the registrant
- The agency and authorities will not accept liability

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Believed to be….

We think that….

It is assumed….

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GO AWAY AND PROVE IT !

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REFERENCE IT PROPERLY AND JUSTIFY STEP-WISE !

Conclusions

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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

Sharing is dangerous and avoided except in extreme cases

Incomplete identification is not excused

Conclusions

If these guys do not or can`t identify their substance……

Conclusions

….why should these guys use it?

Conclusions

….and why should these guys assume anything other than worst case?

ECHA
EUROPEAN CHEMICALS AGENCY

Conclusions

……because these guys certainly can`t take the responsibility!

Conclusions

……and neither can these!

Dr Stuart Niven

Head of Regulatory Affairs, Switzerland Office

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