

**RPD**TOOL

Rapid Product Development

# **Automated Stability Assessment**

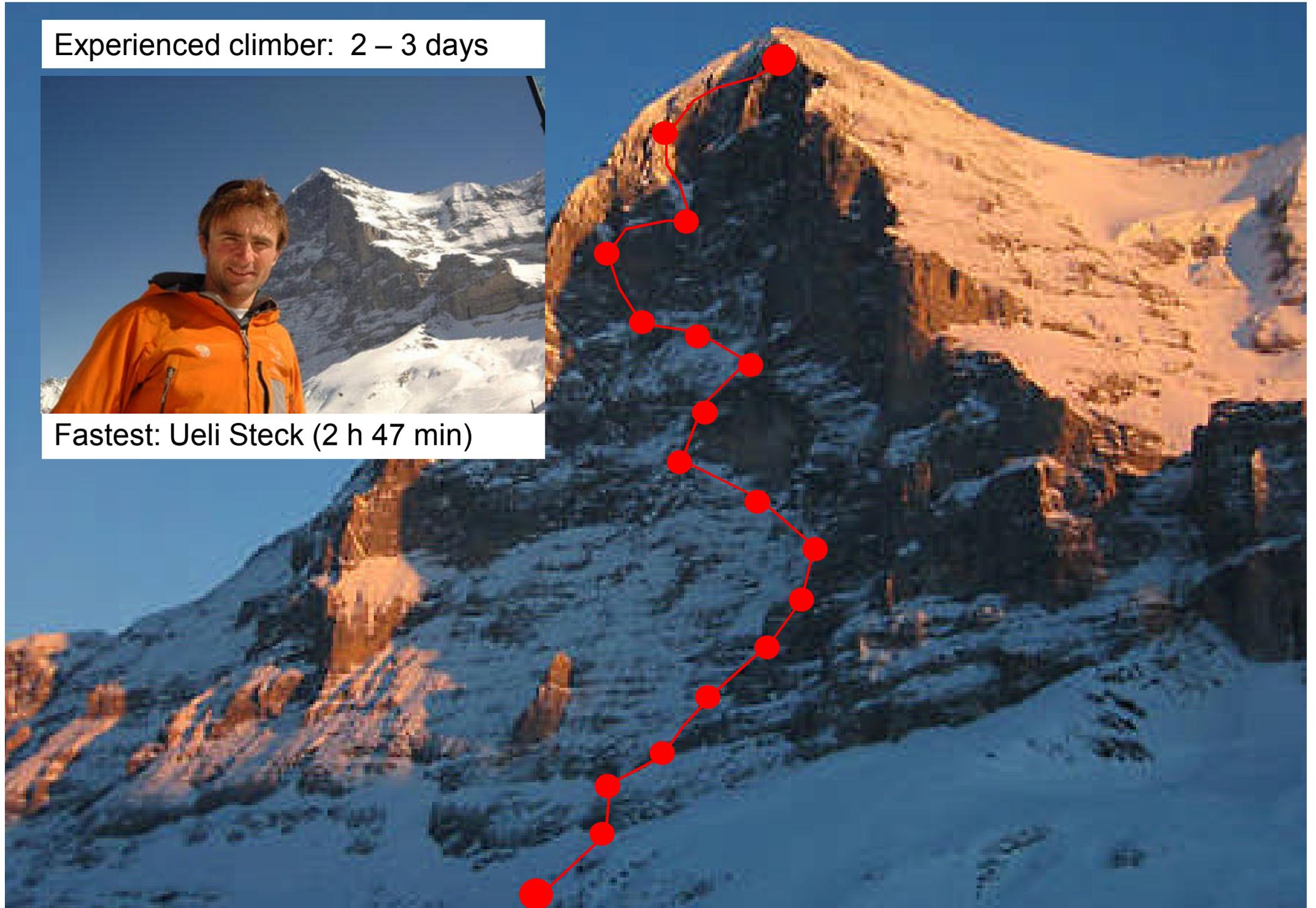
***An approach for  
rapid formulation development***

---

Experienced climber: 2 – 3 days



Fastest: Ueli Steck (2 h 47 min)



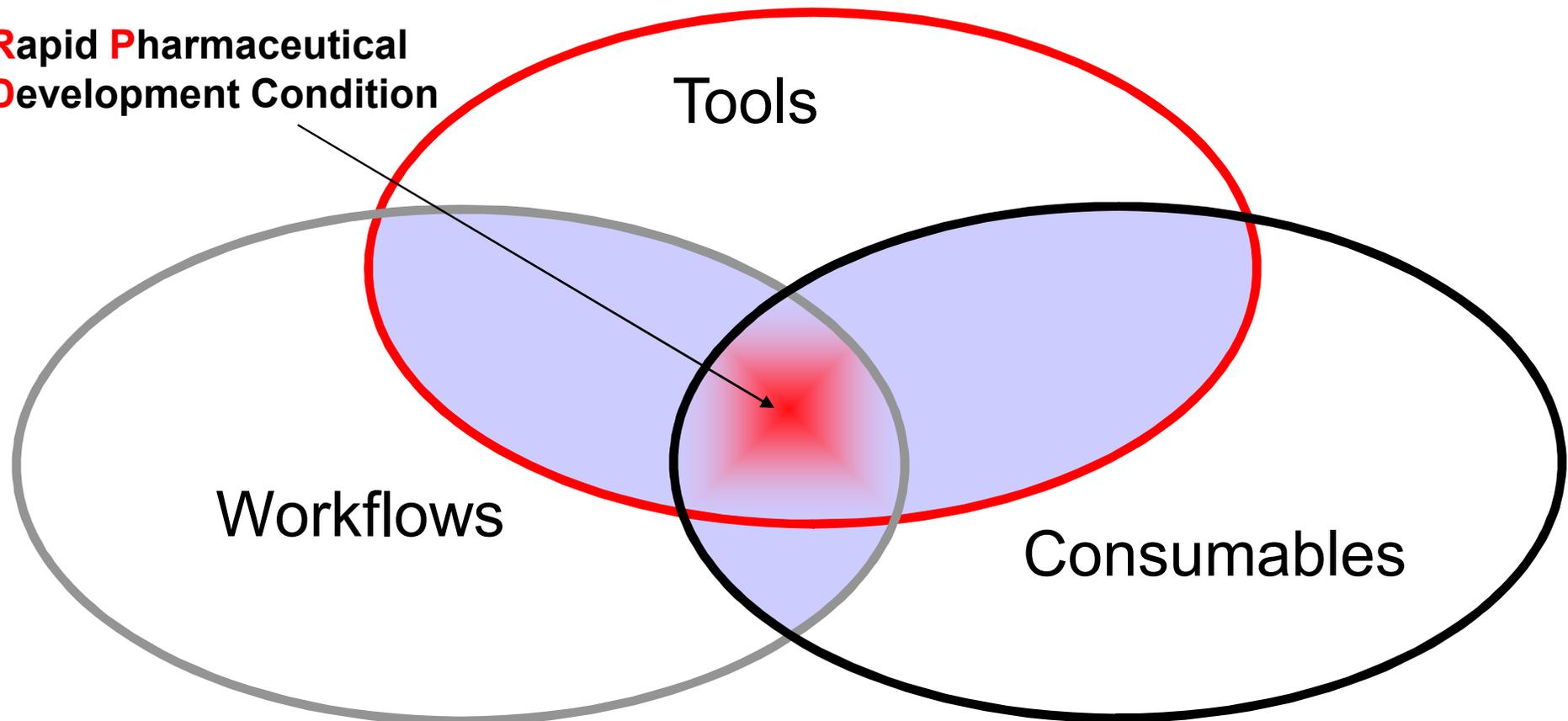
## Table of Content

- Rapid Pharmaceutical Development Condition
  - Workflows, Consumables, Tools
  - Chemical Storage Stability Assessment
  - Trends in Drug Discovery
  - Physical Stability Assessment
  - Discussion
-

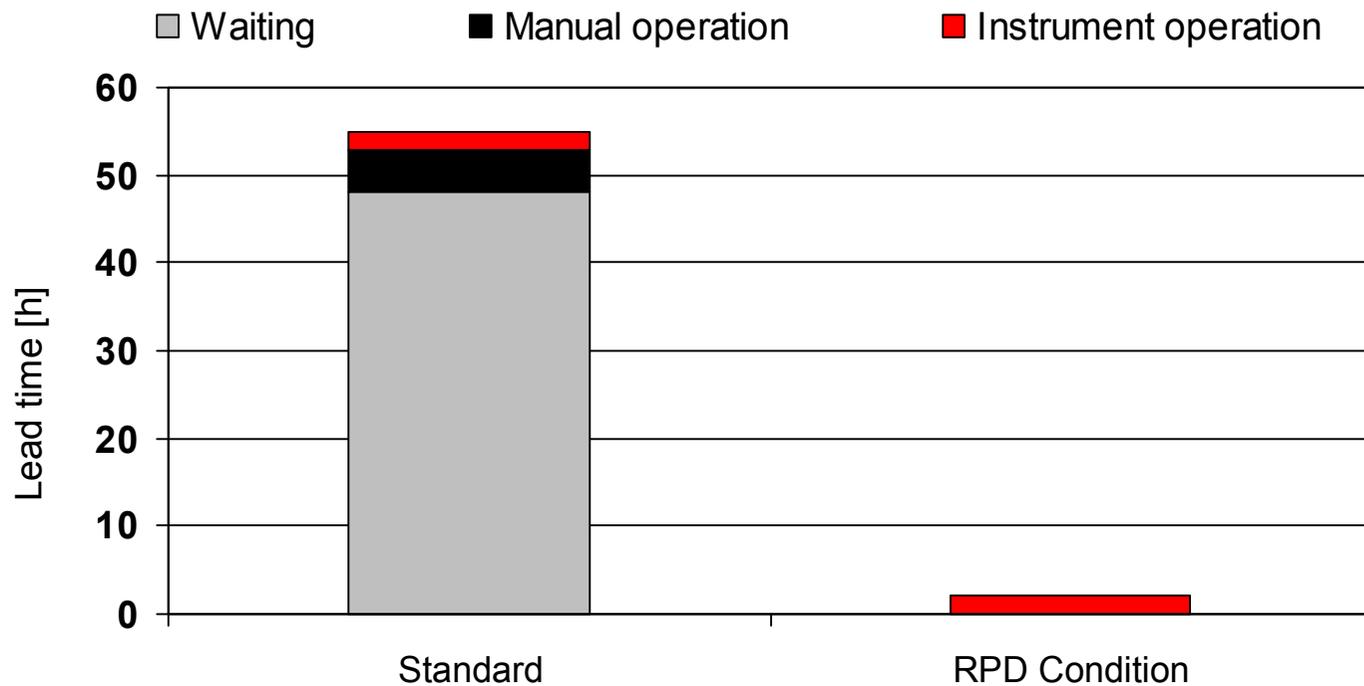


## RPD Conditions

Rapid **P**harmaceutical  
Development Condition



## Example of RPD Conditions: Chemical stability



Up to 80 % reduction of cost for RPD condition

## Workflows



Salt selection  
Polymorphism &  
Co-crystal screening



Solubility  
Chemical stability  
Physical stability



Solubilisation rate  
Chemical stability  
Physical stability



Dissolution rate  
Chemical stability  
Physical stability

---

## Consumables: Storage vials

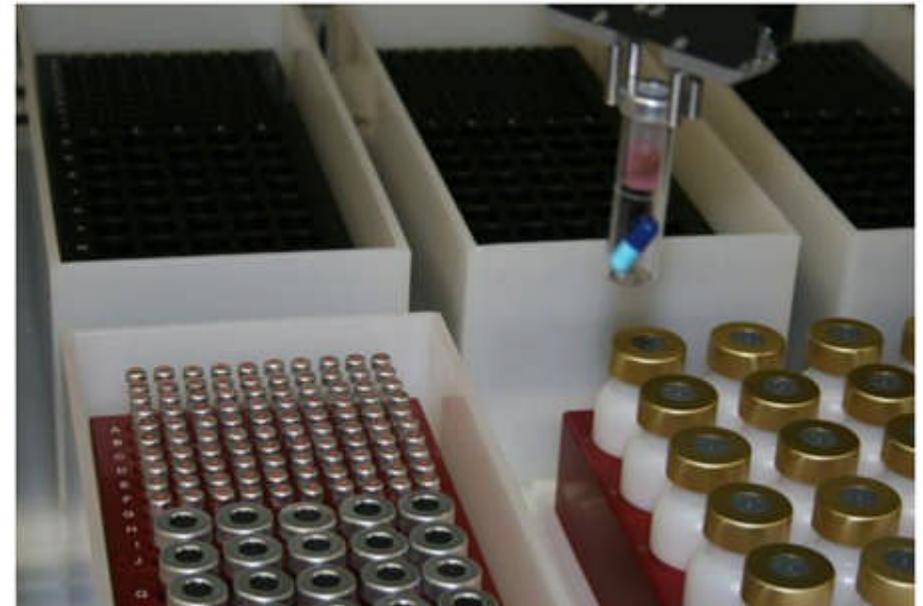
Crimping cap

Humidity control

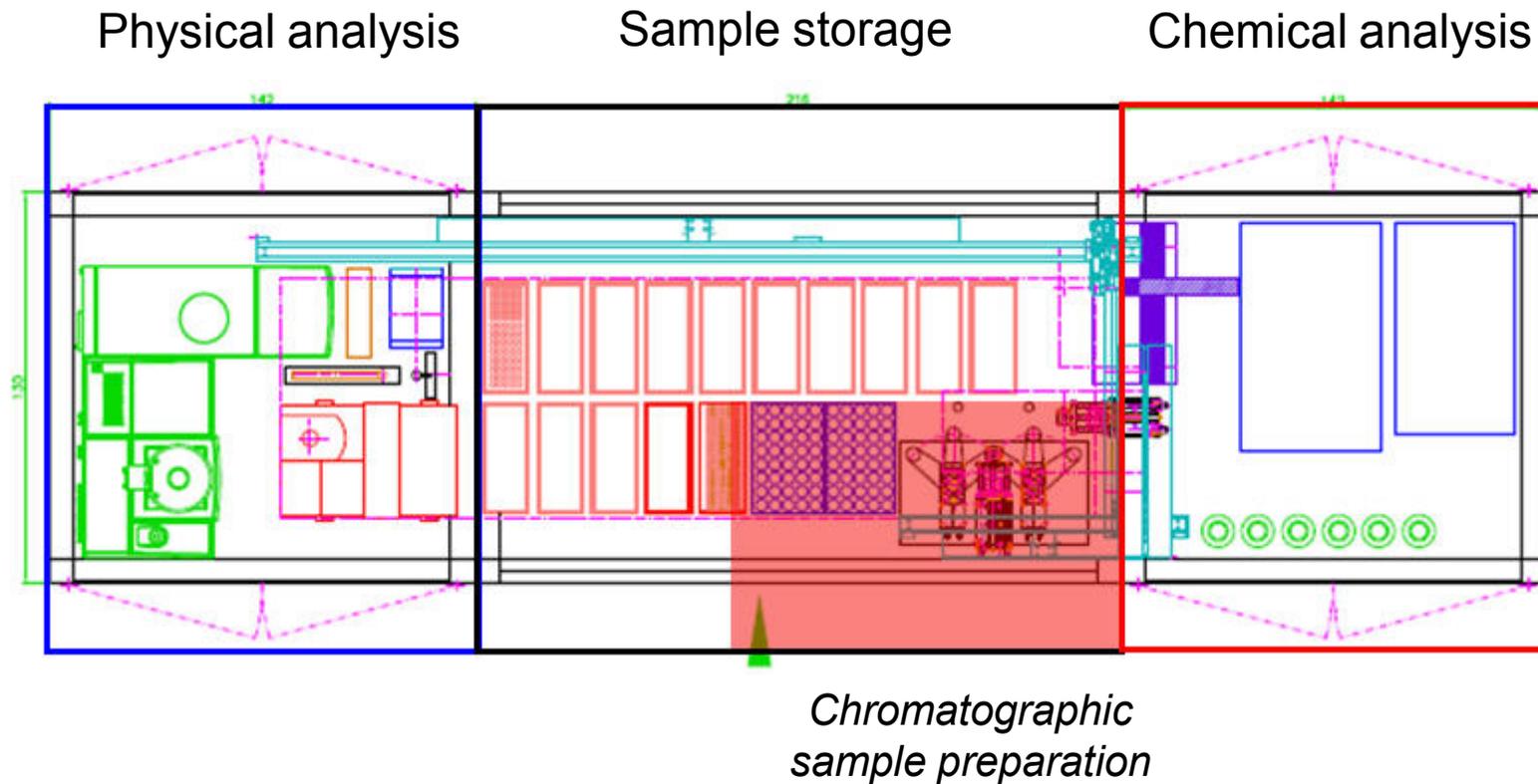
Sample identification

Breaking point

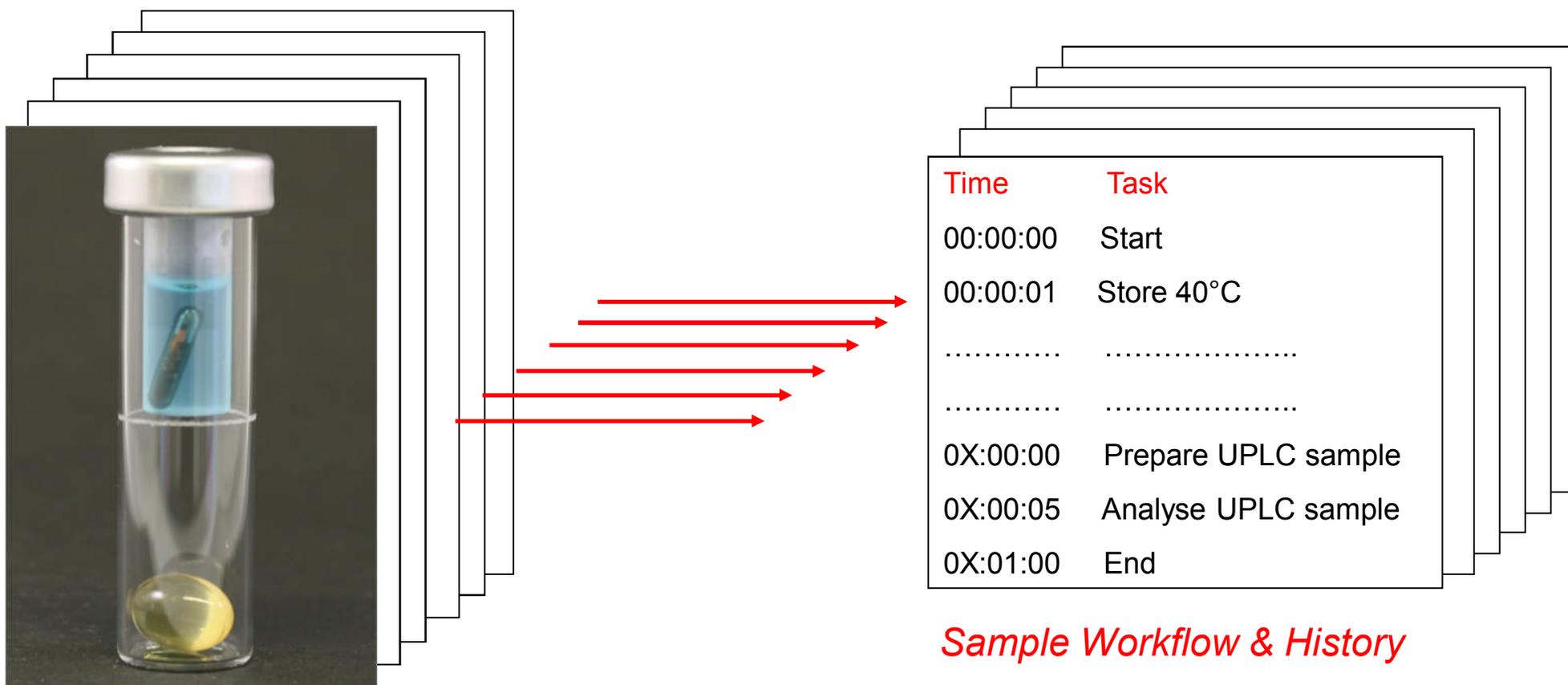
Sample compartment



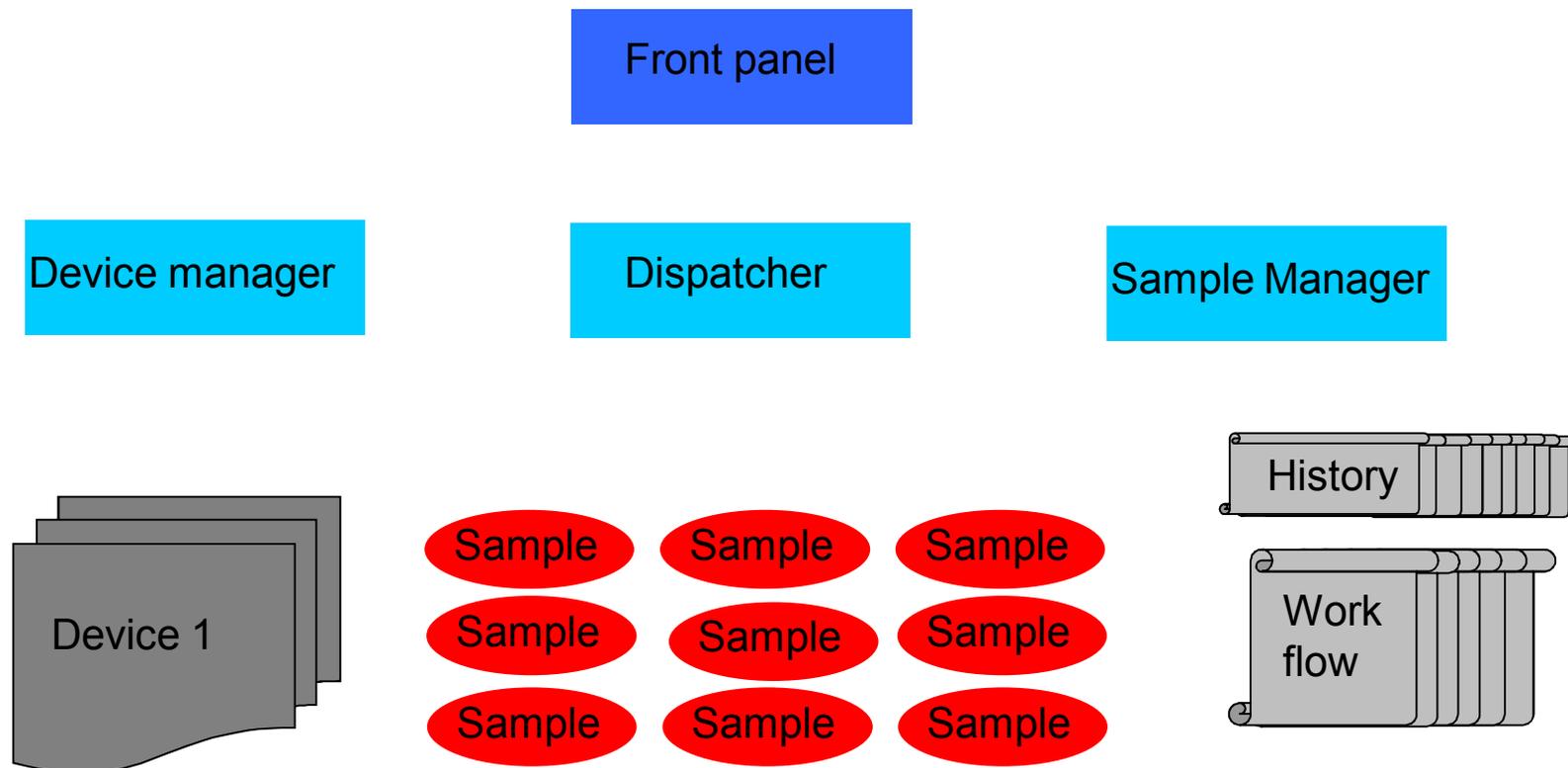
## System for Automated Storage Stability



## Workflow based sample processing

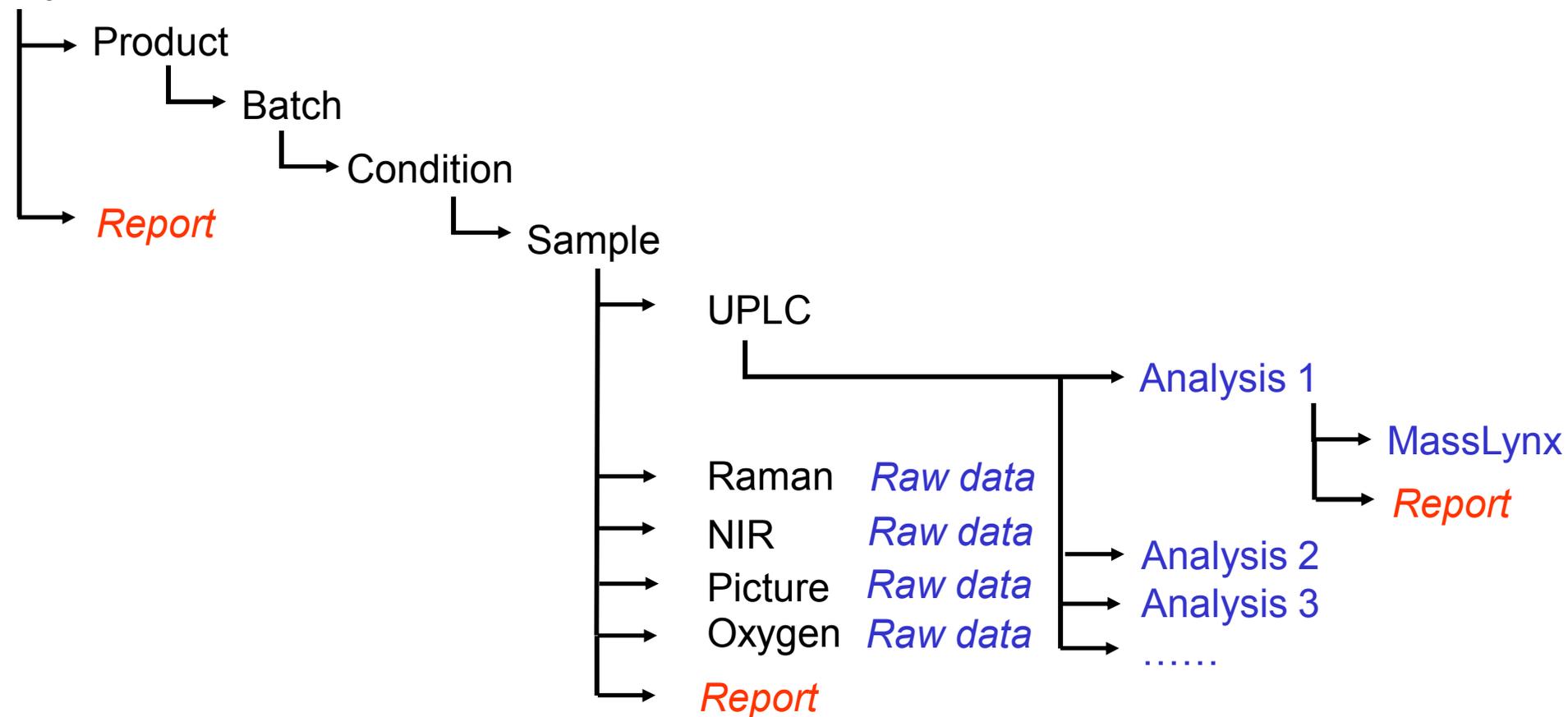


## Software concept for system operation



## Data management & reporting

Project



### Reporting tool

- Single analysis report
- Sample report
- Project reports
- ...

#### Summary report

Project: New solid form

| Formulation |            | Hygroscopicity | Morphological | Chemical | Photochemical |
|-------------|------------|----------------|---------------|----------|---------------|
| 1           | 25°C/dry   | Green          | Green         | Yellow   | Green         |
|             | 25°C/65%RH | Green          | Green         | Yellow   | Green         |
|             | 40°C/dry   | Green          | Green         | Yellow   | Green         |
|             | 40°C/75%RH | Red            | Green         | Red      | Green         |
|             | 50°C/dry   | Green          | Green         | Red      | Green         |
| 2           | 50°C/75%RH | Green          | Green         | Red      | Green         |
|             | 25°C/dry   | Green          | Green         | Yellow   | Green         |
|             | 25°C/65%RH | Green          | Green         | Yellow   | Green         |
|             | 40°C/dry   | Green          | Green         | Yellow   | Green         |
|             | 40°C/75%RH | Green          | Green         | Yellow   | Green         |
| 3           | 50°C/dry   | Green          | Green         | Yellow   | Green         |
|             | 50°C/75%RH | Green          | Green         | Yellow   | Green         |
|             | 25°C/dry   | Green          | Green         | Yellow   | Green         |
|             | 25°C/65%RH | Green          | Green         | Yellow   | Green         |
|             | 40°C/dry   | Green          | Green         | Yellow   | Green         |
| 4           | 40°C/75%RH | Green          | Green         | Yellow   | Green         |
|             | 50°C/dry   | Green          | Green         | Yellow   | Green         |
|             | 50°C/75%RH | Green          | Green         | Yellow   | Green         |
|             | 25°C/dry   | Green          | Green         | Yellow   | Green         |
|             | 25°C/65%RH | Green          | Green         | Yellow   | Green         |
| 5           | 40°C/dry   | Green          | Green         | Yellow   | Green         |
|             | 40°C/75%RH | Green          | Green         | Yellow   | Green         |
|             | 50°C/dry   | Green          | Green         | Yellow   | Green         |
|             | 50°C/75%RH | Green          | Green         | Yellow   | Green         |
|             | 25°C/dry   | Green          | Green         | Yellow   | Green         |
| 6           | 25°C/65%RH | Green          | Green         | Yellow   | Green         |
|             | 40°C/dry   | Green          | Green         | Yellow   | Green         |
|             | 40°C/75%RH | Green          | Green         | Yellow   | Green         |
|             | 50°C/dry   | Green          | Green         | Yellow   | Green         |
|             | 50°C/75%RH | Green          | Green         | Yellow   | Green         |
| 7           | 25°C/dry   | Green          | Green         | Yellow   | Green         |
|             | 25°C/65%RH | Green          | Green         | Yellow   | Green         |
|             | 40°C/dry   | Green          | Green         | Yellow   | Green         |
|             | 40°C/75%RH | Green          | Green         | Yellow   | Green         |
|             | 50°C/dry   | Green          | Green         | Yellow   | Green         |
| 50°C/75%RH  | Green      | Green          | Yellow        | Green    |               |

## Chemical storage stability



*Mixtures & Prototype formulations*



*Market formulation*

## Sample storage



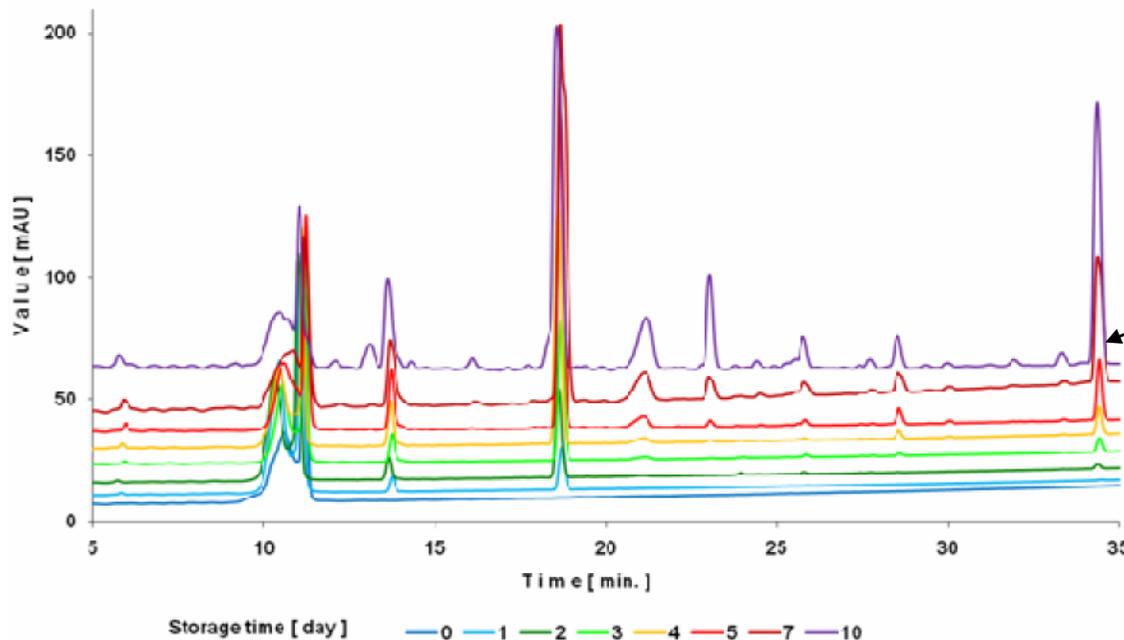
- Up to 15 storage racks
- Heat foil equipped (25 to 100°C)
- Peltier element equipped (5 to 30°C)
- Photodegradation (Illuminated storage rack)
- Storage capacity (> 1000 samples)
- Automated loading/unloading

## Automated HPLC/UPLC workflow



- Sample grinding
- Solvent addition
- Solvent extraction
- Solvent filtration
- Dilution step (optional)
- Chromatographic analysis
- Data analysis/reporting

## Automated Reporting – Chromatographic data



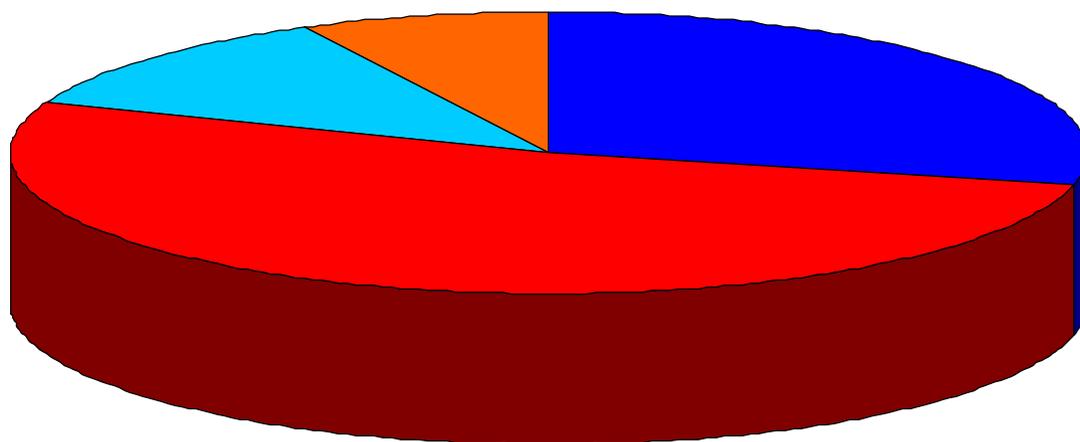
Overlay plot of chromatograms in chronological order

| Test sample | Condition    | Storage Time | API  | BP 1 | BP 2 | BP 3 | BP 4 | BP 5 |
|-------------|--------------|--------------|------|------|------|------|------|------|
| Formul. 1   | 40°C / 75%RH | 0            | 99.7 | 0.1  | 0.0  | 0.1  | 0.0  | 0.1  |
| Formul. 1   | 40°C / 75%RH | 1            | 99.5 | 0.1  | 0.0  | 0.1  | 0.2  | 0.1  |
| Formul. 1   | 40°C / 75%RH | 2            | 99.4 | 0.1  | 0.1  | 0.1  | 0.1  | 0.2  |
| Formul. 1   | 40°C / 75%RH | 3            | 99.2 | 0.1  | 0.1  | 0.1  | 0.4  | 0.1  |
| Formul. 1   | 40°C / 75%RH | 4            | 99.3 | 0.1  | 0.2  | 0.1  | 0.2  | 0.1  |
| Formul. 1   | 40°C / 75%RH | 5            | 99.1 | 0.1  | 0.2  | 0.1  | 0.3  | 0.2  |
| Formul. 1   | 40°C / 75%RH | 6            | 98.9 | 0.1  | 0.3  | 0.1  | 0.4  | 0.2  |
| Formul. 1   | 40°C / 75%RH | 7            | 98.7 | 0.1  | 0.3  | 0.1  | 0.6  | 0.2  |
| Formul. 1   | 40°C / 75%RH | 8            | 98.5 | 0.1  | 0.4  | 0.1  | 0.7  | 0.2  |
| Formul. 1   | 40°C / 75%RH | 9            | 98.1 | 0.1  | 0.4  | 0.1  | 1.1  | 0.2  |
| Formul. 1   | 40°C / 75%RH | 10           | 97.8 | 0.1  | 0.5  | 0.1  | 1.3  | 0.2  |

Peak table

Rule based peak assessment visualised by background color (green, amber, red)

## Trends in Drug Discovery



### Biopharmaceutical classification system

- Class I (high sol. & perm.)
- Class II (low sol., high perm.)
- Class III (high sol., low perm.)
- Class IV (low sol. & low perm.)

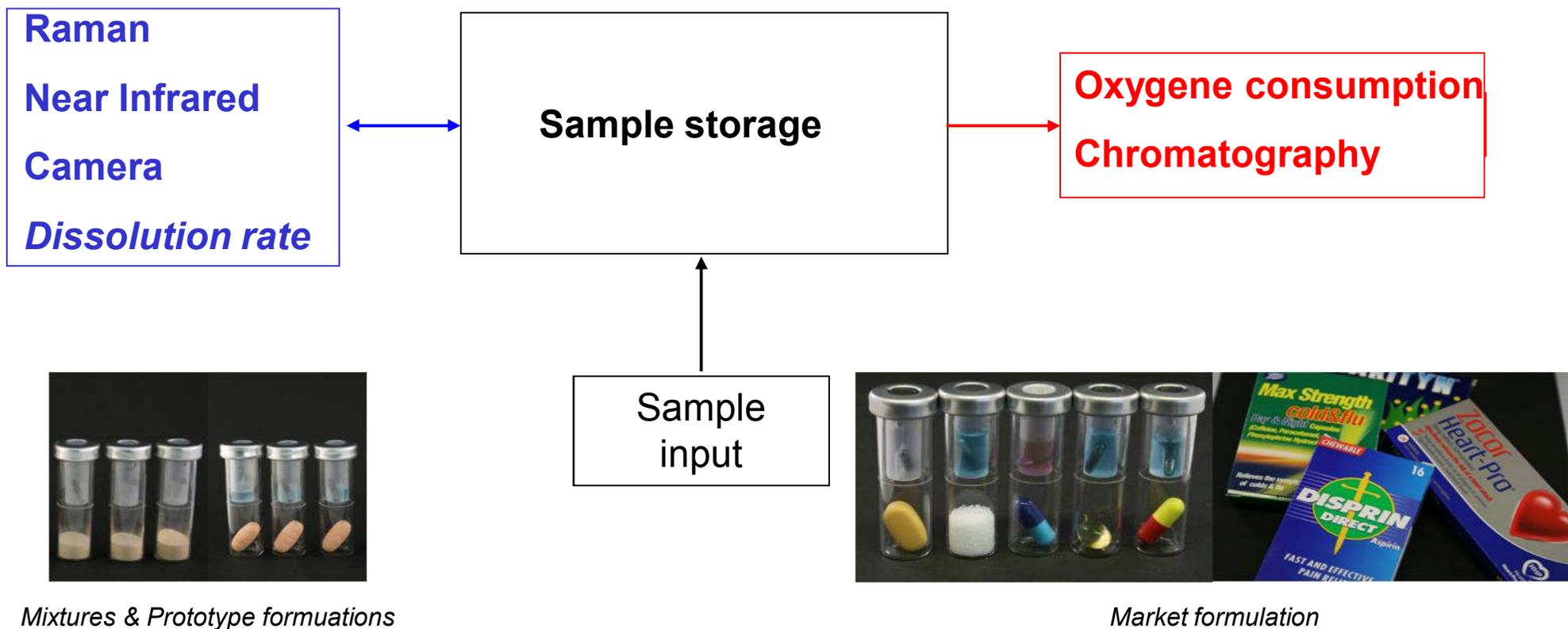
- More than 40 % of newly discovered drugs have little or no water solubility
- More than 90 % of drugs approved since 1995 have poor solubility/ permeability or both

Source: Connors R.D & Elder, E.J.; Solubilisation solutions, [www.drugdelivery.com](http://www.drugdelivery.com)

A profound knowledge about the **physical** and **chemical stability** of the solid state essential for successful product development especially for Class II and IV compounds

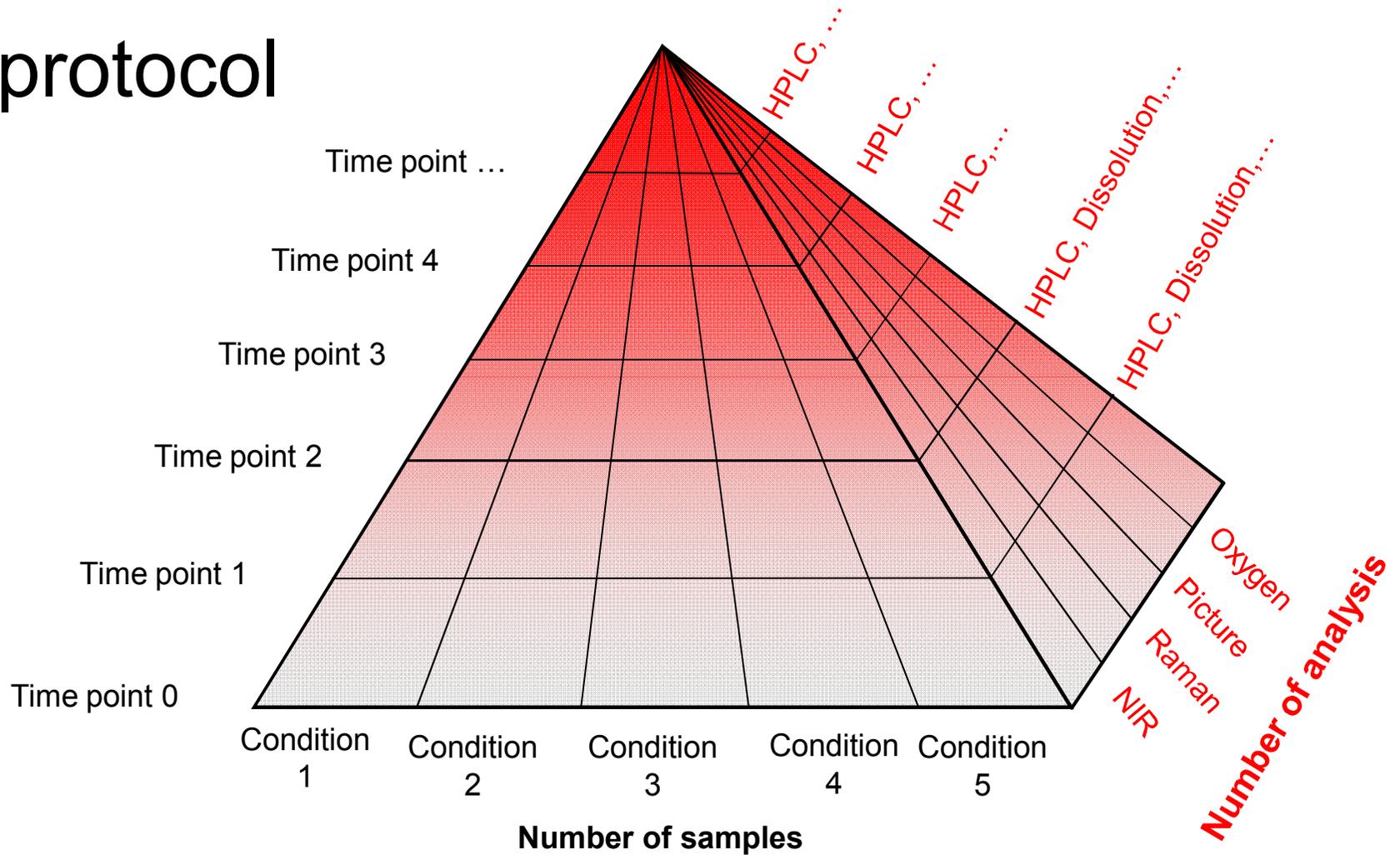
---

## Chemical and physical storage stability

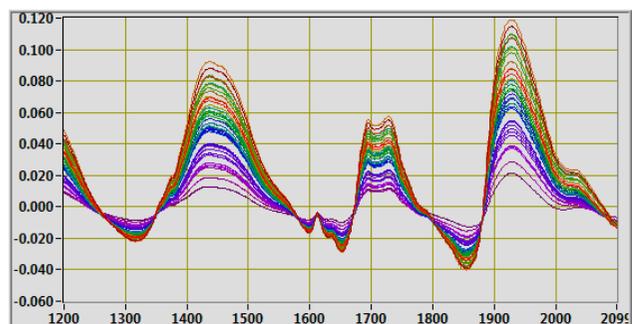
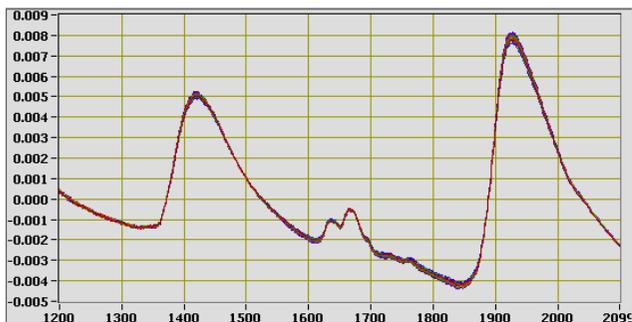




### Study protocol

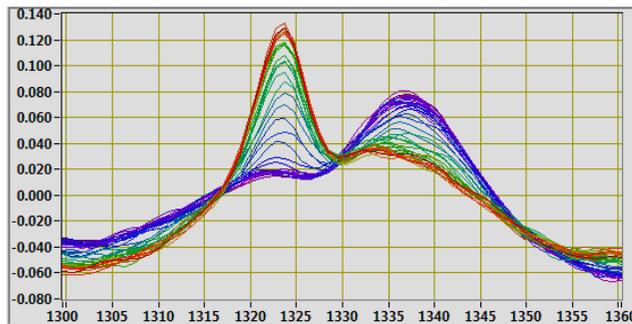
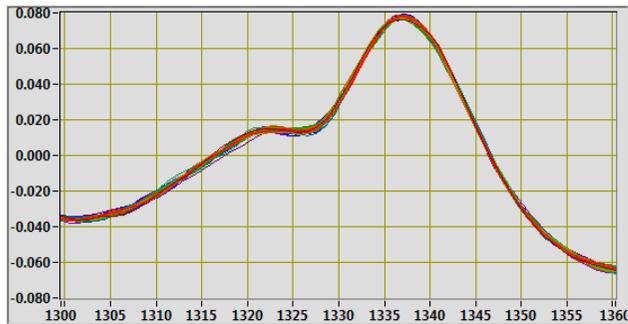


## Hygroscopicity



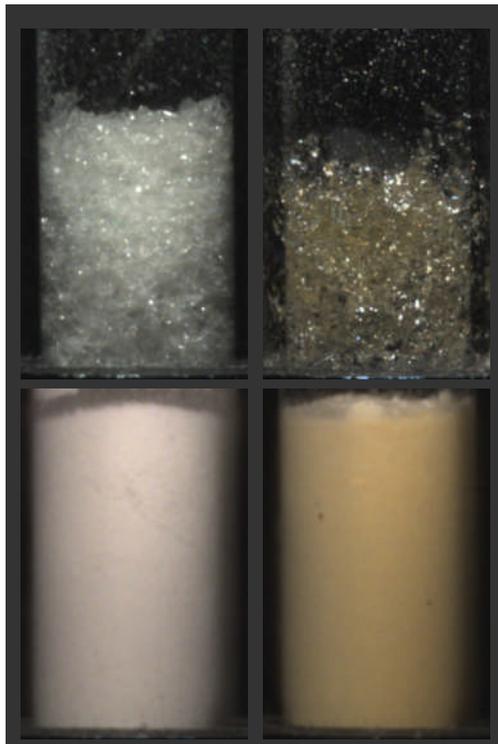
| Formulation no. | 20°C/dry | 24°C/65% RH | 40°C/dry | 40°C/75% RH |
|-----------------|----------|-------------|----------|-------------|
| 1               | 0.10%    | 0.50%       | 0.10%    | 0.80%       |
| 2               | 0.10%    | 1.00%       | 0.10%    | 1.50%       |
| 3               | 0.20%    | 0.20%       | 0.20%    | 0.40%       |
| 4               | 0.10%    | 0.40%       | 0.10%    | 0.60%       |
| 5               | 0.10%    | 2.50%       | 0.10%    | 3.50%       |
| 6               | 0.10%    | 5.00%       | 0.10%    | 7.00%       |
| 7               | 0.20%    | 0.50%       | 0.20%    | 0.90%       |
| 8               | 0.10%    | 0.10%       | 0.10%    | 0.30%       |
| 9               | 0.50%    | 10%         | 0.40%    | 8.00%       |
| 10              | 0.10%    | 0.10%       | 0.10%    | 0.20%       |

## Morphological stability



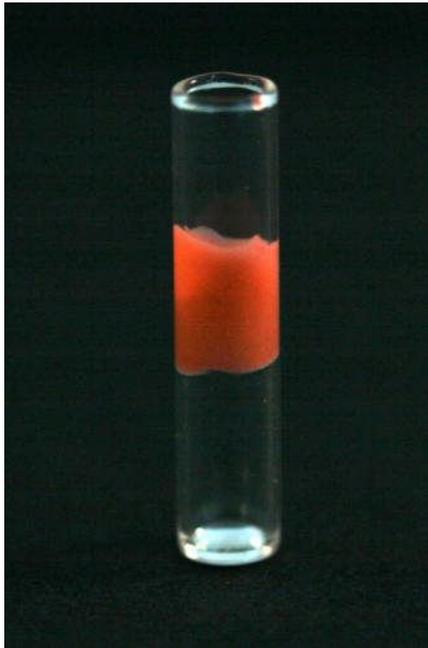
| Formulation no. | Storage condition | Week 1 | Week 2 | Week 3 | Week 4 |
|-----------------|-------------------|--------|--------|--------|--------|
| 1               | 25°C/dry          | Green  | Green  | Red    | Red    |
|                 | 25°C/60%RH        | Green  | Orange | Red    | Red    |
|                 | 40°C/dry          | Green  | Orange | Red    | Red    |
|                 | 40°C/75%RH        | Green  | Orange | Red    | Red    |
| 2               | 25°C/dry          | Green  | Green  | Green  | Orange |
|                 | 25°C/60%RH        | Green  | Green  | Orange | Red    |
|                 | 40°C/dry          | Green  | Green  | Green  | Orange |
|                 | 40°C/75%RH        | Green  | Orange | Red    | Red    |
| 3               | 25°C/dry          | Green  | Green  | Green  | Green  |
|                 | 25°C/60%RH        | Green  | Green  | Green  | Green  |
|                 | 40°C/dry          | Green  | Green  | Green  | Green  |
|                 | 40°C/75%RH        | Green  | Green  | Green  | Green  |
| 4               | 25°C/dry          | Green  | Green  | Green  | Green  |
|                 | 25°C/60%RH        | Green  | Green  | Green  | Green  |
|                 | 40°C/dry          | Green  | Green  | Green  | Green  |
|                 | 40°C/75%RH        | Green  | Green  | Green  | Orange |

## Picture acquisition



| Formulation no. | Storage condition | Week 1 | Week 2 | Week 3 |
|-----------------|-------------------|--------|--------|--------|
| 1               | 25°C/dry          | Green  | Green  | Green  |
|                 | 25°C/60%RH        | Green  | Orange | Red    |
|                 | 40°C/dry          | Green  | Green  | Green  |
|                 | 40°C/75%RH        | Green  | Orange | Red    |
| 2               | 25°C/dry          | Green  | Green  | Green  |
|                 | 25°C/60%RH        | Green  | Orange | Red    |
|                 | 40°C/dry          | Green  | Green  | Green  |
|                 | 40°C/75%RH        | Green  | Orange | Red    |
| 3               | 25°C/dry          | Green  | Green  | Green  |
|                 | 25°C/60%RH        | Green  | Orange | Red    |
|                 | 40°C/dry          | Green  | Green  | Green  |
|                 | 40°C/75%RH        | Green  | Orange | Red    |
| 4               | 25°C/dry          | Green  | Green  | Green  |
|                 | 25°C/60%RH        | Green  | Green  | Green  |
|                 | 40°C/dry          | Green  | Orange | Red    |
|                 | 40°C/75%RH        | Orange | Red    | Red    |

## Photostability Testing



| Storage condition    | 1 day  | 3 day  | 5 day  | 7 day  |
|----------------------|--------|--------|--------|--------|
| 20°C/dry<br>dark     | Green  | Green  | Green  | Green  |
| 20°C/dry<br>light    | Green  | Green  | Orange | Orange |
| 24°C/65% RH<br>dark  | Green  | Green  | Green  | Green  |
| 24°C/65% RH<br>light | Green  | Orange | Orange | Red    |
| 40°C/dry<br>dark     | Green  | Green  | Green  | Green  |
| 40°C/dry<br>light    | Orange | Orange | Red    | Red    |
| 40°C/75% RH<br>dark  | Green  | Green  | Green  | Green  |
| 40°C/75% RH<br>light | Red    | Red    | Red    | Red    |

Identification of degradation products by UPLC/MS

## Automated storage stability: Results

- Morphological stability vs. time and condition
  - Chemical stability vs. time and condition
  - Hygroscopicity vs. time and condition
  - Oxygenation stability vs. time and condition
  - Visual appearance vs. time and condition
  - Dissolution rate vs. time and condition
  - .....
-

## Automated storage stability: Conclusions

- Improvement of **data quantity**
- Improvement of **data quality**
- Reduction of **analysis time**
- Reduction of **cost per analysis**

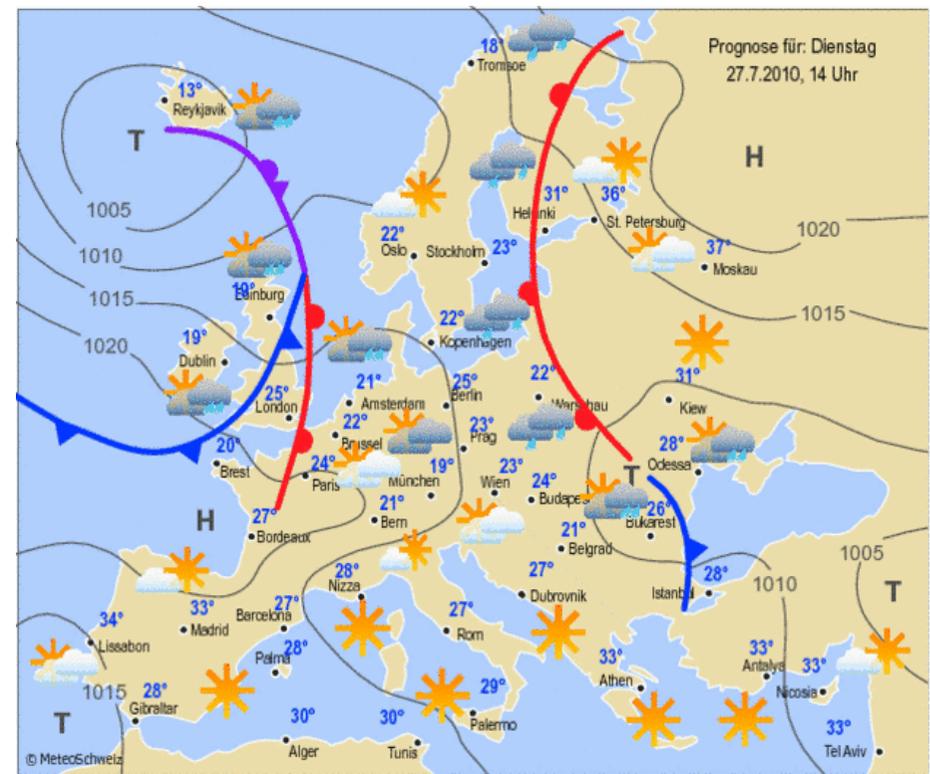
*What's the benefit ?*

---

# RPD TOOL



## Rapid Product Development



## Opportunities

- Rapid Prototyping & testing
    - StabScreen & Prototyping tool
  - Acceleration of formulation development
    - More (accelerated) storage conditions
  - QbD approach for market formulation
    - Bioequivalence with preclinical and first clinical forms or original drug
-