Semi-automated method for high-throughput *in-vitro* release testing

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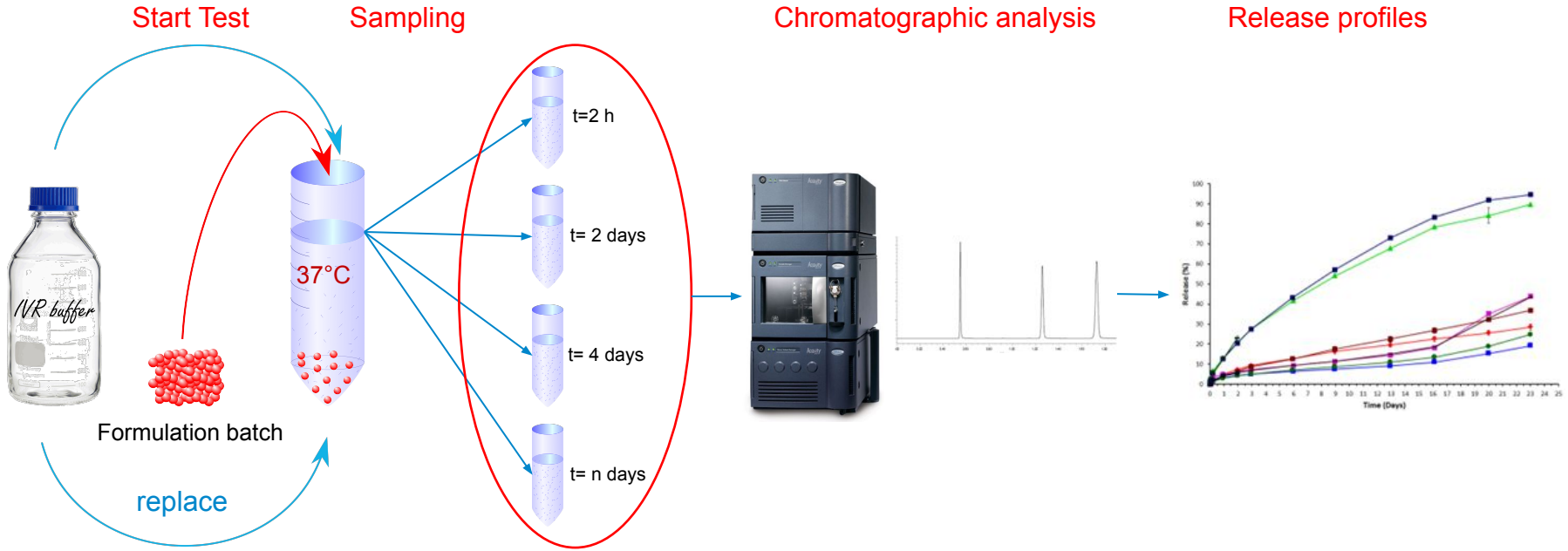
Company Context

- **Development of sustained release formulations**
  - **Encapsulation of API in bio-degradable polymer matrix**
- **Multiple clients**
- **> 20 projects / year**
  - **Multiple formulation types**
    - Micro particles
    - Solid implants
    - In situ forming depots
  - **Multiple API's**
  - **Varying API loads**
  - **Different release characteristics: 1 day – 1 year**
- **> 400 R&D formulation batches**
- **IVR most important test for evaluation of formulations and decision making**
- **Lot of administrative work**
- **Manual data transcription**
- **Data checking and reviewing**

Please, automate!

IVR experiment (in brief)

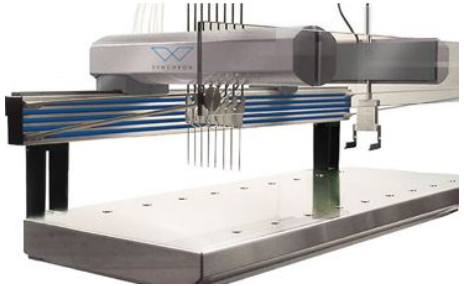


- **Sample & Replace : removed buffer is replaced by fresh buffer**
- **Sample Only : no replacement of IVR buffer**

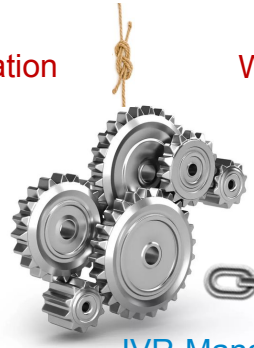
Automation idea

Database
- Experimental data

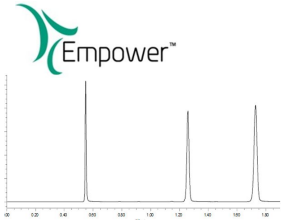
Pipetting robot
- Sampling



Worklist Generation
Data exchange

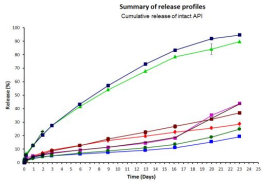


Worklist Generation



IVR-Manager

Experimental details



Excel
- Curve calculation

Data input and control

Requirements

Software

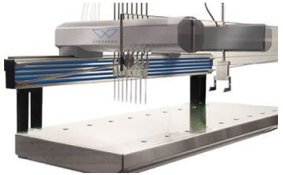
- **Maximum flexibility**
- **Expandable / scalable**
- **System must adapt to company workflow, not vice versa**
- **Deal with deviations from planned procedure**
  1. Skipped sampling points
  2. Change sampling times halfway experiment
  3. Stop part of experiment or individual sample replicates
  4. Etc, etc…..
- **No commercially available products**

Hardware

- **Pipetting robot**
  - Expandable
  - User programmable
  - Interaction with external sources
  - Database based
- **Not fully automated**
  - Sample weighing
  - Centrifugation
  - Sample transfer robot □□ incubator

Custom made IVR Manager software development

Synchronlab Experimate Pipetting Robot



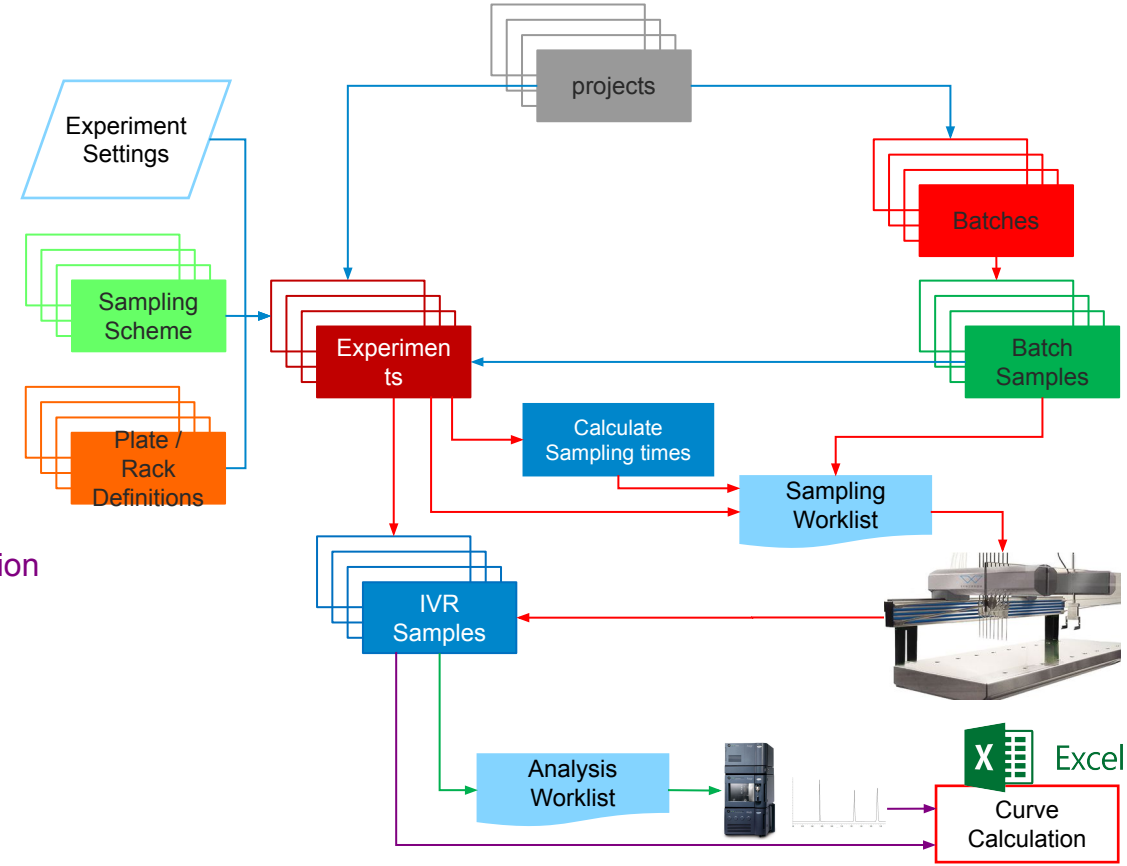
Automated IVR process work-flow

- **Projects**
  - **Umbrella part**
  - **No mix-up**
- **Batches (formulations)**
- **Experiments**
  - **Start date / time**
  - **Volumes**
  - **Sampling protocol**
  - **Batch samples**
    - Sample mass
    - Position on plate / rack
- **IVR samples**
  - **Sampling time**
  - **Location on plate**

Sampling

Analysis

Curve Calculation



IVR Manager development

- **Application development outsourcing…….**

Joke : Truth

20 : 80

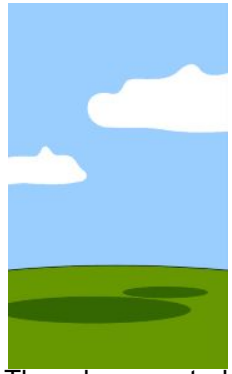

We explained

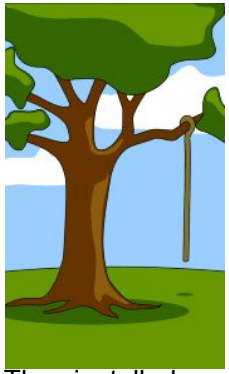

They understood


They promised

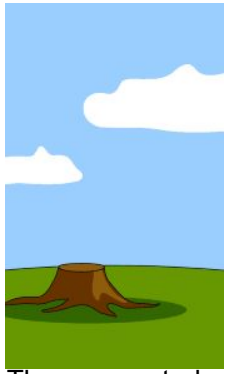

They designed


They coded


They documented


They installed

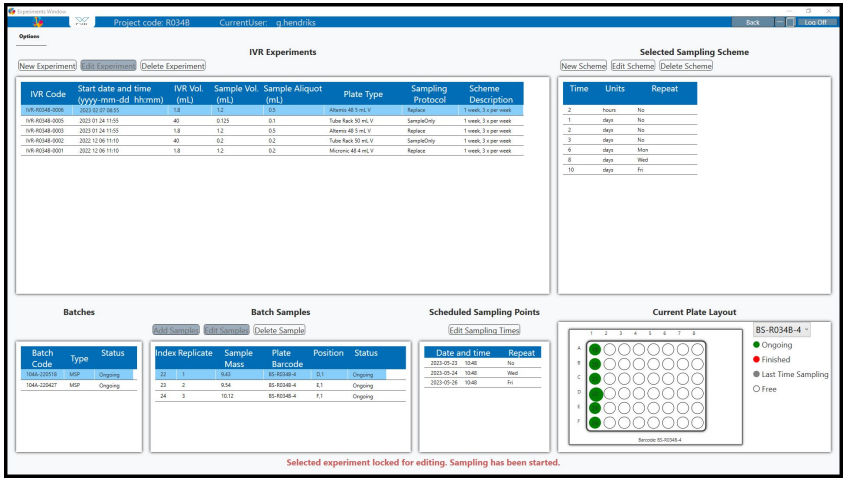

They billed us


They supported

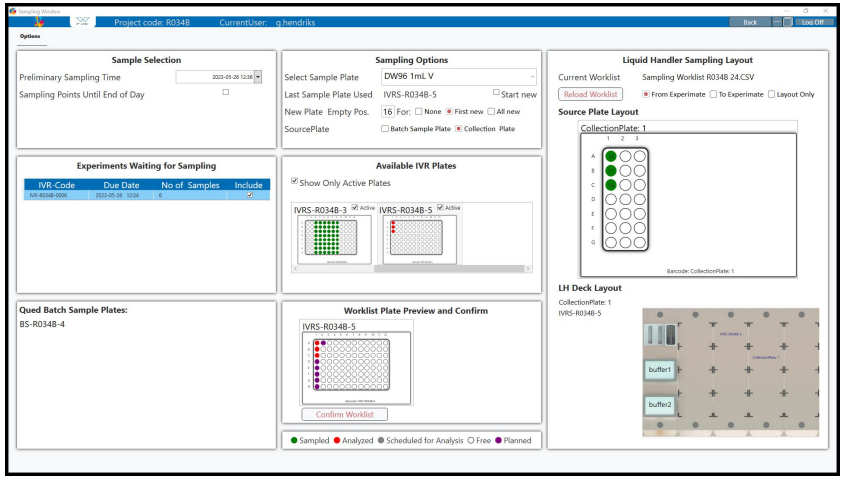

What we needed

IVR Manager

- In-house development
- Good overview
  - Process
  - Sampling status
- User is in control
- Direct worklist upload to robot
- Results exchange with robot
- Analysis worklist as Excel file
  - Copied to Empower
- During development
  - Additional features
  - Ideas
  - Unforeseen issues
  - Fast action



Experiment window



Sampling window

Test experiments

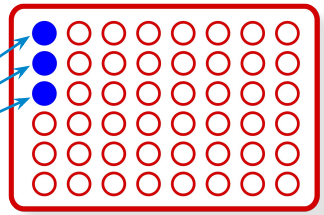
Sampling scheme: 2h, 1, 2, 3, 6 days, every Mon, Wed, Fri, until complete

700 µL to waste

500 µL to collection plate

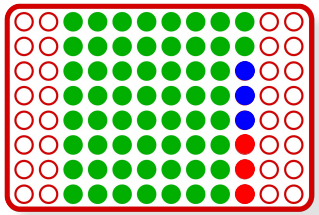
Replace with 1.20 mL of fresh buffer

4 mL tubes



- S & R
- 10 mg MSP's
- 1.8 mL buffer

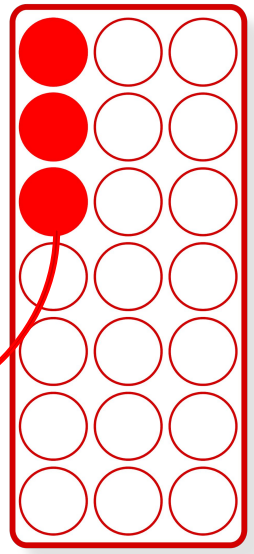
DW96 plate



Collection plate

- Sample Only
- 20 mg MSP's
- 40 mL buffer

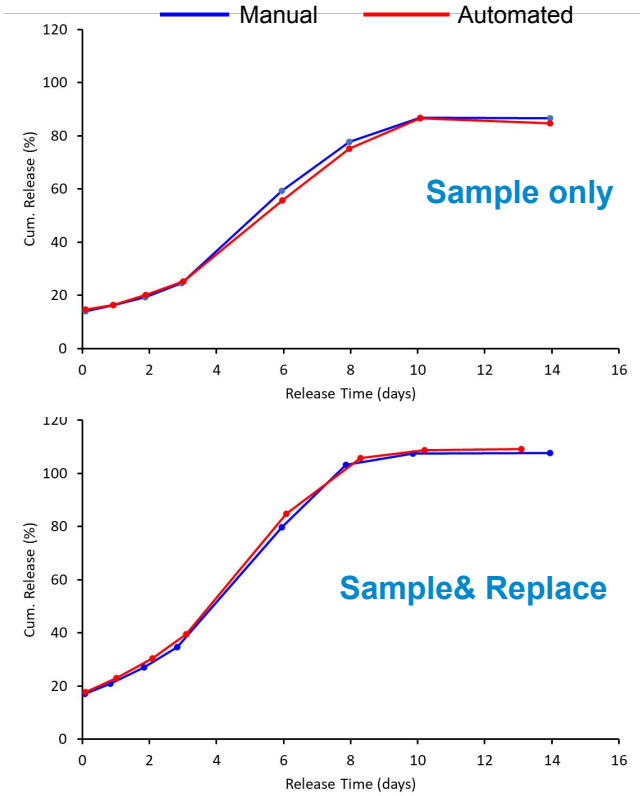
50 mL tubes



200 µL to collection plate

- **Duplicate experiments**
  - Manually
  - Simultaneously
  - According to current procedures
- **14 days release time**
- **Weekly analysis**
  - Two different collection plates

Results



- **Identical curves for manual and automated experiments**
  - **No interference with other projects**
  - **Good scheduling of sampling time points**
  - **Good tracking of sample positions**
  - **Handle different tube / plate formats simultaneously**
  - **Accurate result summary output for IVR curve calculation**
  - **Perform different IVR experiments simultaneously**
  - **Separation of samples**
    - **no double samples in one well**
    - **no sample mix-up**

Conclusions

- In-house software development is efficient for highly specialized applications
- Our IVR Manager application + pipetting robot fulfills all our needs
- The IVR automation approach is:
  - Reliable and efficient
  - Highly flexible and expandable
  - 2-3 times faster than manual procedure
  - Able to handle large numbers of samples

Best swing setup ever!

Acknowledgements

- **Wilma Steeman**
  - Head of analytical department
  - Facilitating and encouraging this project
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- **Jeannette Visscher**
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  - Experimental work
- **SynchronLab**
  - Etten-Leur, The Netherlands
  - Communication with pipetting robot

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Thank you!

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