The British Pharmacopoeia & AQbD

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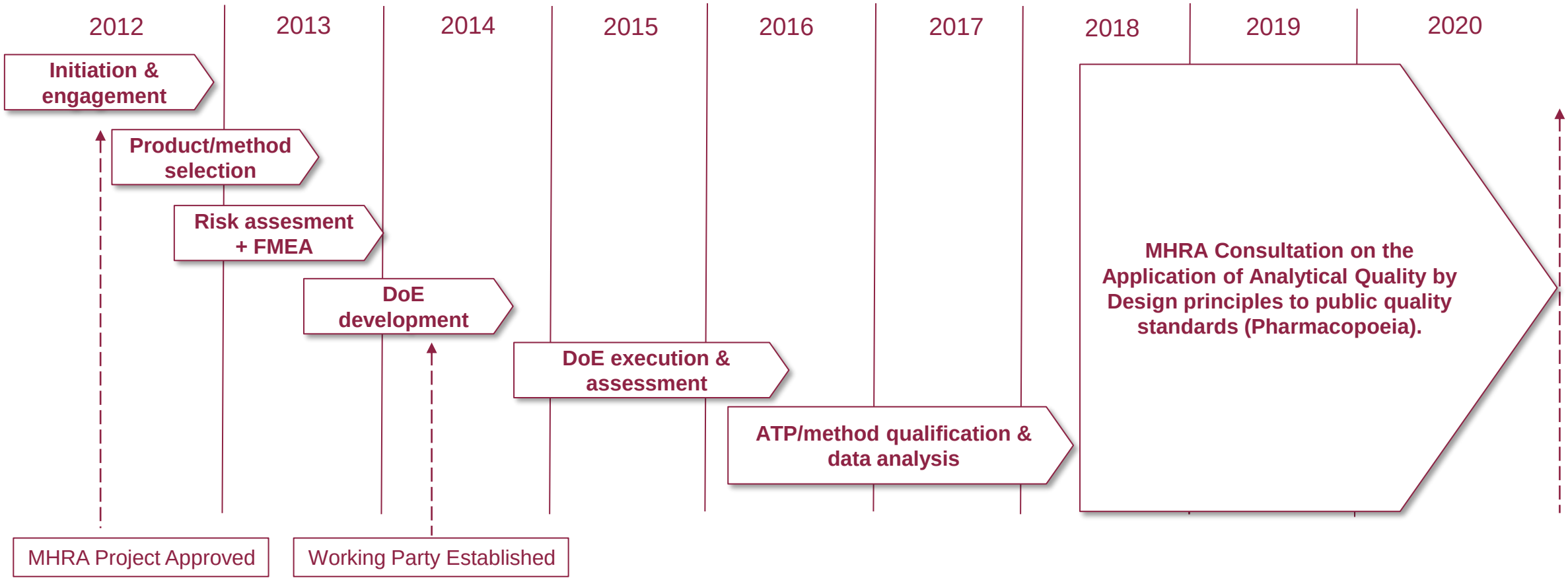
MHRA Project timeline

British Pharmacopoeia



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MHRA Project timeline

British Pharmacopoeia

2020

MHRA consultation response and ongoing Strategy

- Supporting and Enabling Innovation
- Collaboration, Engagement & Knowledge Transfer
- Application to public quality standards

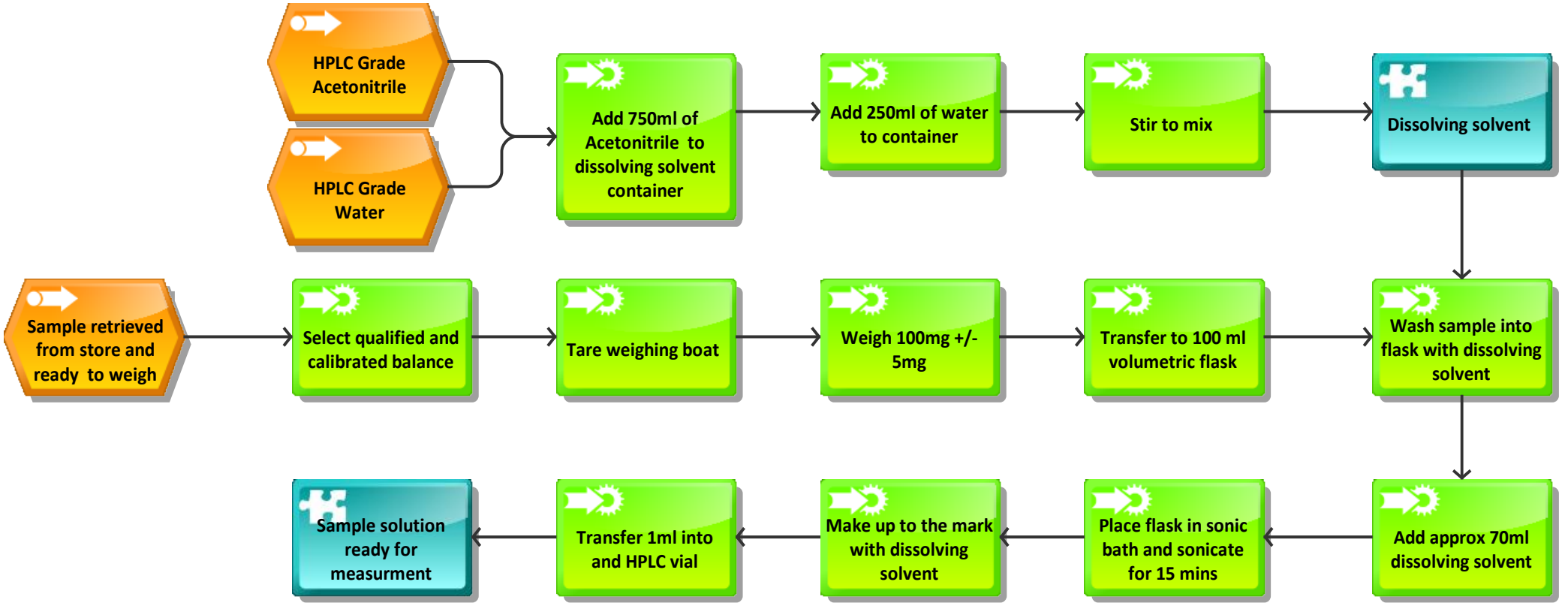
2021+

- The Analytical Target Profile (ATP)
- Industry project collaborations
- Impurity methods/related substances
- Publication of AQbD Supplementary Information - BP
- Publication of Atorvastatin Tablets + Pharmacopoeial Robustness
- Ongoing and evolving efforts

BP Supplementary Chapter

- Title: Use of Analytical Quality by Design Concepts for analytical procedures
- Contents:
  - Introduction, Background, Application to the BP
  - Quality Risk Management
  - Establishment of Method Understanding
  - Analytical Control Strategy

QRM – Risk Identification



QRM – Risk Analysis/Evaluation

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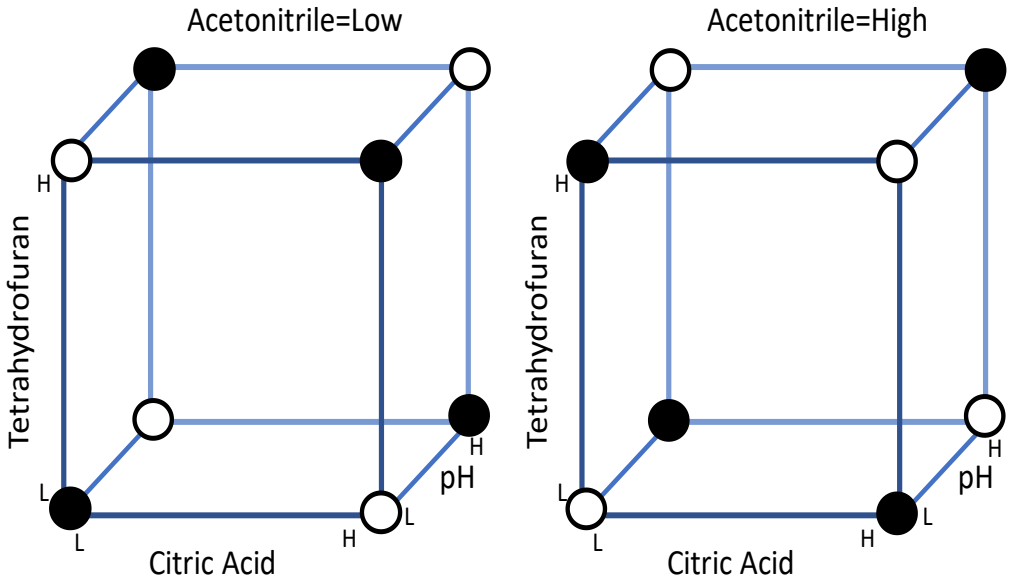
Variable	Severity (1 low, 5 high)	Probability of variation (1 low, 5 high)	Risk score
% Acetonitrile in dissolving solvent	3	4	12
Sonication Time (mins)	4	3	12
% Acetonitrile in the mobile phase	3	4	12
Wavelength	4	2	8
Humidity %	1	5	5
Equilibration time	1	2	2

Method understanding - Development



		Factor A	Factor B	Factor C	Factor D	Response 1
Run Order	Space Type	Citric Acid (g)	pH	Tetrahydrofuran (mL)	Acetonitrile (mL)	Tailing Factor Atorvastatin
1	Factorial	8.66	3.8	130	175	1.12
2	Factorial	8.66	3.8	70	95	1.05

Variation in Method operating conditions

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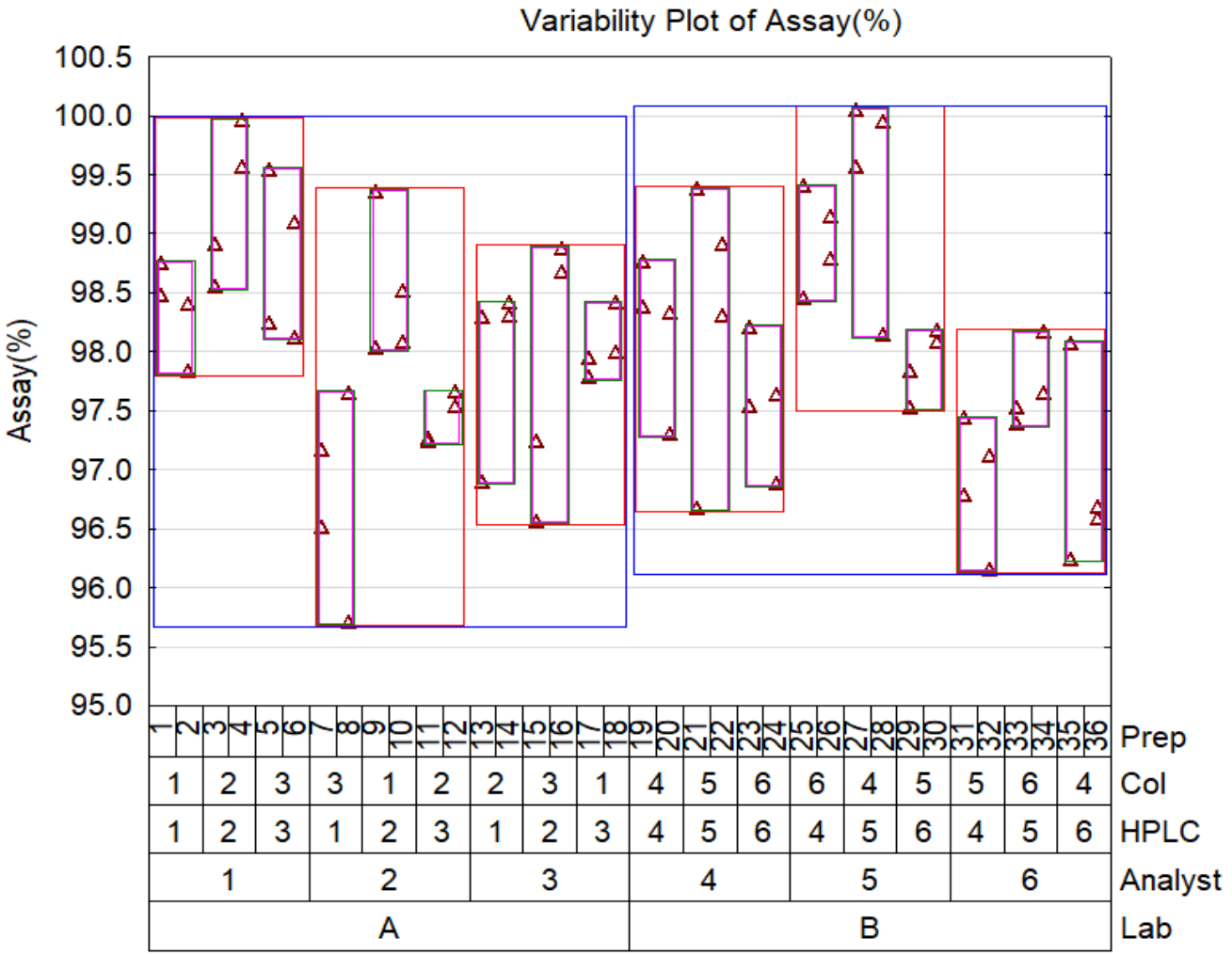
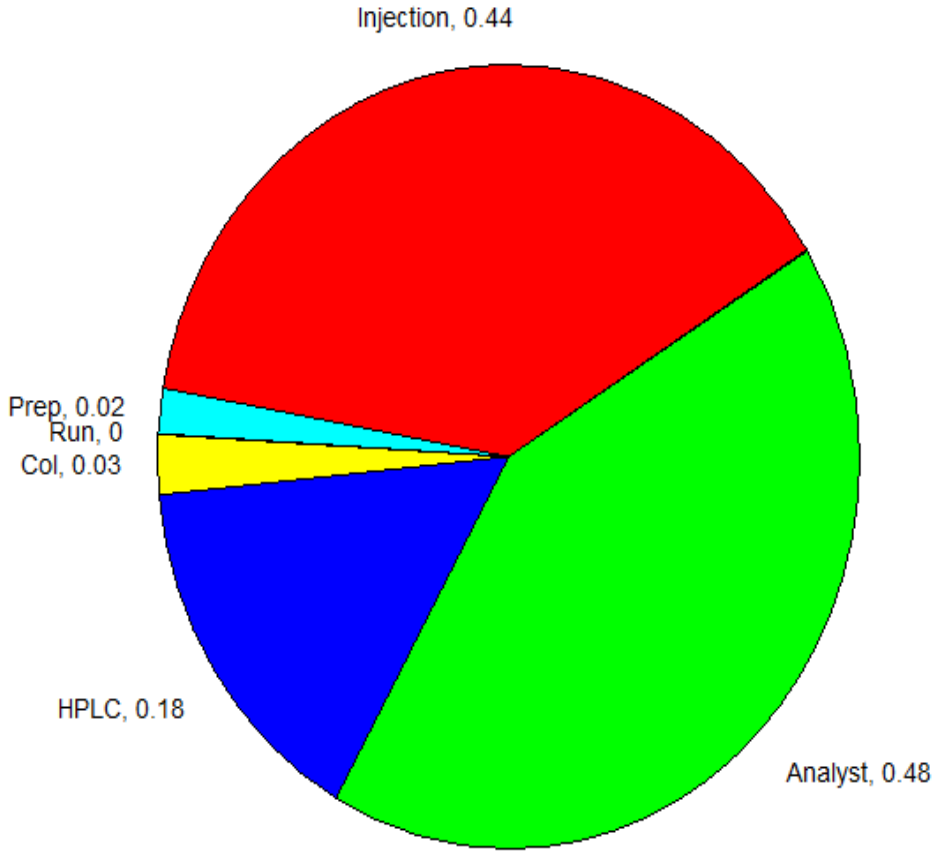
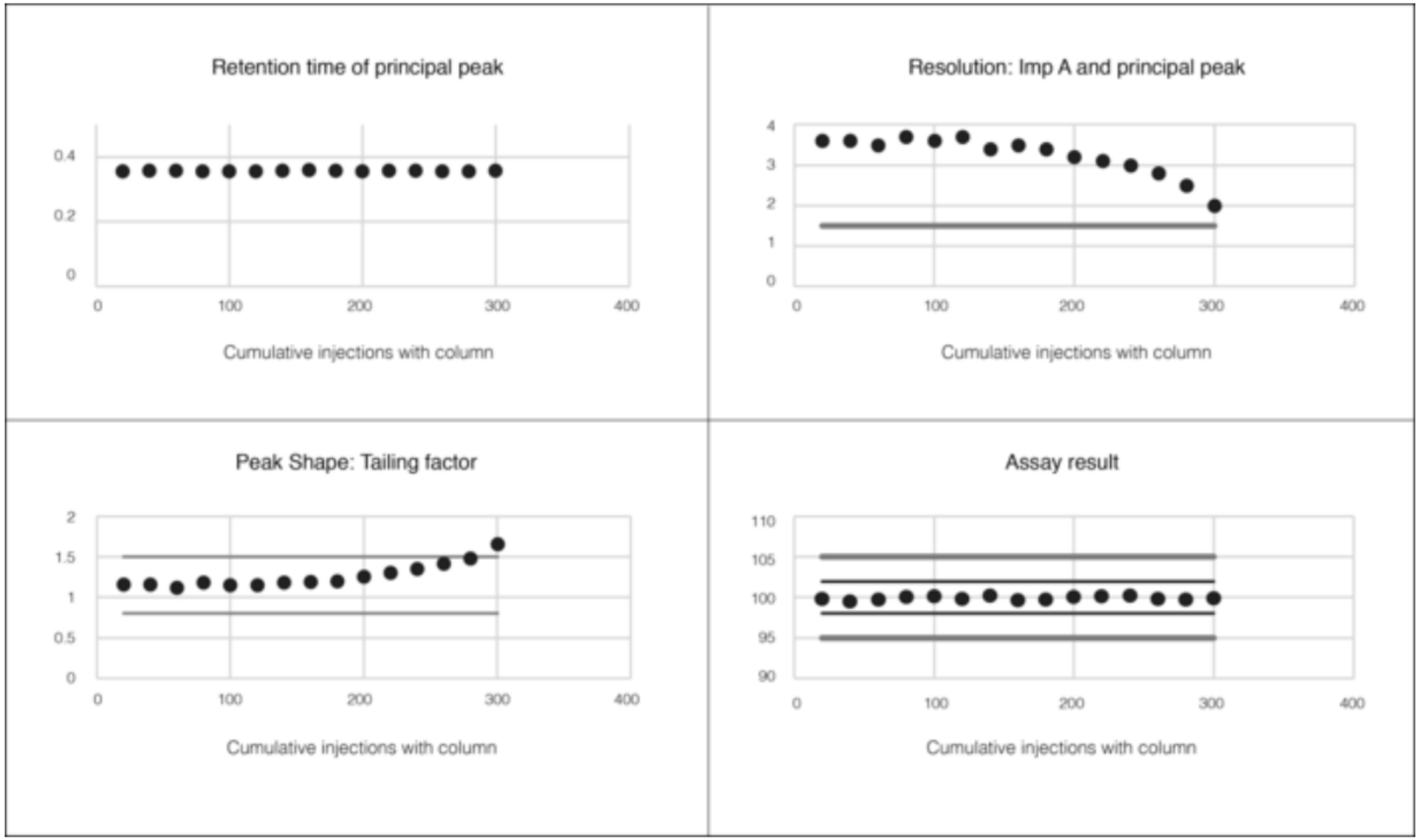




Method control



Future Publications

- The Analytical Target Profile
- User Case stories
- Introduction into compendial finished product monographs.
- Further tests, wider scope

Feedback welcome!

Current project - Impurities

- Analytical methods – compendial perspective
  - Queries, known issues, old products

- How can AQbD Concepts help?
  - Prior knowledge!
  - Focussed Experimental Design
  - Translation to the user?

The Issue

- Impurity Elution order changes
- 4 product monographs for same Active ingredient
  - Nuances in each procedure
- Actual pH Vs Apparent pH – Mobile phase
- Old column technology – differences in manufacturing process?

The approach – Prior Knowledge

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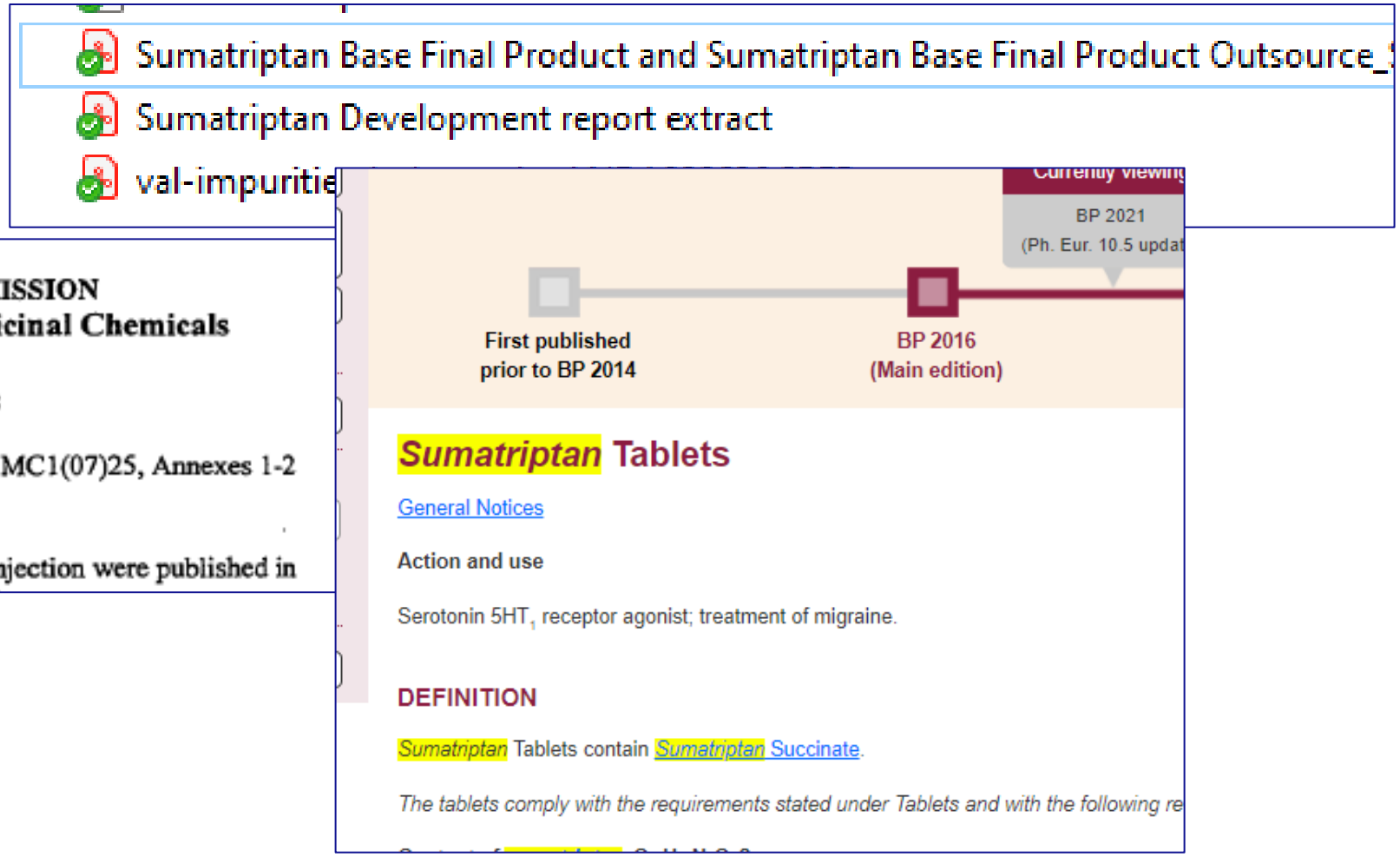

The approach – Prior Knowledge

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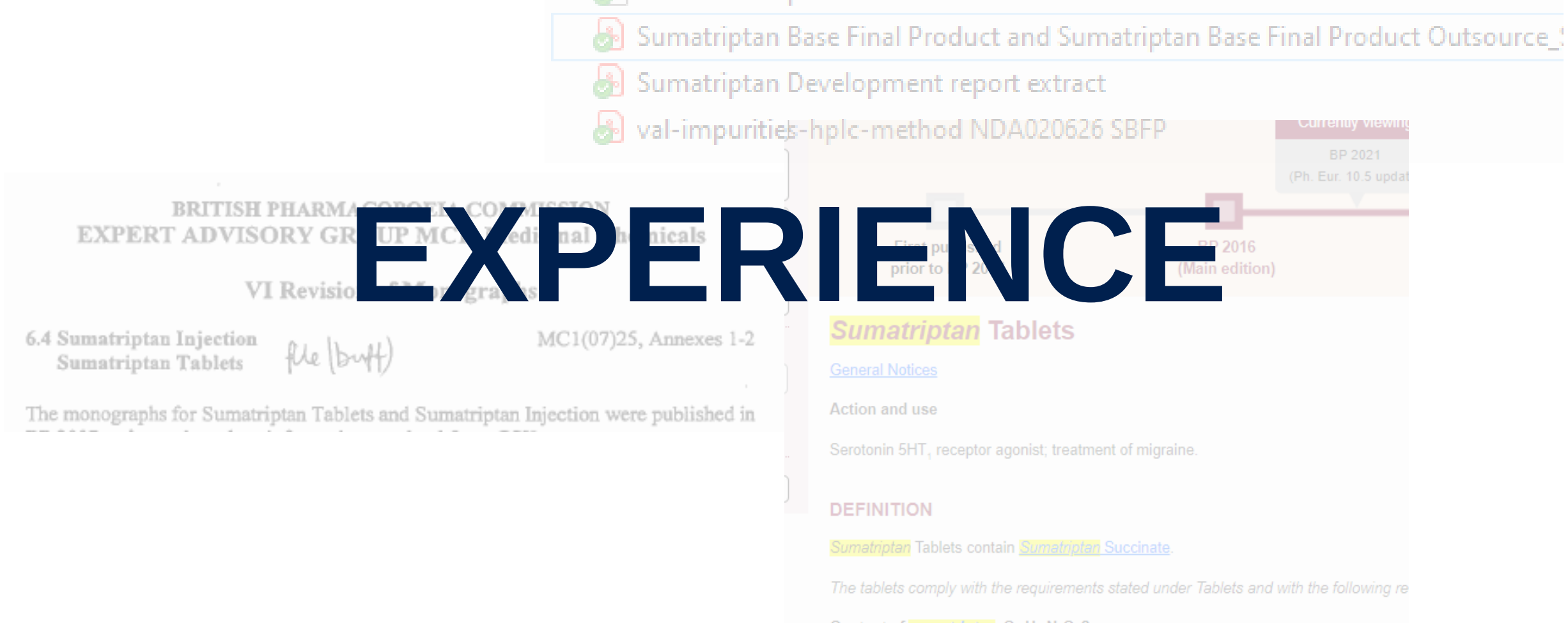
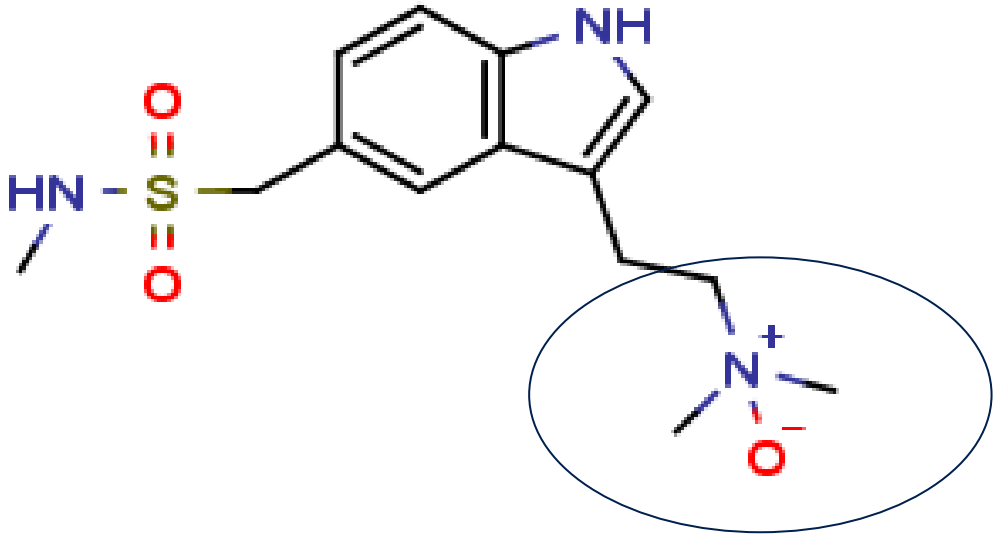


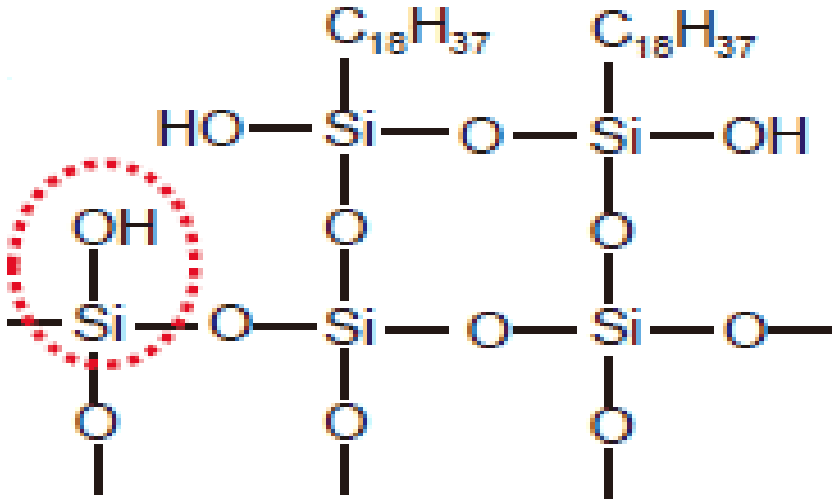
EXPERIENCE

The Approach - Findings

- Mobile phase pH (validated range pH 6-8).
- Stationary Phase – ODS1

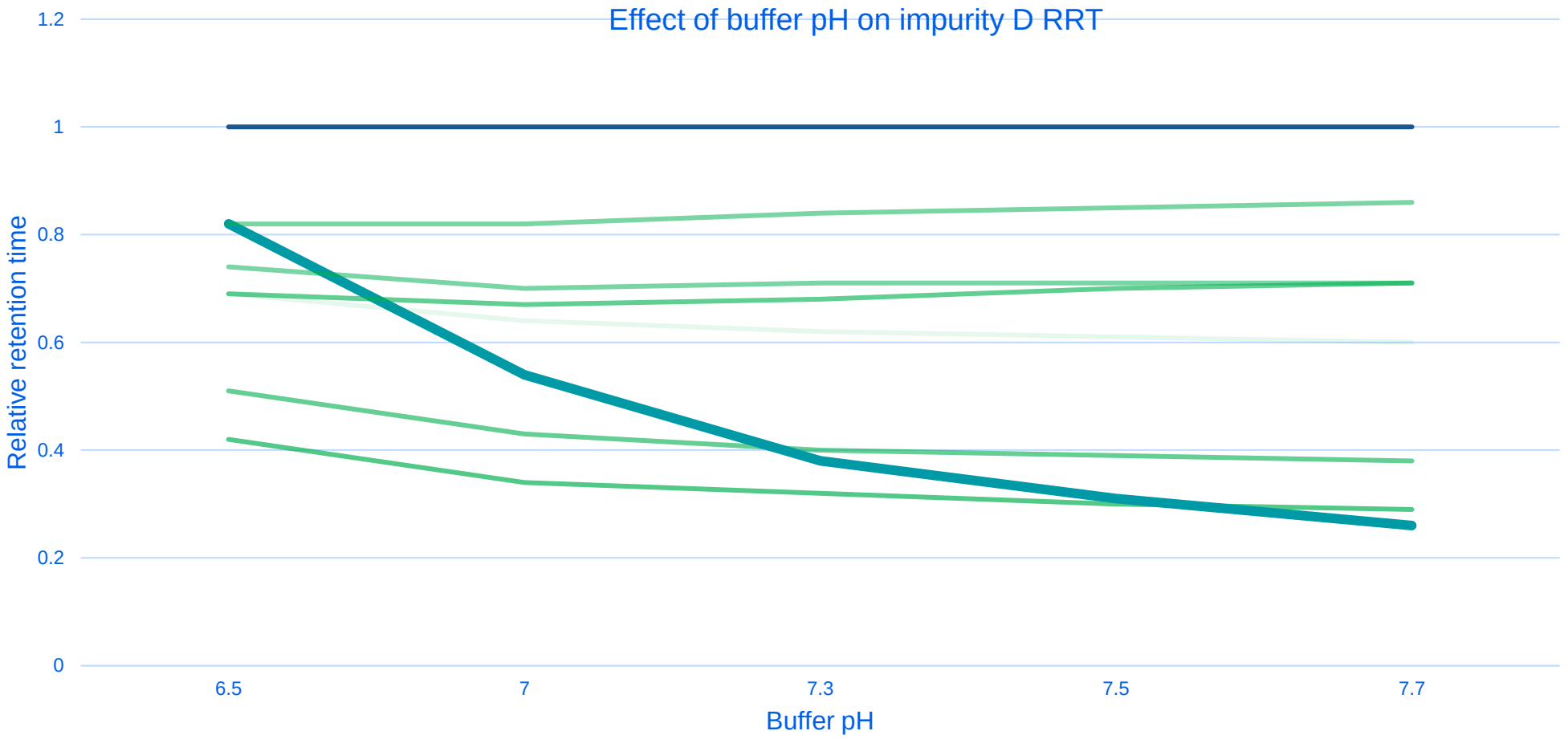


Approx pKa 5-7 (depending on model).



Approx pKa 1.2, pKb 4.5

The Approach: In -Silico



The Approach: In-silico

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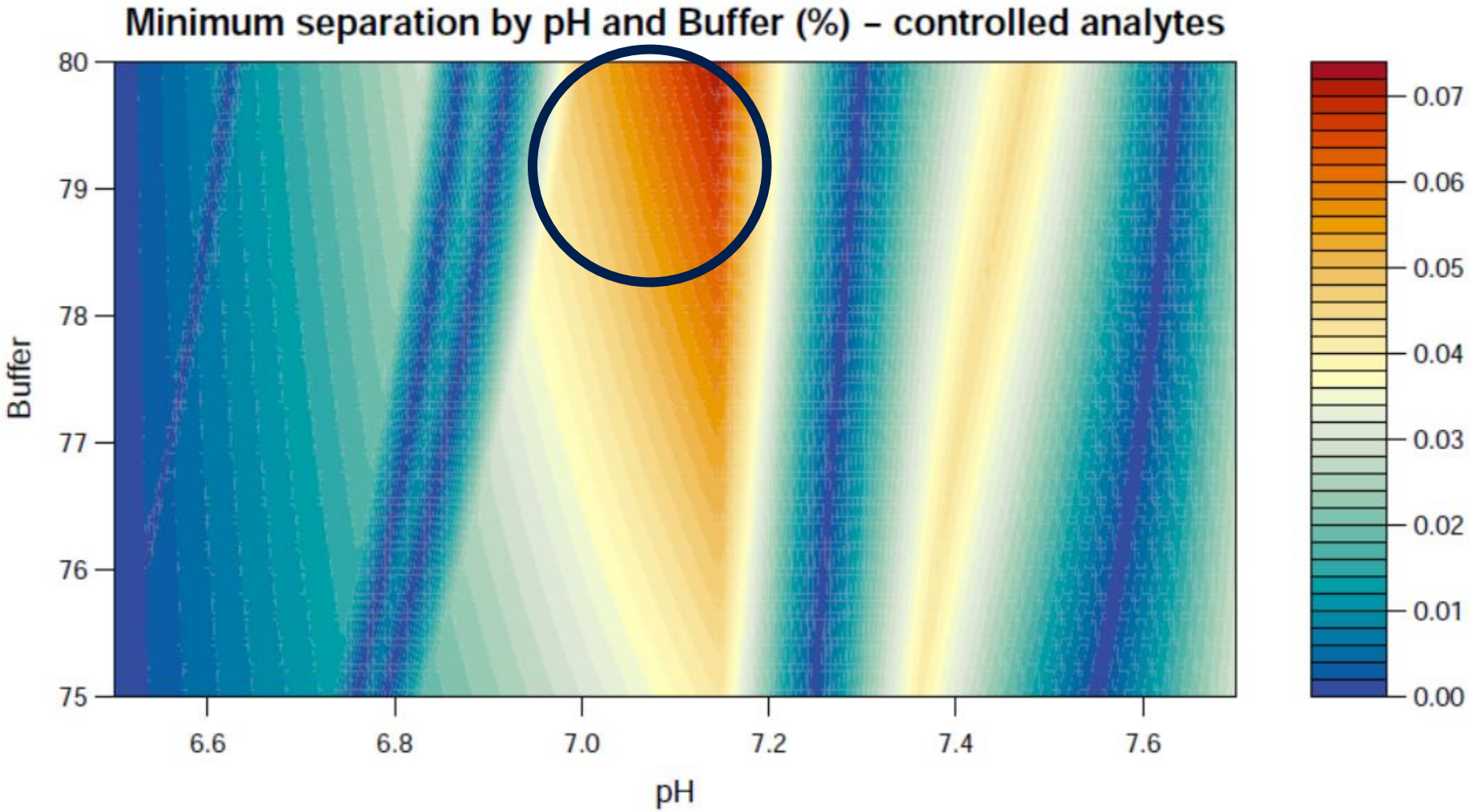

The Approach - Experimental

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- Flexible laboratory protocol
- Silico-modelling performed alongside
- Initial review will inform experimental design.

- Experimental design built taking into account prior knowledge, silico models and initial review.

Experimental Design

Table 1: Sumatriptan LC study - Parameter ranges

Parameter	Low	High
pH	7	7.2
Buffer	78	82.0
Temperature (C)	25	30.0

Monitoring key method attributes

- Retention time impurities and API
- Resolution of all peaks
- Theoretical plates (API)

Power of replication

- Treat columns independent of design
- Repeat entire design
- Potential modifications based on results

Desired outcomes

- To publish 4 high-quality, robust and easy to use monographs
- To provide additional, helpful information on method performance to users
- To utilise good practices within our monograph investigations
- To evaluate the benefits/drawbacks of paper/laboratory based exercises