intertek
Total Quality. Assured.

Common Practices and Gaps Associated to Extractable and Leachable Testing for Transdermal Delivery Systems

György (George) Vas Ph.D.

Intertek Pharmaceutical Services,
Trace Organic Analytical Group, Whitehouse, NJ, US

Outline

- Applicable guidances for transdermal testing, and their limitations
- Extractable testing of TDS components, common gaps in study designs
- Leachable testing and the associated design flaws

Always Keep in Mind

- The FDA review/approval is a scientific-evidence based multidisciplinary process
- "All submissions are required to contain sufficient details to support the toxicological risk assessment. Based on the quality of the data presented, the regulatory review team makes informed decision about the safety of the drug product or the medical device. If the submission is incomplete or does not support the safety assessment of the product, additional data may be required, which often delays product approval."*

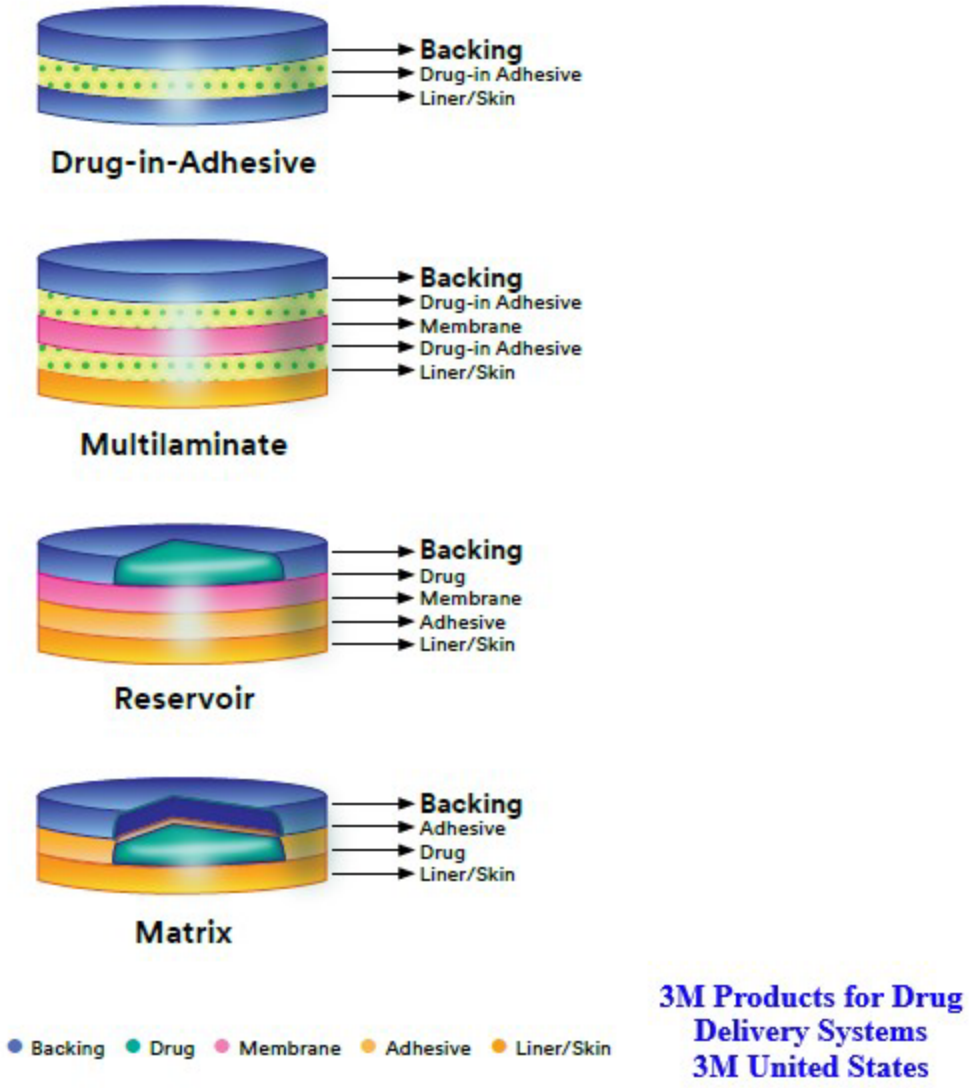
***Dunn et al. Reporting Analytical Data for Regulatory Submissions: A CRO Perspective on Implementing the BP4NTA Study Reporting Tool in the Healthcare Industry. Accepted for publication in Reviews in Separation Sciences**

General Overview of TDS Systems

- According to the United States Food and Drug Administration (FDA), transdermal drug delivery systems are considered combination products, where the device part ("patch") is responsible for controlled delivery of a single or multiple active agents or vaccine(s)*. Transdermal drug delivery systems are relatively complex pharmaceutical products. The formulations typically contain multiple excipients along with a dermal contact adhesive. The performance of the delivery systems depends on the quality of the dermal adhesive and the formulation, which delivers the drug on a pre-determined rate.

*http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101496.htm

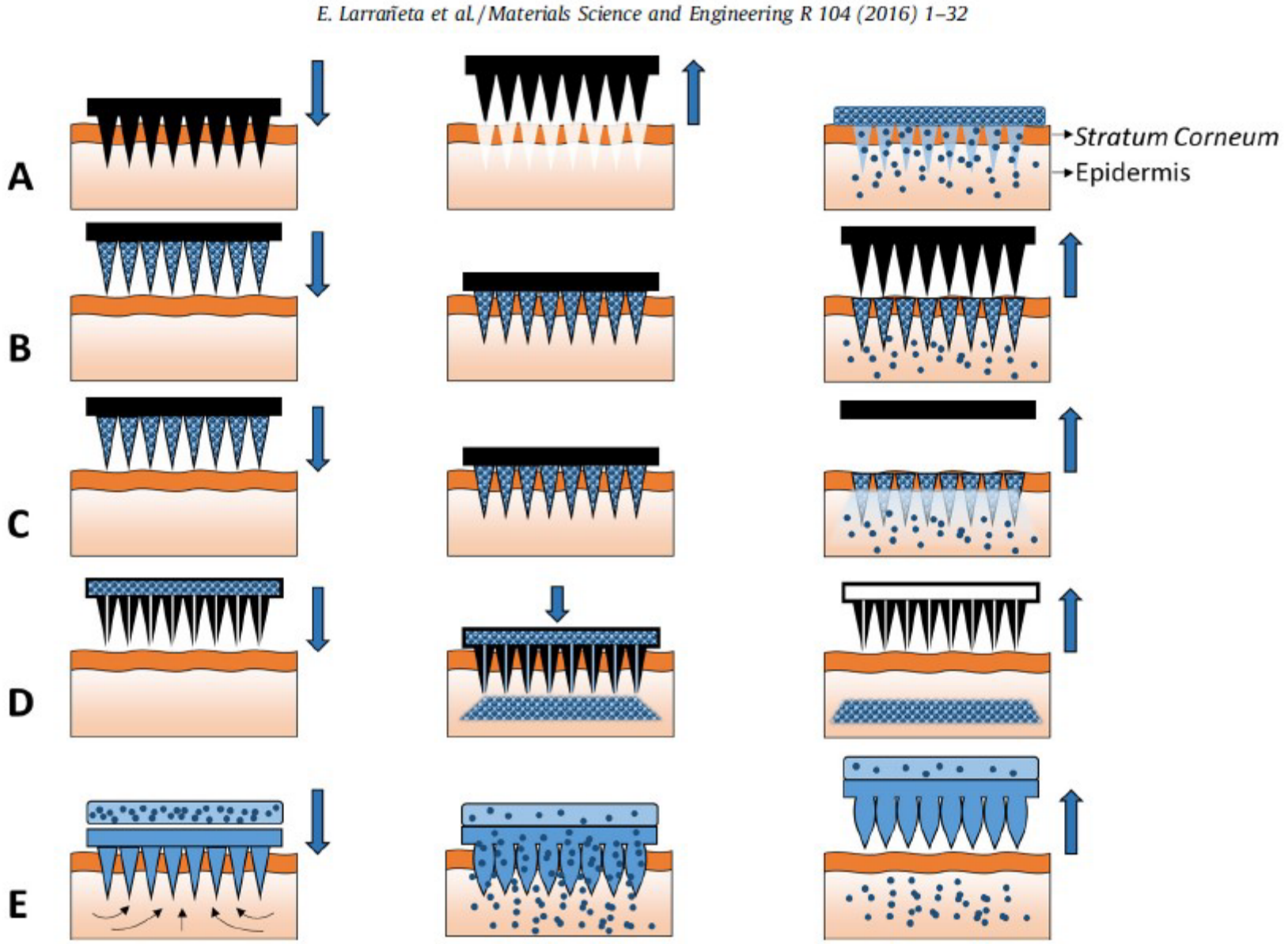
General Overview of TDS Systems



3M Products for Drug Delivery Systems
3M United States

General Overview of TDS Systems

- A: Solid Microneedle
- B: Coated Microneedle
- C: Microneedles are manufactured from drug formulations
- D: Hollow Microneedle System
- E: Hydrogel Needle



Applicable Regulations and Guidances for TDS Evaluation

- FDA Packaging Guidance (1999)
  - Based on the FDA guidance transdermal delivery products present a medium risk for the route of administration, and a high risk for potential interaction between the formulation and the packaging system.
- USP <3> "Topical and Transdermal Drug Products—Product Quality Tests"
  - This USP General Chapter provides an overview of general quality related and some limited TDS specific tests. The general quality test listed include description, identification, assay, impurities, uniformity of dosage units, water content, microbial limits, antimicrobial preservative content, sterility, pH, particle size, crystal formation, and in-vitro release test. The TDS specific tests are listed as: release liner peel test, tack test, shear test, static shear test, leak test, and packaged product testing.
- USP <1031> The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants
  - TDS systems are combination products designed to deliver drugs through the skin and include a skin contact device component. It can be expected this supplemental chapter may provide some level of support for the E&L testing since it is a significant part of the biocompatibility assessment, however there is no indication in the chapter for assessment of extractables and leachables.

Applicable Regulations and Guidances for TDS Evaluation

- USP <1664>

Table 1. Modified FDA/CDER/CBER Risk-Based Approach to Consideration of Leachables[a] (*1*)

Examples of Packaging Concerns for Common Classes of Drug Products			
Degree of Concern Associated with the Route of Administration	**Likelihood of Packaging Component-Dosage Form Interaction**		
	High	**Medium**	**Low**
Highest	Inhalation Aerosols and Sprays	Injections and Injectable Suspensions; Inhalation Solutions	Sterile Powders and Powders for Injection; Inhalation Powders
High	Transdermal Ointments and Patches	Ophthalmic Solutions and Suspensions; Nasal Aerosols and Sprays	—
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	—	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules; Topical Powders; Oral Powders

[a] While this table provides a convenient overview of the general level of regulatory concern with various dosage forms regarding leachables, it should not be inferred that "low-risk" dosage forms (e.g., oral tablets) by that definition carry no risk for leachables issues.

Applicable Regulations for TDS Evaluation

- European Medicines Agency (EMA) Guideline on Quality of Transdermal Patches
  - Based on this guidance, there are significant differences regarding the requirements for product approval in the EU vs. in the US. One of the major significant differences is the US guidance inclusion of relatively strict requirements for E&L testing, which is needed to be completed in order to have regulatory approval, while this type of testing is not required for the market approval in the EU. Also, EU use TDDS vs. US use TDS
- OECD Guidance Notes on Dermal Absorption
  - No direct connection to TDS, however many aspects for the dermal absorption can be useful to justify the testing design for E&L
  - Providing useful and practical guidance for dermal absorption studies
  - The in-vitro absorption database contains dermal absorption data for over 6800 chemicals
  - Guidance based on assumption of a chemical absorption through intact skin (higher absorption rates (%) at lower concentration level)
  - Reduced absorption rate (10%) proposed for species molecular weight > 500
- ICH Q3D
  - Addressing allowable limits for elemental impurities
  - Updated in Sept 2022 with PDE values for dermal/cutaneous route of administration

Applicable Regulations for TDS Evaluation

- FDA Guidance for Industry Transdermal and Topical Delivery Systems - Product Development and Quality Considerations (2019) (draft guidance)
  - Comprehensive and practical guidance identifying 4 critical quality aspects:
    - Transdermal delivery system as a finished drug product
    - Drug substance(s)
    - Excipients and components
    - Identifying labeling
  - Section IV part 3g focusing on E&L testing
  - Requires correlation between extractables and leachables
  - Adhesive testing (as it is an excipient), should be separated from the E&L testing, however impurities of the adhesive system must be evaluated in a 3 tier test approach (adhesive polymer, adhesive as a laminate and adhesive in the final product)
  - 1.5 µg/day SCT based evaluation for chronic applications (5 µg/day may applicable for others)
  - one of the solvents must be the same as used for the proposed adhesive platform when the extractable evaluation is performed (unique solvents such as ethyl-acetate, or diethyl ether)
  - Biologically relevant simulation media should be used for the leachable testing

Extractable Testing
Most Common Gaps and Deficiency Letter Situations

- Maximum daily dose not considered for the study design
- Non appropriate SCT value used to calculate the AET (1.5 vs. 5 vs. 50 µg/day)
- Selection of solvents not justified
- Extraction conditions not justified
- Identification of E&L species not performed according to the best scientific practice*
- Evaluated parts are not identical to the final packaging and TDS system to be marketed
- Elemental impurities not evaluated properly (uncommon elements can be associated to the ink/colorant components of packaging or the TDS system;
  - Al, B optional element, Ti, Ce is not listed in ICH Q3D(R2).
  - The Australian Health Authorities reviewing the health effect of Zn and Ti oxide based nanoparticles in dermal contact products)

***Sussman, Oktem et al: Chemical Characterization and Non-targeted Analysis of Medical Device Extracts: A Review of Current Approaches, Gaps, and Emerging Practices; FDA review paper published in ACS Biomater. Sci. Eng. 2022, 8, 3, 939–963**

USP General Chapter <1663>

Extractable Testing
AET

- SCT based Analytical Evaluation Threshold must be used for E&L testing
- The SCT of 1.5 µg/day in chronic application can result analytically challenging situations
- The AET must be calculated based on the maximum daily dose scenario vs. the typical use scenario

$$Typical\ dose\ AET\ (\mu g/cm^2\ of\ TDS) = \frac{1.5\ \mu g/day\ x\ 1\ days}{units\ x\ 140\ cm^2/unit} = \mathbf{0.0108\mu g/cm^2}$$

$$MDD\ based\ AET\ (\mu g/cm^2\ of\ TDS) = \frac{1.5\ \mu g/day\ x\ 1\ days}{9\ units\ x\ 140\ cm^2/unit} = \mathbf{0.0012\mu g/cm^2}$$

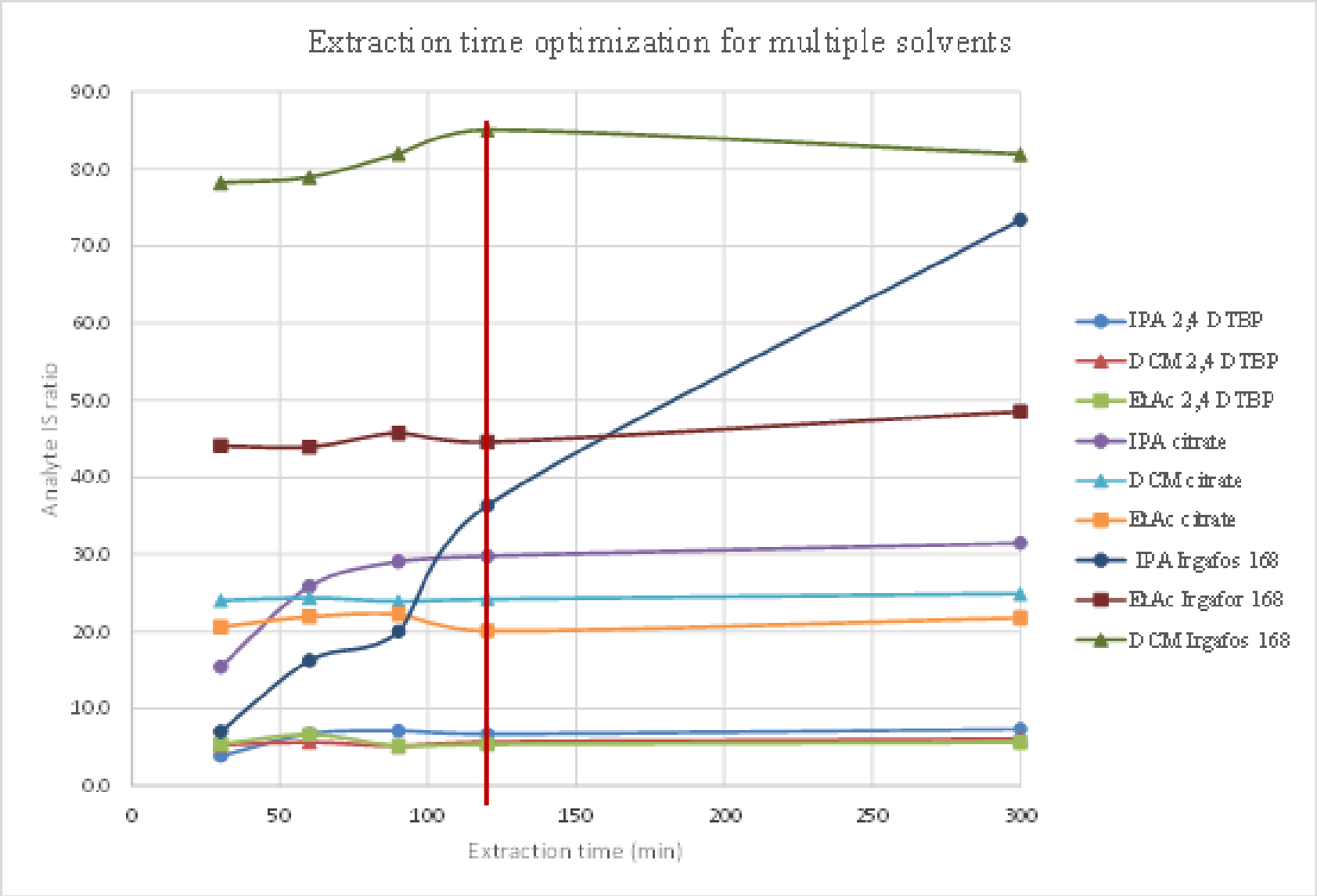
Extractable Testing Optimization

- "Non-adhesive and non-API components should be exposed to variety of solvents with a range of polarities and subjected to vigorous laboratory extraction conditions in order to maximize the levels of extractables, providing a "worst-case" picture of potential leachables levels. One of the extraction solvents used in the studies should include the solvent of the proposed adhesive system or the known residual solvents of the finished drug product. The solvent of choice should be justified."*
- The TDS system components and the final packaging configuration must be used for the evaluation
- Extraction time, temperature and the solvent volume must be justified (the 3-6 cm^2/mL surface to volume ratio is justifiable for extractable studies)
- Appropriate system suitability evaluation must be performed as a part of the testing
- LOD (or LOQ) should be at least 3-10 times lower than the AET of the study

***FDA Guidance for Industry Transdermal and Topical Delivery Systems - Product Development and Quality Considerations (2019) (draft guidance)**

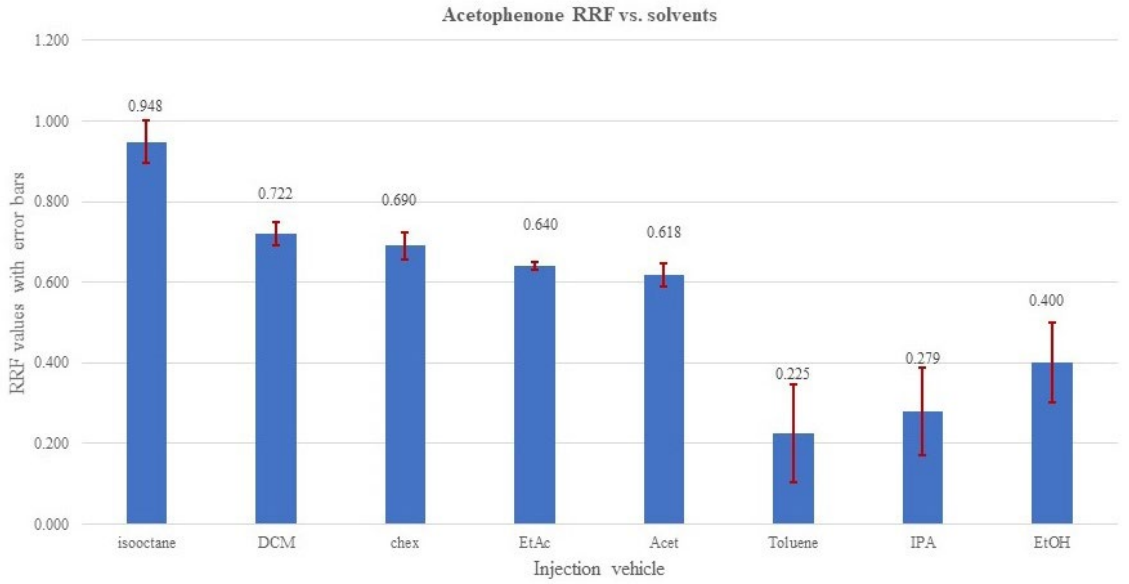
Extractable Testing Optimization

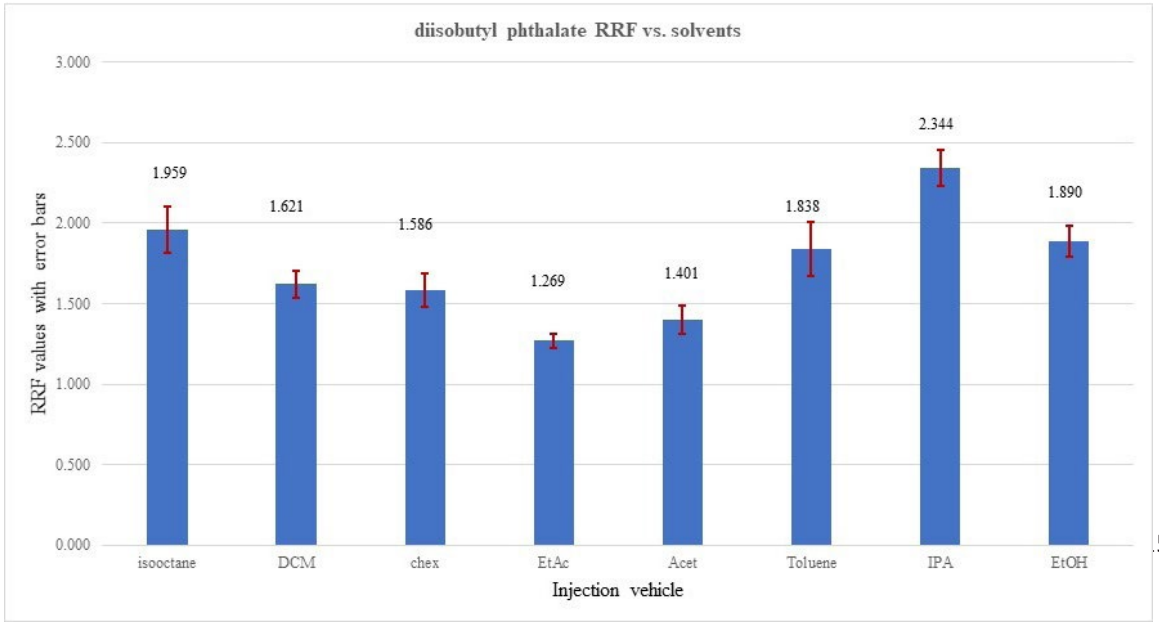
- Extraction solvent and extraction time optimization
- Optimization should be performed with multiple solvents and for multiple target analytes



Extractable Testing Optimization

- In many cases the manufacturing of the TDS system use solvents what are non-conventional for pharmaceutical applications
- "One of the extraction solvents used in the extractable studies should include the solvent of the proposed commercial adhesive(s) platform or the known residual solvents for the finished TDS." (FDA Draft Guidance for TDS and Topical Systems, 2019)
- It must be considered that when the extracts associated to those unique solvents, the analyte response can be impacted by the solvent of use*





*Norwood et al. Impact of the GC-MS Injection Solvent and the Analyte Concentration on Relative Responses for common Extractables. Rev. Sep. Sci. 4(1), e22002 (2022).

Challenges Related to Identification of Chemical Species

- USP <1663> providing detailed information how to perform identification
- Toxicological risk assessment requires at least confident identification
- Proper identification requires state of the art instrumentation and highly skilled analytical chemist
- One of the most common flaw is to report identification based on library search only with a low match score

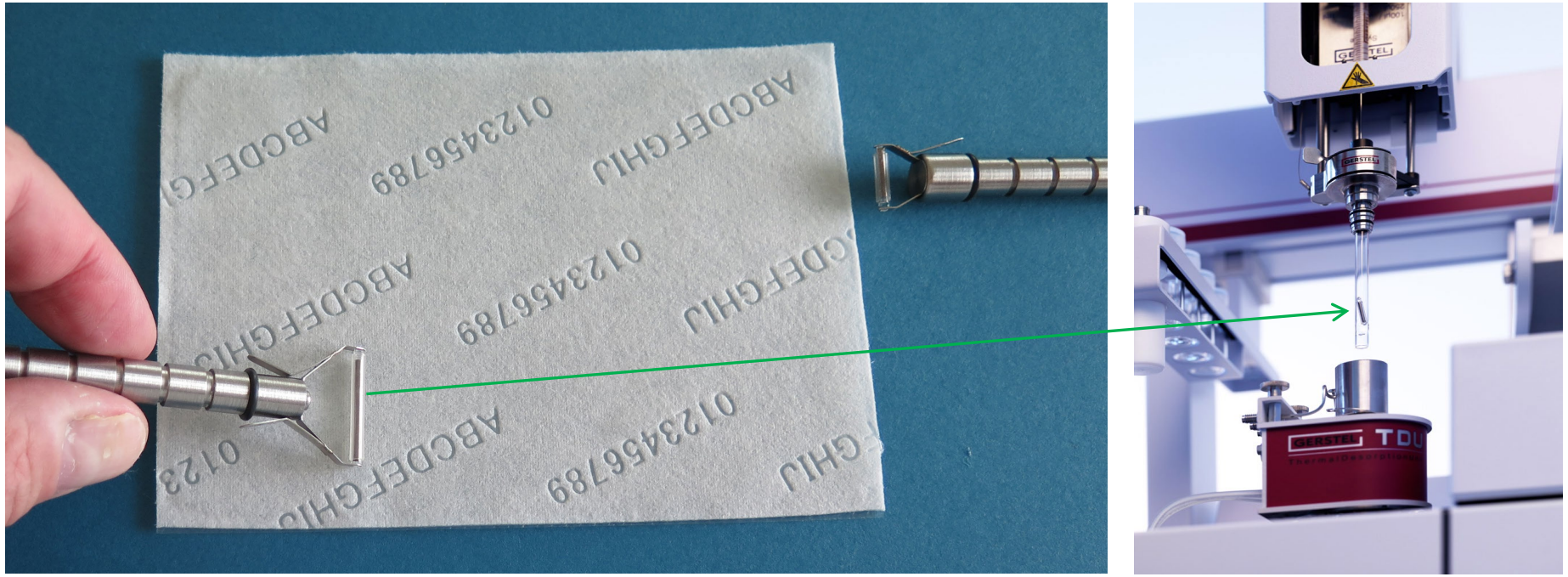
Criteria/technique	Unit resolution GC-MS	HRAM based GC-MS
Expert interpretation	Limited with unit resolution data	Accurate fragment assignment
Confirmation of mw	250.1	250.0740
Confirmation of elemental composition	Not possible based on unit resolution data	C15H10N2O2 (1.2 ppm mass error)
Reference library search	825 (need at least 900 for tentative assignment)	825 (need at least 900 for tentative assignment)
Match to authentic standard	NA	NA
Orthogonal technique such NMR	Limited availability for GC	Limited availability for GC
Identification	Tentative (with low confidence)	Confident
Criteria/technique	Unit resolution LC-MS	HRAM based LC-MS
Expert interpretation	Limited with unit resolution data with MS/MS	Accurate fragment assignment with MS/MS
Confirmation of mw	577.1 (proton adduct)	577.1342 (proton adduct)
Confirmation of elemental composition	Not possible based on unit resolution data	C30H24O12
Reference library search	Not available for LC-MS	Not available for LC-MS
Match to authentic standard	NA	NA
Orthogonal technique such NMR	Limited availability for many of the CRO's	Limited availability for many of the CRO's
Identification	Tentative (with low confidence)	Confident

Leachable Testing

- It is difficult to design and perform (simulation of skin absorption by a liquid extraction media)
- The chemistry of the skin surface impacted by commonly used personal care items (soap, deodorant) and personal hygiene
- Daily activities may impact the leaching rate (active vs. sedentary)
- Temporary health conditions such fewer impact the leaching
- The composition of the extraction media a significant factor (inorganic media vs. media with organic modifier)
- Single- or double-sided testing
- Finished products in a final packaging needs to be tested

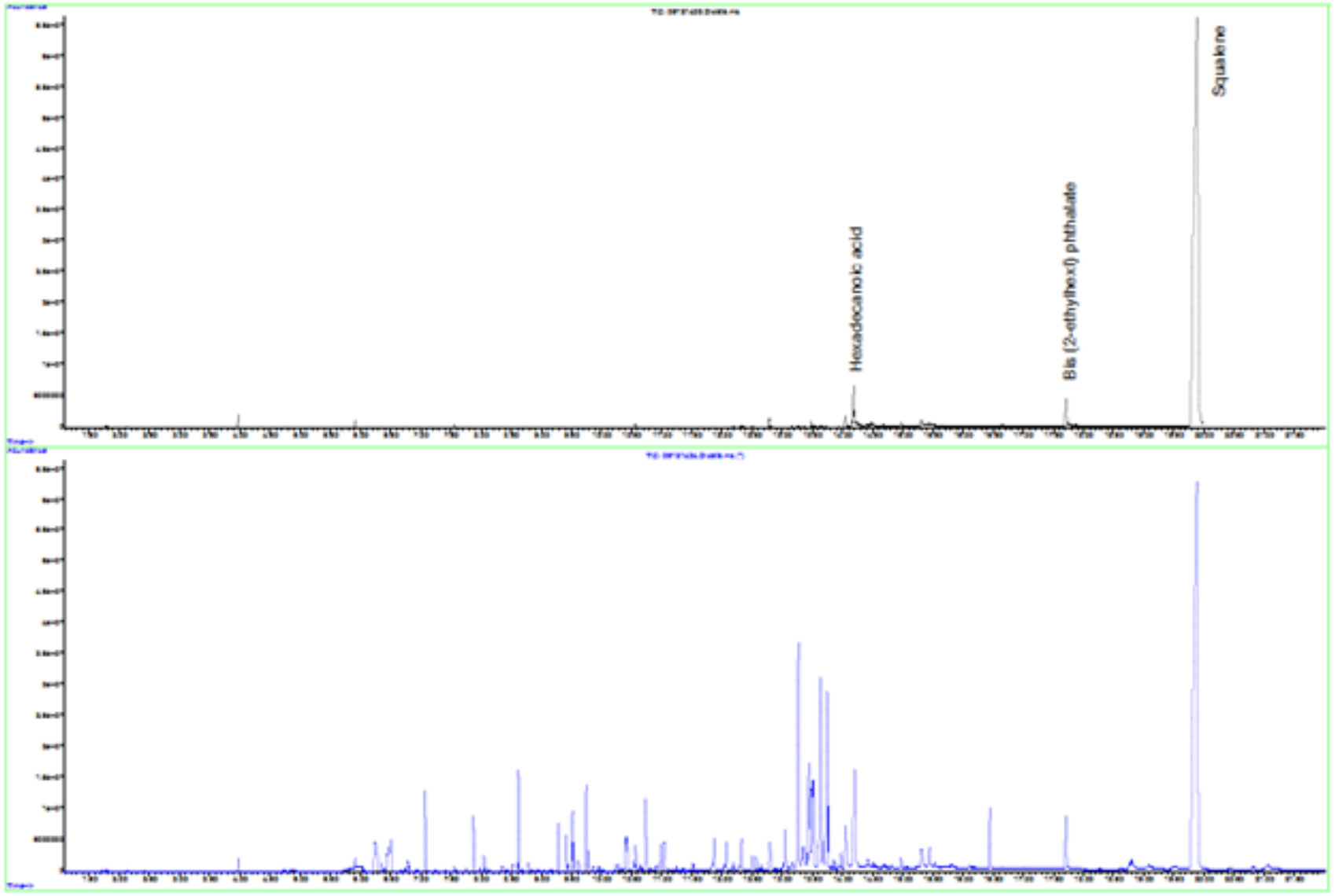
Leachable Testing

- Twister roller, simulating the skin contact, by collecting chemical components from the surface of the product and/or the skin surface



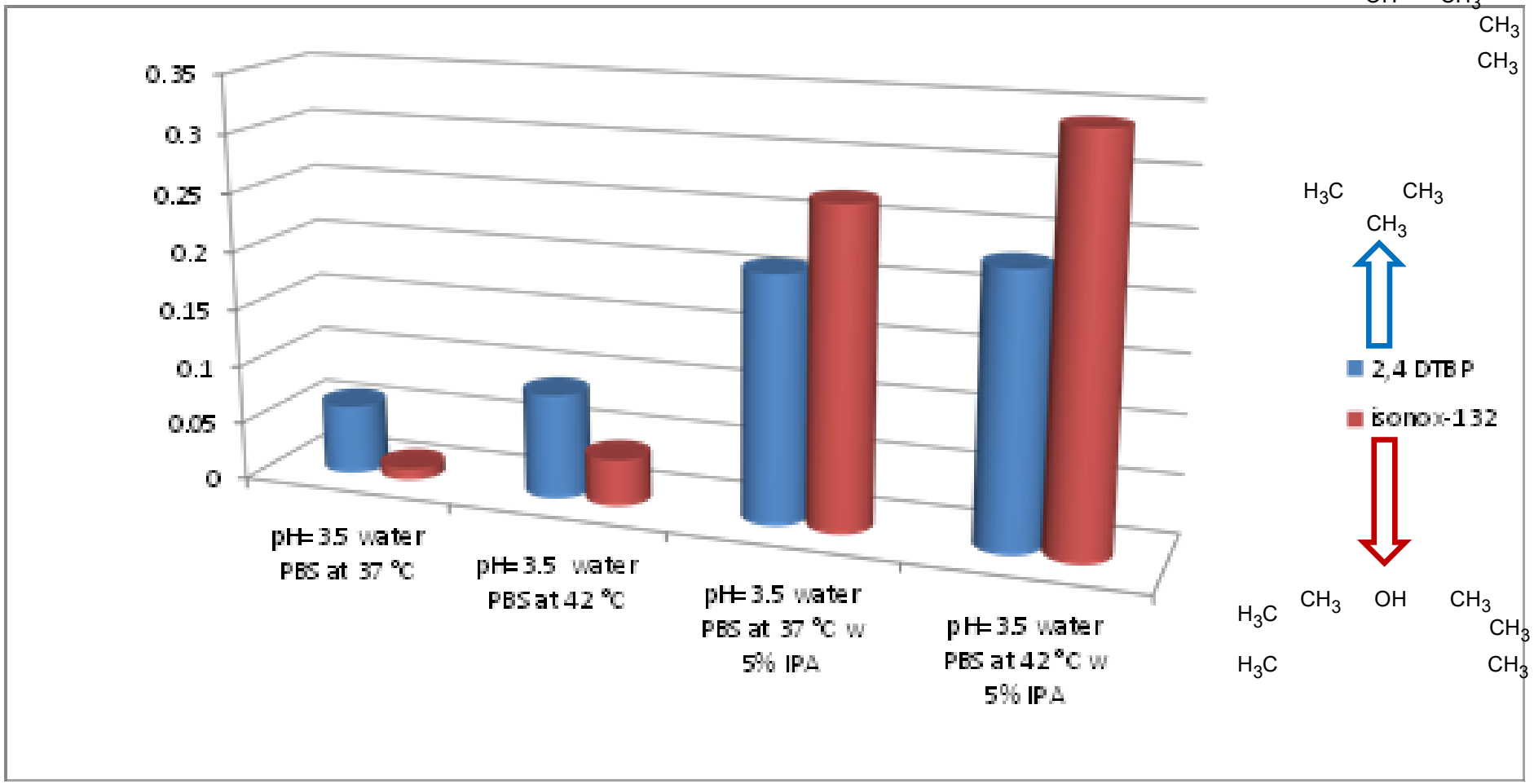
Leachable Testing

- Skin surface before and after application of a personal care product
- Chemicals present on the surface of the skin needs to be considered when a simulation media is designed



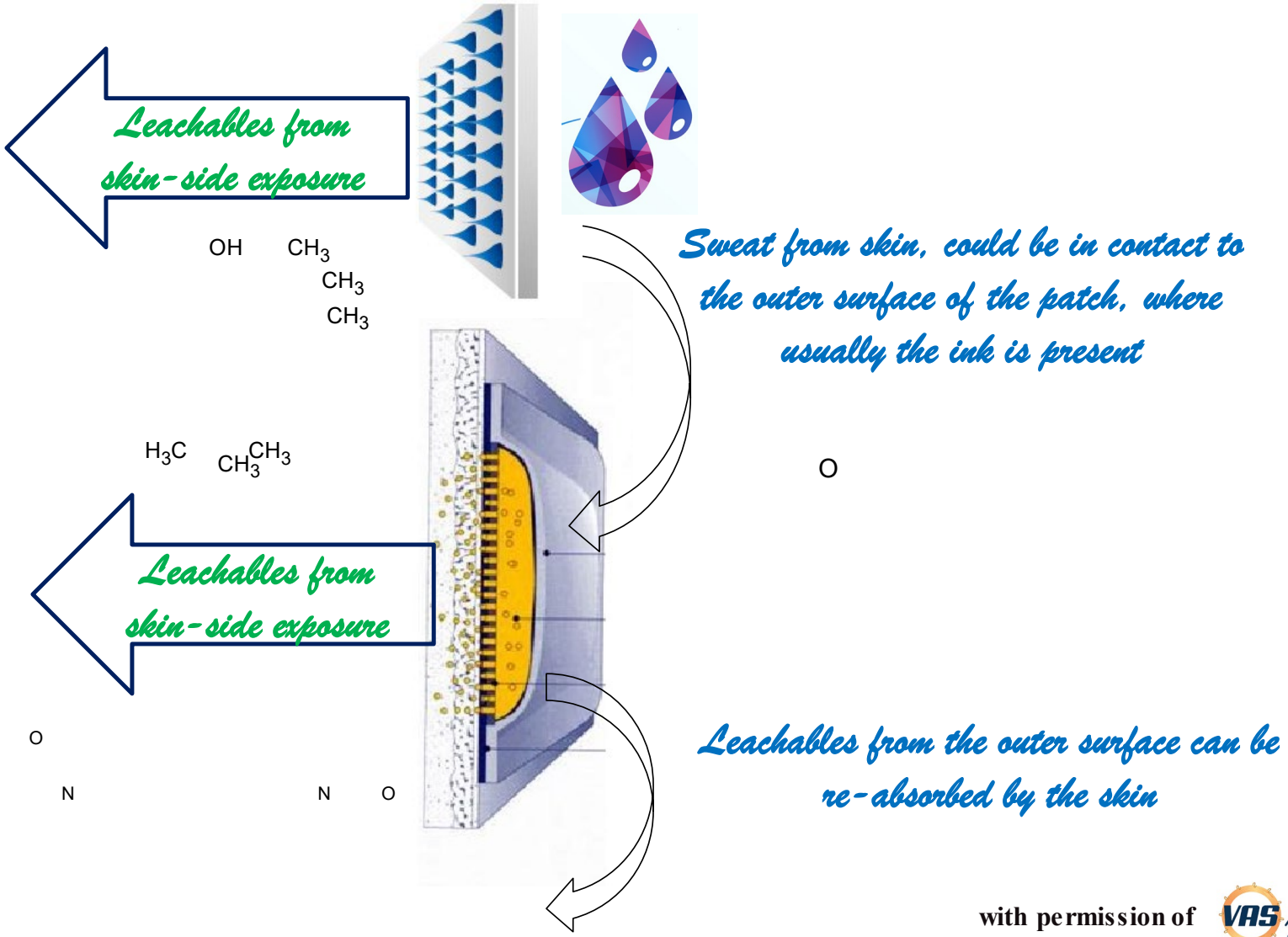
Leachable Testing

- 100% inorganic(saline, PBS) simulation media is not accepted for leachable studies.
- Even as little as 5% organic modifier resulting significant difference for the observed level of leachables



Leachable Testing

- It is often debated, that a single sided or two-sided testing is needed
- Single sided testing not addressing the possible re-absorption of chemicals during exercise or elevated temperature conditions

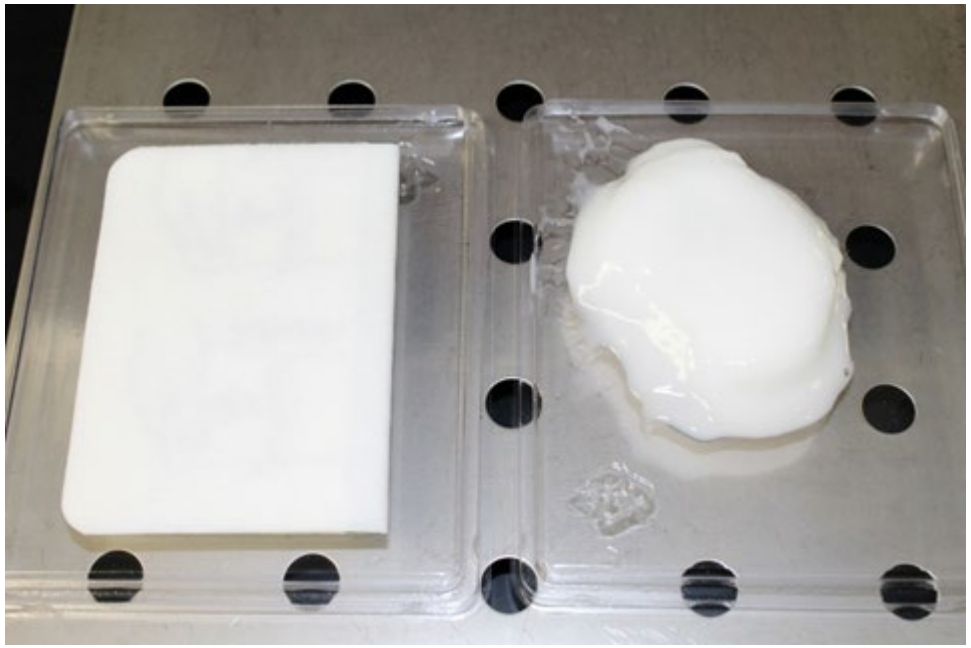


with permission of VAS Analytical

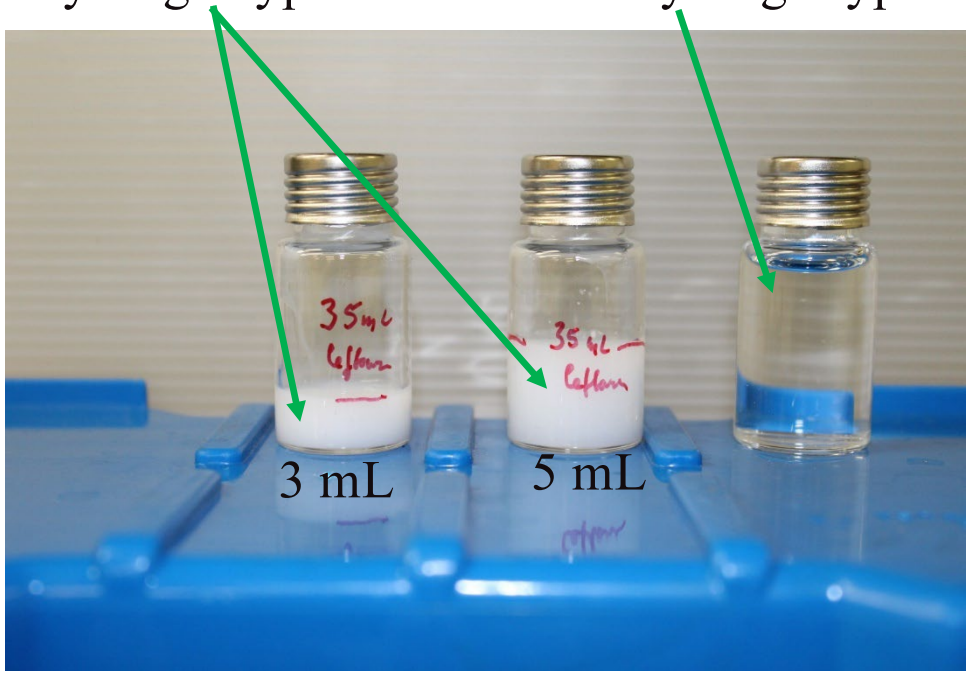
Leachable Testing

- Leachable testing of hydrogel-based systems is very difficult as the hydrogel can absorb the extraction media
- As a result, higher volume of solvent should be used for the leachable testing, which will significantly impact the AET level of the study

Hydrogel type TDS before and after testing



Hydrogel type TDS vs. non-hydrogel type

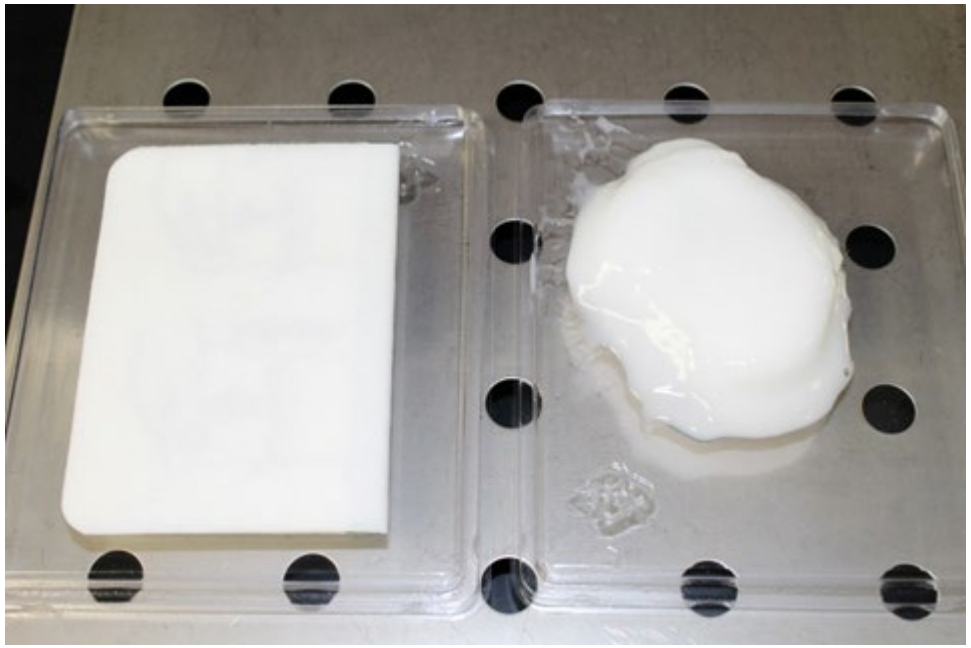


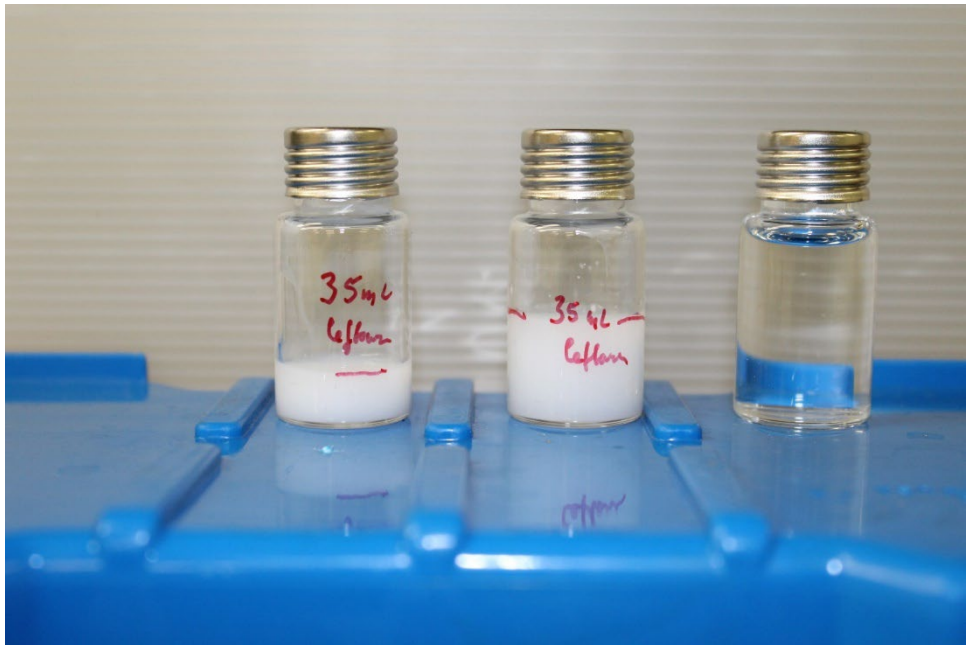
Leachable Testing

- Using higher volume of solvent reducing the AET in this example from 7 ng/mL to 0.6 ng/mL

$$AET\ (\mu g/mL) = \frac{1.5\mu g/day\ SCT}{9\ dose/day\ x\ 140cm2/6cm2/mL} = 0.007\mu g/mL$$

$$AET\ (\mu g/mL) = \frac{1.5\mu g/day\ SCT}{9\ dose/day\ x\ 140cm2/0.5cm2/mL} = 0.0006\mu g/mL$$

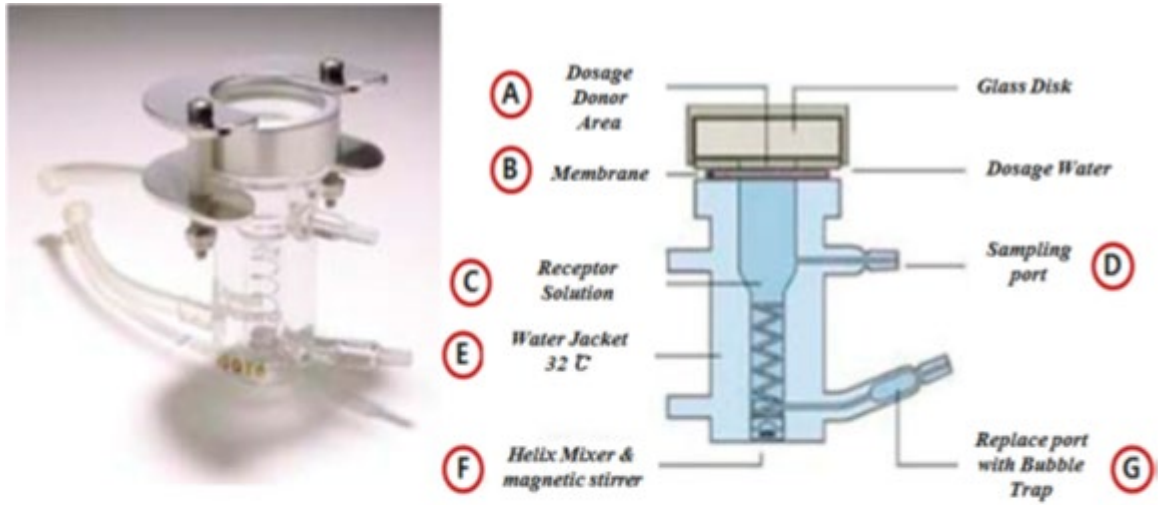




Leachable Testing

- Test vessels options for single sided testing

Glassware designed for single sided Leachable testing



A : Donor chamber : Test substance treatment position

B : Membrane : Position securing the skin samples

C : Receptor chamber : As a position used to store test materials that penetrated the skin, it is used by filling it with an aqueous solution

D : Sampling port : Passage to collect the test samples from test aqueous solution

E : Water jacket : Location where heated water circulates to adjust the temperature

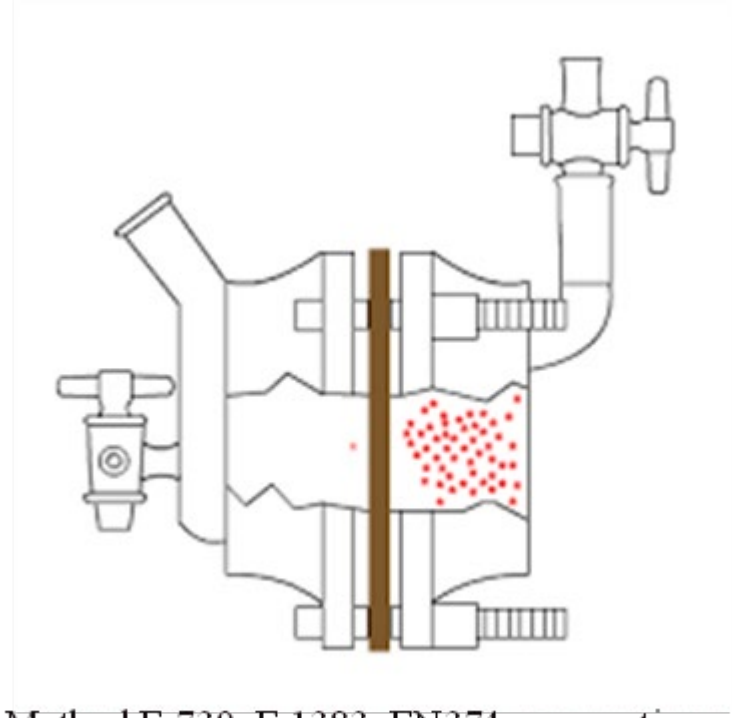
F : Stirrer : Stirring device so that the test substance is well dissolved in the aqueous solution

G : Replace port : Passage that refills new aqueous solution after sampling

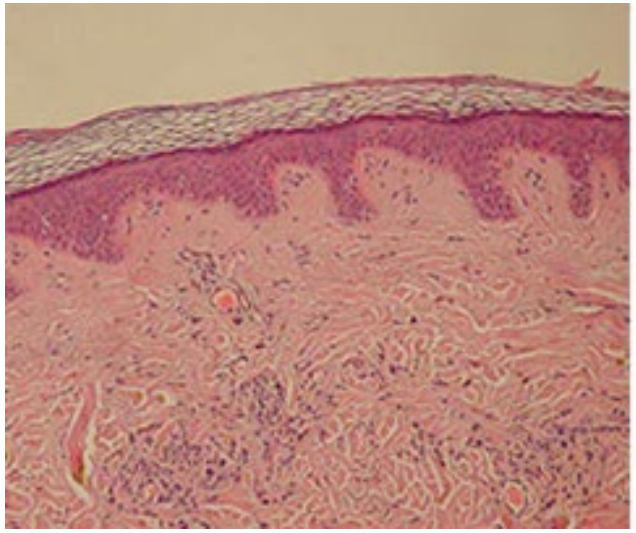
Schematic of Franz-cell

Leachable Testing

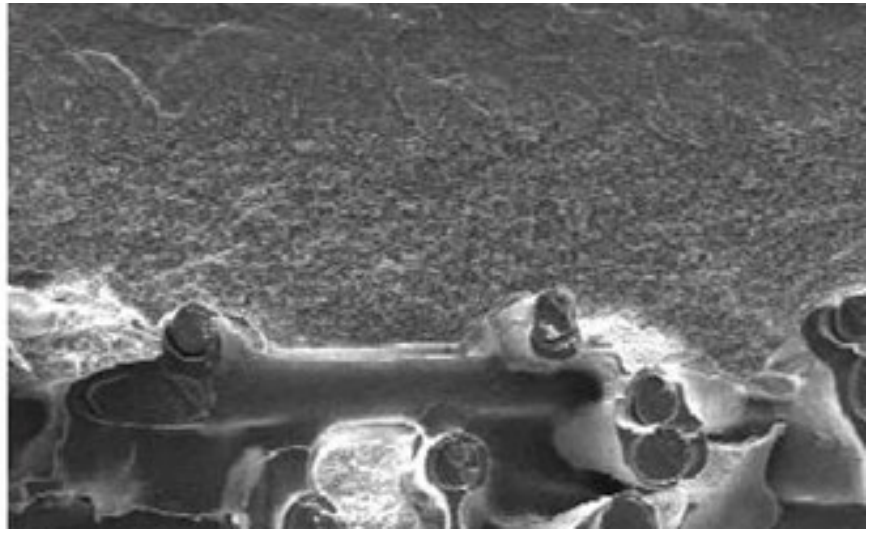
- Test vessel configuration for two-sided testing
- Detailed image of a transdermal simulation membrane (can be used with multiple types of testing cells)



ASTM Method F-739, F-1383, EN374, permeation cell



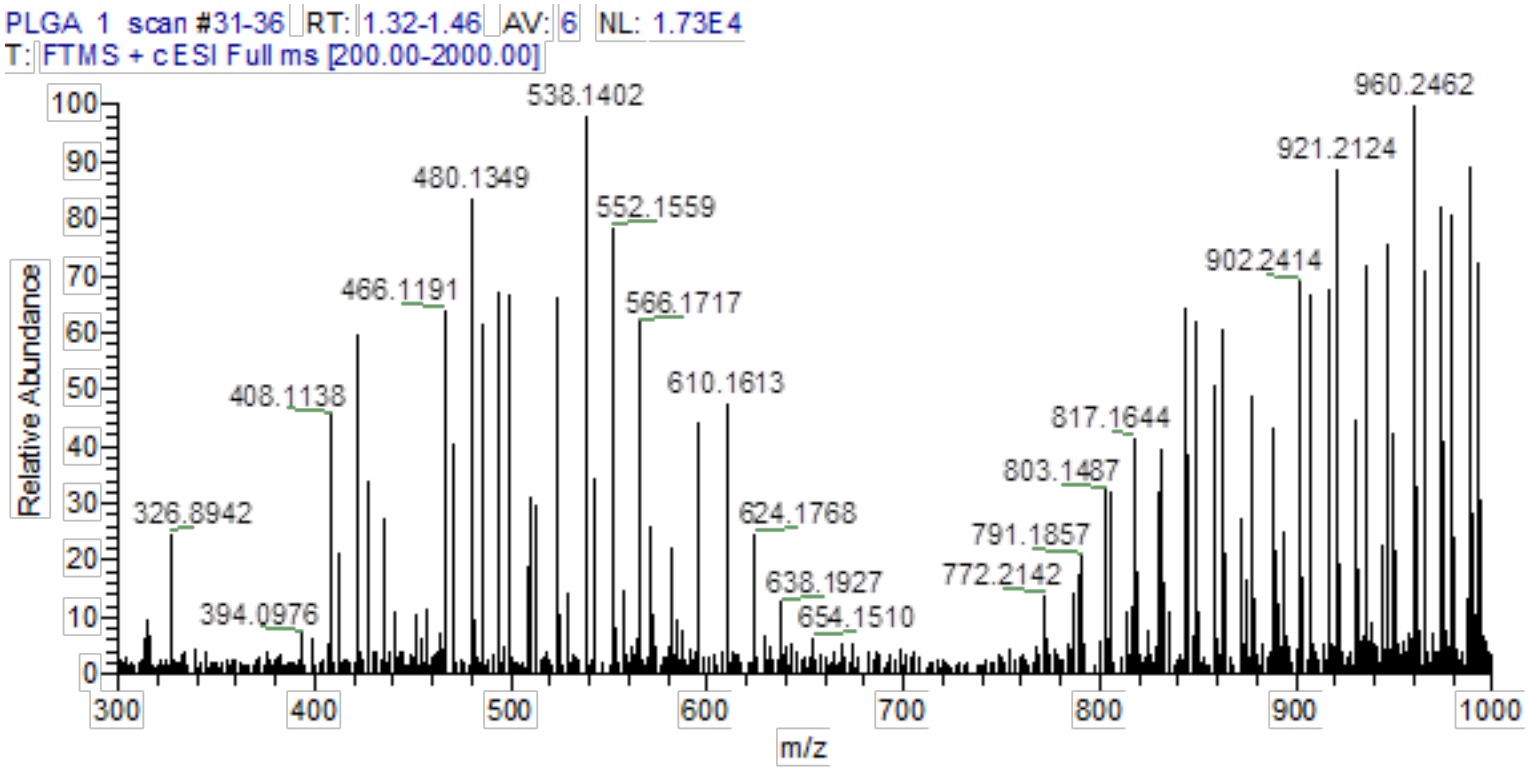
Cross-section of human epidermis



simulation membrane

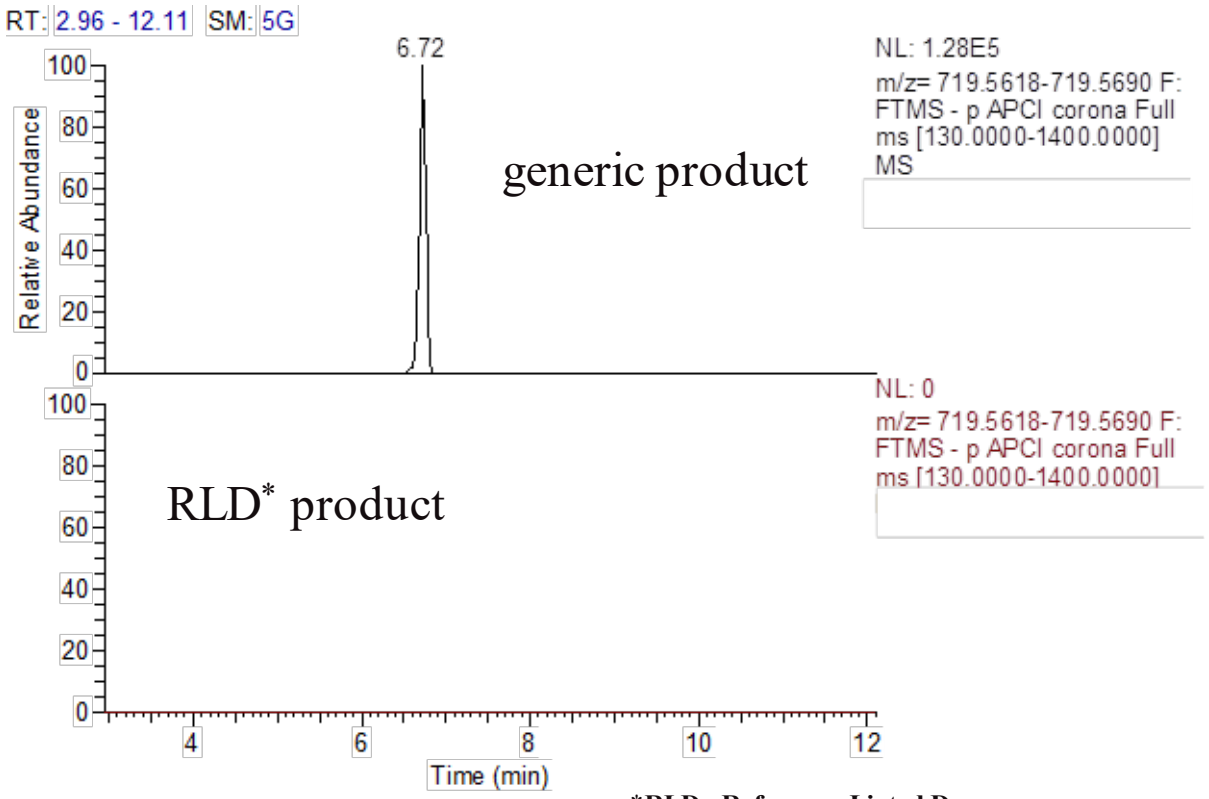
Leachable Testing

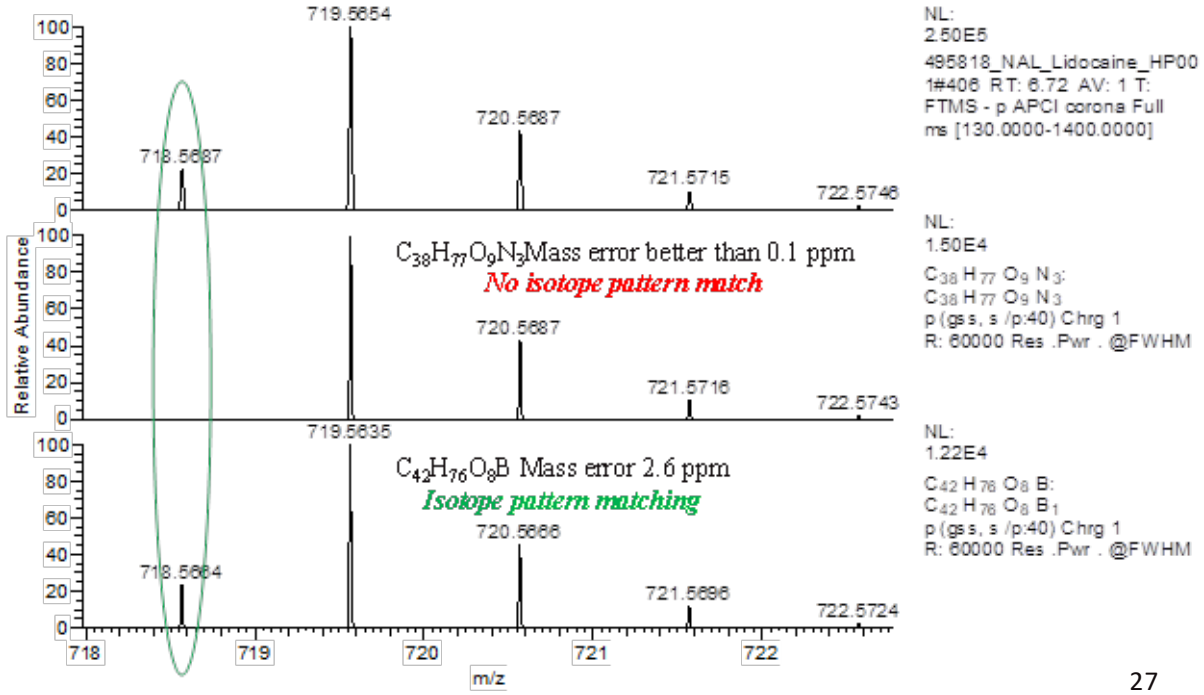
- Few points needs to be considered for leachable testing of microneedle systems manufactured from biodegradable polymers
- Significant interferences associated with the biodegradable polymer matrix (over a 100 oligomers below m/z=1000)



Leachable Testing

- Challenges related to organometallic species
- Difficult to identify and correlate to extractables as sometimes being formed by "reaction" product between the TDS and the packaging





*RLD: Reference Listed Drug

Summary

- Extractable and Leachable testing of Transdermal Delivery Systems is a complex analytical task
- Design and properly execute studies, requires scientific expertise and state of the art analytical instrumentation.
- The testing is associated with complex matrices and very often low AET level (ppb or below)

Thank You for Your Attendance

and

Your Attention

gyorgy.vas@intertek.com