Non-liquid matrix analysis : Challenge and approaches

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Drug Development Evolution and BioA journey

Supporting decision making during drug development :

- *Does the drug reach the target ?*
- *To what extent does the drug reach the target ?*
- *Does the drug induce modulation of Biomarker link to the pathology ?*

Clinical studies using devices to collect samples

- N*on-invasive physical matrix : Strip, D Squames, ….*
- *Specific device : patients perform collection them-self*

Increase of non-liquid matrix analysis

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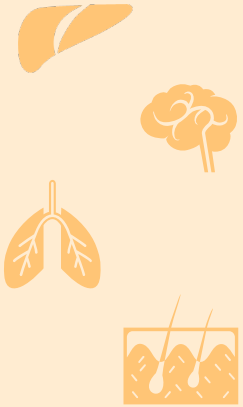
Type of matrix

non-liquid matrix

Tissues

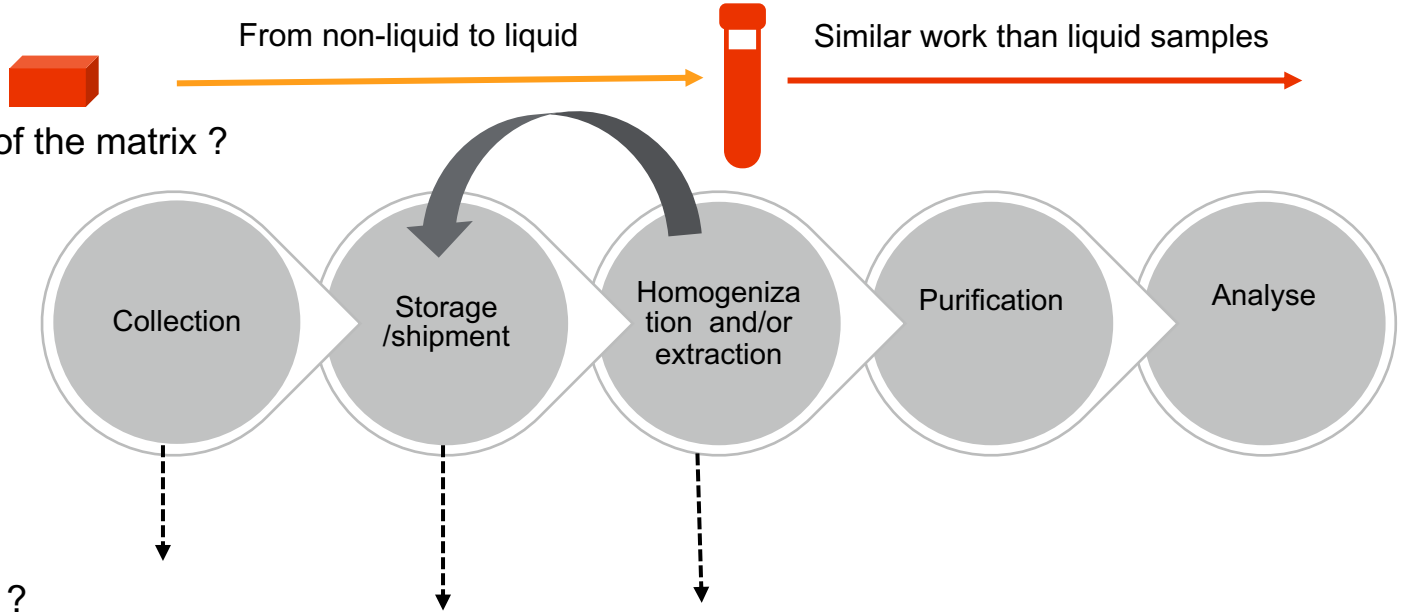
- Liver
- Brain
- Kidney
- Lung
- Muscle
- Skin
- Tumor
- …..



Device / Physical matrix

- Strip / D-squame
- Microsampling
- Device for collection
- Swab
- …..

Look at the process : What are the challenges ?



- Accessibility of the matrix ?
- Right sample ?
- Contamination occurs ?
- Stability ?
- Homogeneous sample (as liquid ?)
- Contamination during process ?
- % Recovery ?

Look at a few examples

non-liquid matrix

Tissues

Liver

Brain

Kidney

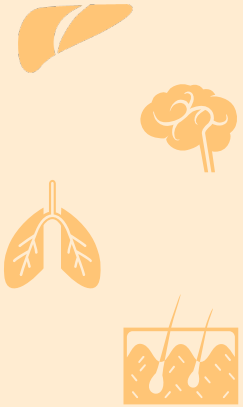
Lung

Muscle

Skin

Tumor

…..



Device / Physical matrix

Strip / D-squames

Microsampling

Device for collection

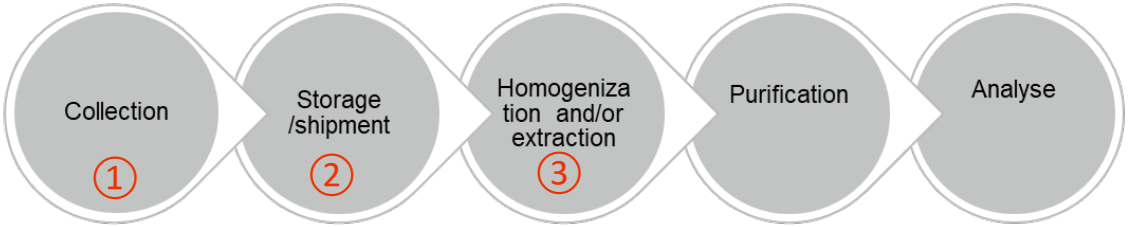
Swab

…..

Skin example : challenge and approaches

- Clinical study
- Application of dermal formulation
- Analyte : small molecule A
- Analyse : skin samples (E+D)
- Possibility to have HV matrix

Look at few steps



Skin example : challenge and approaches

① • Is the skin (E+D) biopsy the right sample ?

→ best compromise and informative for decision making

• Contamination occurs ?

!!! lucky no risk that human absorbs orally the formulation during study as animal which required protective collar to avoid bias

→ develop a proper process for collection

- ✓ Appropriate protocol to « wash » the skin
- ✓ SC removal (HV =20 strips; Pathological skin= 10 or 20 strips)
- ✓ ∅ 2-3 mm skin biopsy after stripping for compound dosing (E + D+ remaining SC)
- ✓ wash correctly the punch equipment between dosing to avoid cross contamination sample to sample

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Skin example : challenge and approaches

②

- Sample(s) to perform a stability as intact
  - Option 1 : Spike skin with X µl of analyte stock solution , let evaporate

Test	Criteria	Conformity
Stability at LLOQ level as intact at -80°C (%Dev)	≤ ± 15 % nominal value	Conforms
Stability at QC1 level as intact at -80°C (%Dev)	≤ ± 15 % nominal value	Conforms
Stability at QC2 level as intact at -80°C (%Dev)	≤ ± 15 % nominal value	Conforms
Stability at QC3 level as intact at -80°C (%Dev)	≤ ± 15 % nominal value	Conforms

  - Option 2 : create a sample by Franz Cell approach and do punch as in clinic
    → not often chosen due to heterogeneity and difficulty to conclude
    → might be relevant to identify a risk of a very specific interaction into the skin

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Skin example : challenge and approaches

③

- Recovery ?

→ skin « easy to have » comparing to other tissues : few tests can be done during development

Spike tissue with analyte stock solution and let's evaporate

Test solvant

Homogenization process

Spike the Blank matrix

Condition	2 hours extraction	4 hours extraction	6 hours extraction
MetOH		CV high Recovery low ✗	
Met/OH H2O 1V/1V	CV conforms Recovery low ✗		CV conforms Recovery conforms ✓
MeOH /H2O 1V/1V grinding condition 6	CV conforms Recovery low ✗		CV conforms Recovery conforms ✓

CV ≤ 15 % and recovery 80 to 120 %

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Brain example : challenge and approaches

- Preclinical study
- Analyte : Hormone
- Brain analysis (limited matrix availability)

Look at few steps

① → Develop a proper process for collection to remove residual biologic fluid (CSF / vascularization)

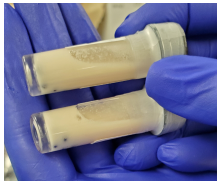
② → Perform stability as intact on a limited number of assays (if possible : n=3 , 2 concentrations)

Brain example : challenge and approaches

③

- Homogenization

→ Optimize the homogenization considering : Tissue size / analyte properties /potential interaction with biological structures…

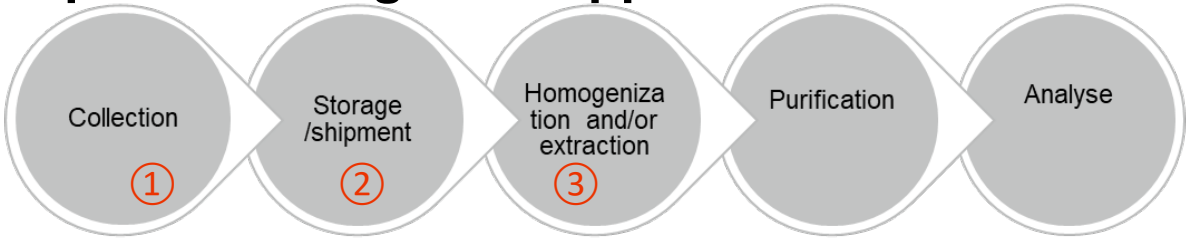


- Recovery testing

Spike tissue with analyte stock solution and let's evaporate

MEAN (n=3)	77.113
SD	4.3547
CV	5.65

Brain example : challenge and approaches



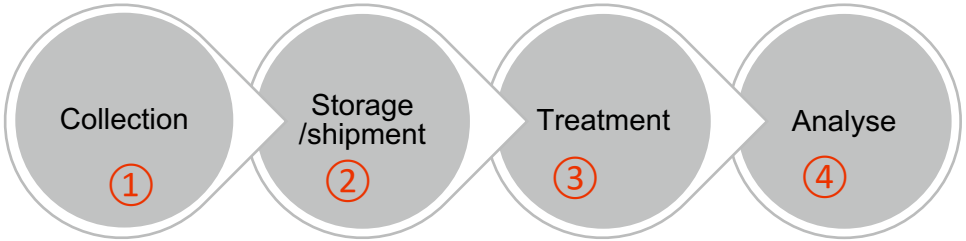
③

- Stability as intact to recommend homogenization before or after shipment

Test	Result	Conclusion
Stability at QCS3 level as intact at 4°C	Stable 2 hours	Recommendation store rapidly at -80°C
Stability at QCS3 level as intact at -80°C	Stable after one freezer cycle	Homogenate can be performed after shipment

Physical device : challenge and approaches

- Context : Clinical studies / patients should take them-selves blood
- Device : Device for collection by patient
- Analyte : biomarkers / large molecules



②③ • Create samples(s) to perform stability or testing recovery :

→ spiking blood with a known quantity of analytes and then reproduce dosing/collection

④ • Equivalent at 20µL

→ highly sensitive method

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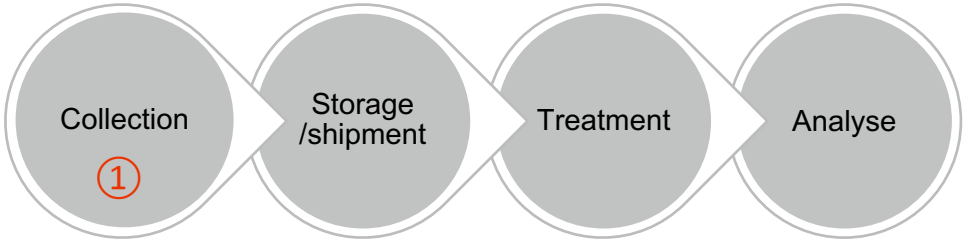
Physical device : challenge and approaches



① • Contamination occurs ?

→ develop a process to ensure appropriate using of the tool to avoid contamination at home

- The samples manipulated without gloves showed a bad accuracy. It will be important that patients wear gloves for the sampling and doesn't touch the end of the tip

Test	Response obtained
Device manipulate with gloves and precaution	Equivalent to fresh blood
Device manipulate without gloves	Far from fresh blood

- Note : pre-rinse / dry process has been tested

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Drug Development Evolution and BioA journey

Increase of non-liquid matrix analysis

What are the challenges ?

Look at the process

Think scientifically

at each step evaluate risk regarding the purpose / context / the real evidence

Thanks to all my colleagues and the EBF

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