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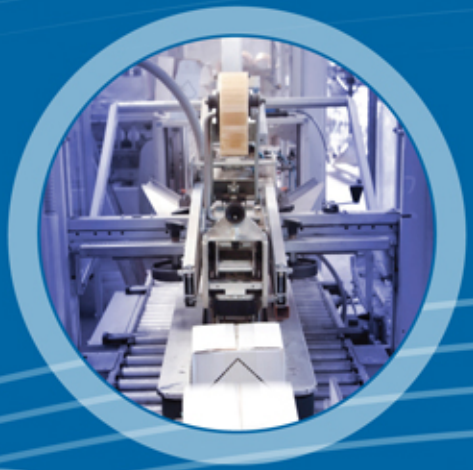
# Case Study 6: Novo Nordisk Experience in the Application of QbD

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Joint Regulators/Industry QbD Workshop
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# Case Study team

## Regulators

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# Case Study 6: Overview

- Introduction to Case Study
- Overview of vatreptacog alfa
- Discussion Topics
  1. Model verification in laboratory and commercial scale
  2. Movement within the design space
  3. Recalibration / adjustment of model constants
  4. Criticality of process parameters
  5. Control strategy

# Introduction to Case Study

- Vatreptacog alfa is a recombinant human Factor VIIa analogue engineered for enhanced activity. It was intended for by-pass therapy for haemophilia patients with inhibitors against Factor VIII or Factor IX
- The manufacturing process include an activation step developed with a design space
- All other manufacturing steps are traditional set-point steps operated within proven acceptable ranges
- The project was terminated due to anti-drug antibody formation and not submitted for approval
- This case study summarises learnings from EMA scientific advice and interactions with other health authorities

# Biotech vs. Small Molecules

Biotechnological products are more complex than small molecules

- They are typically a mix of isoforms, e.g.
  - A mixture of different glycosylated forms
    A change in glycosylation profile may impact bioavailability (efficacy) or potentially increase immunogenicity (safety)
- There are often a wide range of degradation products
  - Not always easy to distinguish between product related substances (active and safe – not CQA's) and product related impurities (not active or with safety concerns – CQA's)

# Biotech vs. Small Molecules

- Consequently, for biotechnological products
  - Identification of all relevant CQA's can be a challenge and new CQA's may be identified during commercial manufacture
  - Changes to manufacturing process may affect product quality
  - Release against specifications alone does not necessarily confirm product quality
- Therefore, an appropriate control strategy is necessary to ensure product quality

# Drug substance purification process

- Cultivation
- Filtration
- Capture
- Chromatography
- Chromatography
- Chromatography
- Chromatography
- Treatment
- Activation
- Virus filtration
- Drug substance

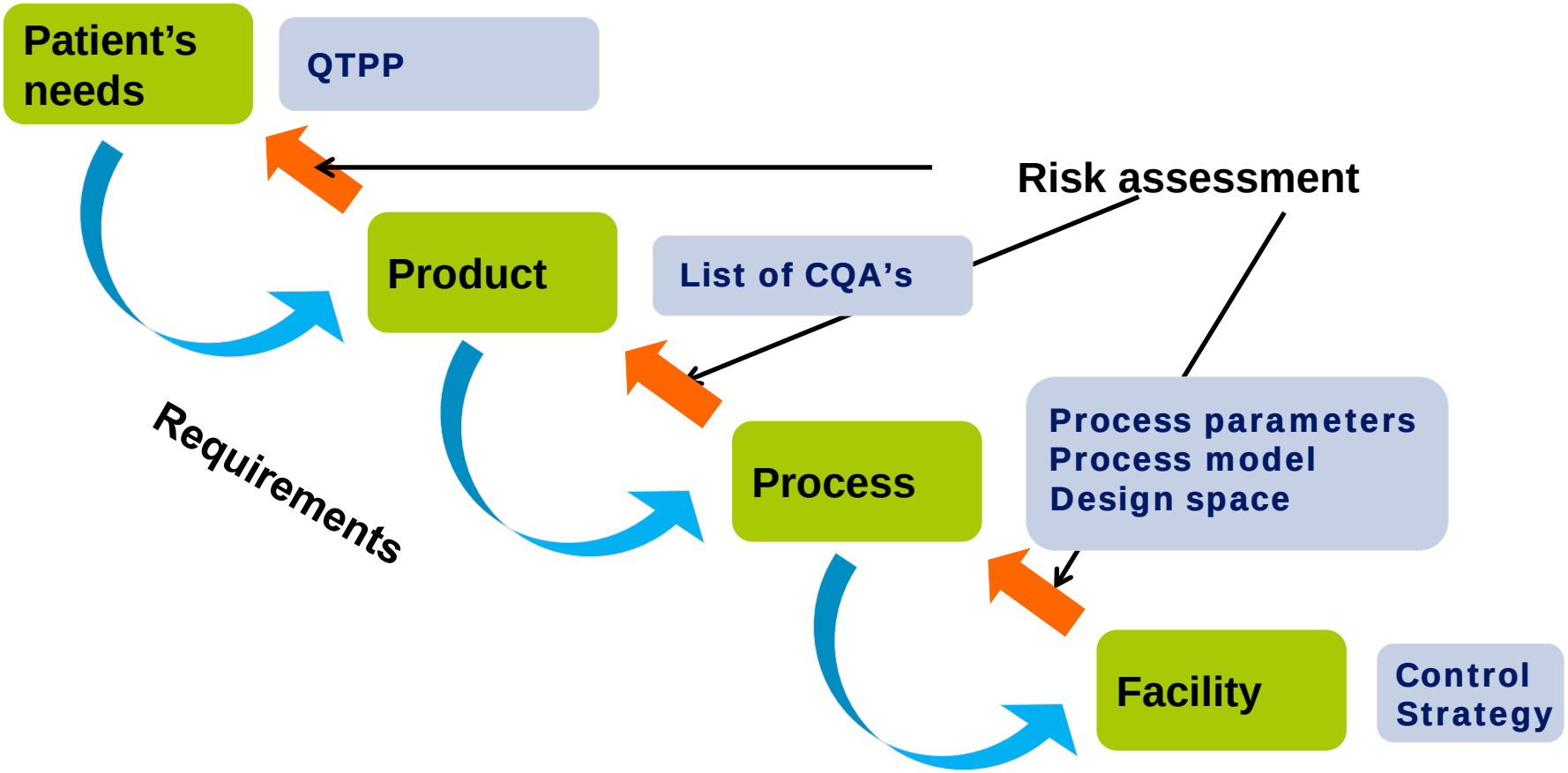
- Upstream process conditions are set to minimize activation and subsequent degradation

- Activation is performed late in the process to minimize further degradation

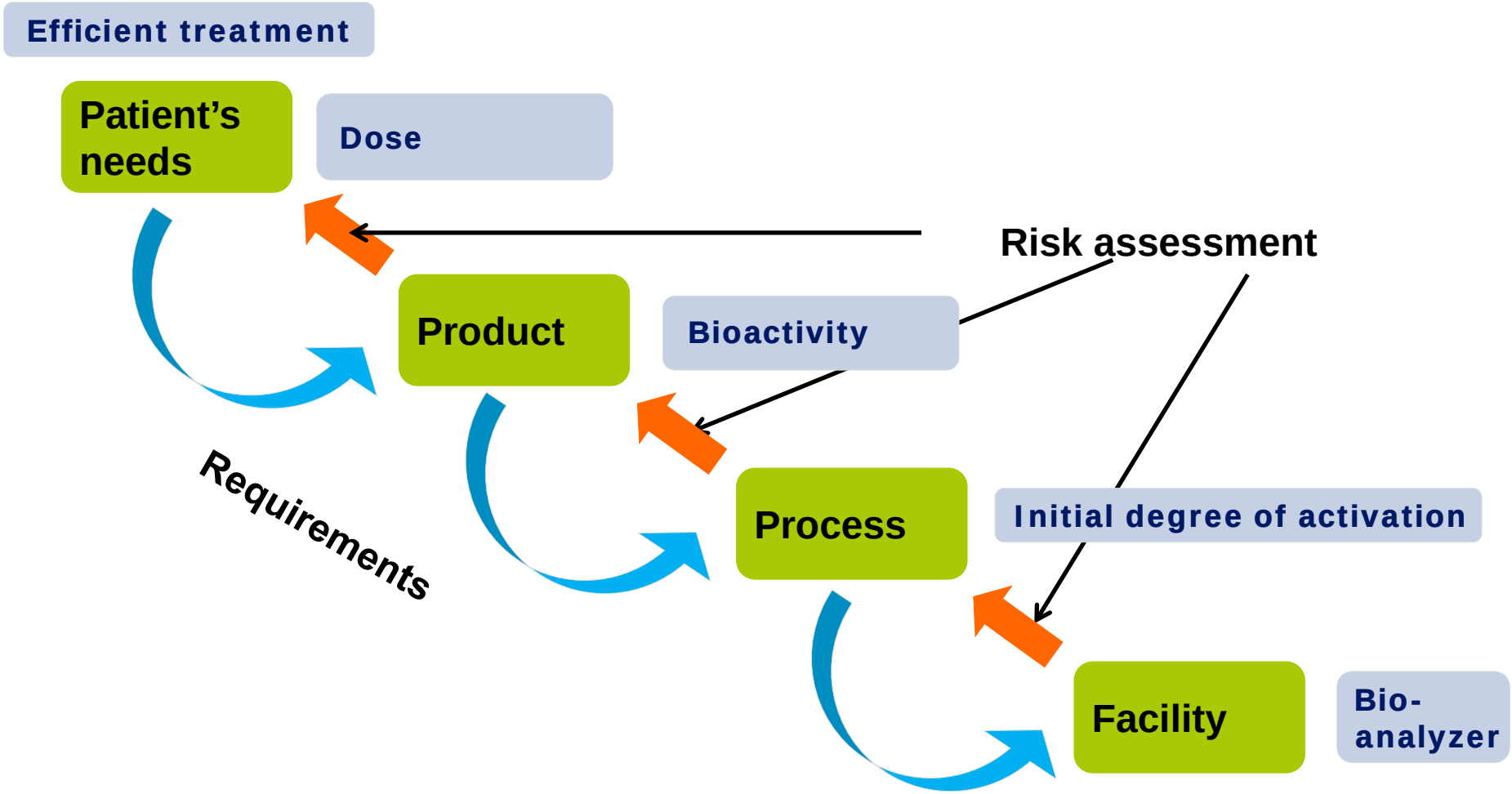
# Purpose of activation step

- To obtain a degree of activation within the proposed drug substance specifications without inducing unacceptable formation of degradation products
- Activation is described by a mechanistic model

# Linking patient's needs to control strategy



# Linking patient's needs to control strategy



# Critical Quality Attributes

| Severity class | Definition | Consequence |
|---|---|---|
| 5 | Serious adverse event with fatal outcome | Medical consequence |
| 4 | Serious event without fatal outcome | |
| 3 | Non-serious event | |
| 2 | Discomfort | No medical consequence |
| 1 | Dissatisfaction of quality expectation | |

# Excerpt from CQA list

| CQA | DS | DP | S | Rationale for severity rating |
|---|---|---|---|---|
| Glycosylation pattern | X | | 3 | Results from clinical trials [ref] have shown that the differences in degree of sialylation did not impact the clinical PK profiles. In spite of these results the different glycosylation patterns may result in less active forms. |
| HMWP | X | X | 4 | May increase the risk of inhibitor formation. Potential immunogenicity, cross-reaction to patients own FVIIa |
| Desamido forms | | | NA | Degradation by desamidation has not been observed for vatreptacog alfa |
| Oxidated forms | X | X | 4 | Known from rFVIIa to have less clinical effect. Same lack of effect is expected for vatreptacog alfa.<br>May increase the risk of inhibitor formation. Potential immunogenicity, cross-reaction to patients own FVIIa |
| Heavy-Chain degraded forms | X | X | 4 | New forms of the molecule can cause immunogenicity, but those antibodies are less likely to be cross-reacting to the patient's own FVIIa.<br>Heavy-chain degraded forms of vatreptacog alfa have reduced clotting activity. |
| Host cell protein | X | | 4 | Potential immunogenicity |
| Sterility | | X | 4 | Injection of a non-sterile product could lead to infection, due to bacterial contaminations |
| Pyrogens | X | X | 5 | Pyrogens/bacterial endotoxin can cause endotoxemia, and lead to septic shock |
| Isotonicity (Injection pain) | X | X | 2 | May cause discomfort |
| Product appearance | | X | 1 | Product may not meet customer expectation |

# Impact of process steps on CQAs

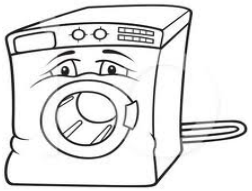
| CQA | Cultivation | Harvest and Filtration | Capture | Chromatography 1 | Chromatography 2 | Chromatography 3 | Chromatography 4 | Treatment | Activation | Virus filtration |
|---|---|---|---|---|---|---|---|---|---|---|
| Amount of API | | | | | | | | | X | |
| Glycosylation pattern | X | X | | | | | | | | |
| HMWP | | | | | | | | X | X | |
| Oxidated forms | X | | | | | | | | | |
| Heavy chain degradation forms | | | | | | | | | X | |
| Host cell protein | X | | X | | | X | X | | | |
| ..... | | | | | | | | | | |

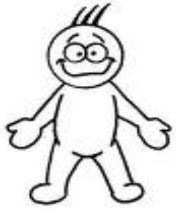
# Process risk assessment

- Based on FMECA methodology
- Severity, occurrence and detection scores assigned to process failure modes (process parameter excursions)
- Integrates determination of process parameter criticality by linking to severity of the CQA's
- Criticality ≠ Risk
  - CPP → A failure will have high impact on quality
  - A insufficiently controlled CPP is high risk
  - A well-controlled CPP is low risk

# Severity evaluation in the FMECA

**Process failure** → **Product quality (CQA's)** → **Patient**





*Reasonably foreseeable and realistic failures*

**I** × **$S_{CQA}$** = **SI**

| I | $S_{CQA}$ | SI |
|---|---|---|
| *Impact number* | | *SI number* |
| *0 – 3* | *1 – 5* | *0 - 15* |

# Criticality

SI number is converted into a Criticality value

| SI number | Criticality value |
|---|---|
| 0 – 2 | 0 |
| 3 – 4 | 1 |
| 5 – 6 | 2 |
| 8 – 9 | 3 |
| 10 – 12 | 4 |
| 15 | 5 |

Criticality value = Severity score in the FMECA

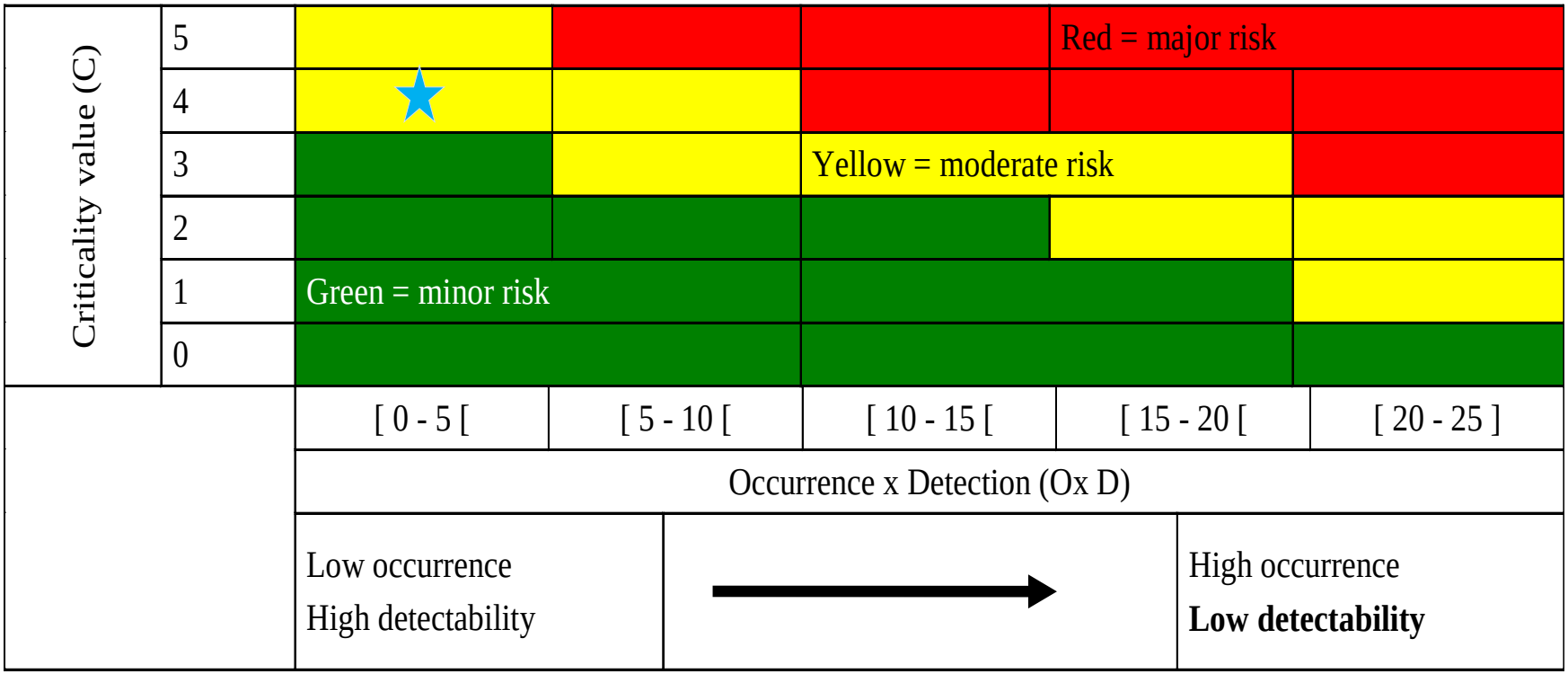
# FMECA step-by-step example

| PROCESS DESCRIPTION | | | | CAUSE & EFFECT MATRIX | | | | | | | PROCESS FMECA | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Critical Quality Attributes $S_{CQA}$ | | | | | | | | | | | | | | | |
| | | | | | 3 | 4 | 4 | 3 | 4 | | | | | | | | | | | |
| Process parameter | Setpoint | Operational range | Potential failure mode (*What may go wrong*) | | Amount of API/Bioactivity | Heavy-chain degradation | HMWP by size-exclusion | Single chain (bioanalyzer) | Gla-domainless forms | Max. SI number | Potential effect(s) of failure (*How does failure impact product quality*) | Criticality value, C | Potential Cause(s) of Failure (Occurrence) (*Why does failure happen*) | Occurrence | Current Controls (Detection) (*How is failure detected*) | Detection | Risk evaluation number | Risk class | Comments | Recommended action(s), responsible and timing |
| **Activation** | | | | | | | | | | | | | | | | | | | | |
| pH | 6.2 - 6.8 | Set point ± 0.1 | pH > Set point + 0.1 | Impact | 2 | 3 | 0 | 0 | 0 | 12 | Too high pH will lead to increased heavy chain degradation and lower bioactivity | 4 | Inaccuracy of pH measurement or human error | 3 | Will be detected by API specification testing for heavy chain degradation | 1 | 12 | | The pH meter is routinely calibrated before ech measurment and there is a double control of the measurement. Based on these measures combined w ith the high detection probability for heavy chain degradation, it is concluded that the risk is at an acceptable level. | No further actions |
| | | | | SI | **6** | **12** | **0** | **0** | **0** | | | | | | | | | | | |

**Process description and failure mode** | **Impact assessment** | **Seve-rity/ Critica-lity** | **Occurence and detectability** | **Risk evaluation and control**

27 individual failure modes were assessed for the activation step

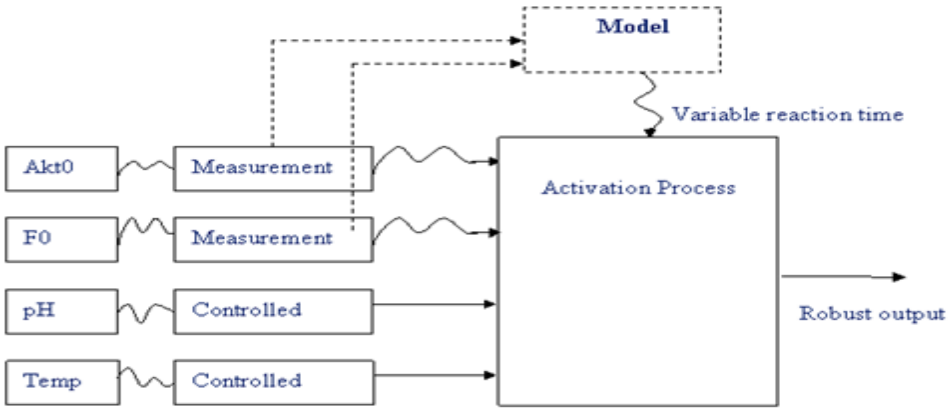
# Risk Evaluation




**„Heat Map“**

# The Activation Step

- Activation occurs by auto-proteolysis
- When activated the enzyme may auto-degrade
- The enzyme activity is strongly pH dependent
  - Essentially inactive below pH 5.8
- The input stream is the eluate from a chromatography step and varies inevitably in protein concentration and initial degree of activation
- The activation time depends on initial degree of activation, protein conc., pH and temperature and can be calculated by a mechanistic model
- 100% agreement between model and actual value is not required as long as all batches complies with the specification




akt 0 Initial degree of activation
F 0 Total amount of protein (activated and un-activated)

# Derivation of model

- The model for activation is based on general mechanistic models
  - pH dependency based on protonation/de-protonation of the active catalytic site
  - Concentration dependency of the autocatalytic reaction

$$FVII \xrightarrow{FVIIa} FVIIa$$

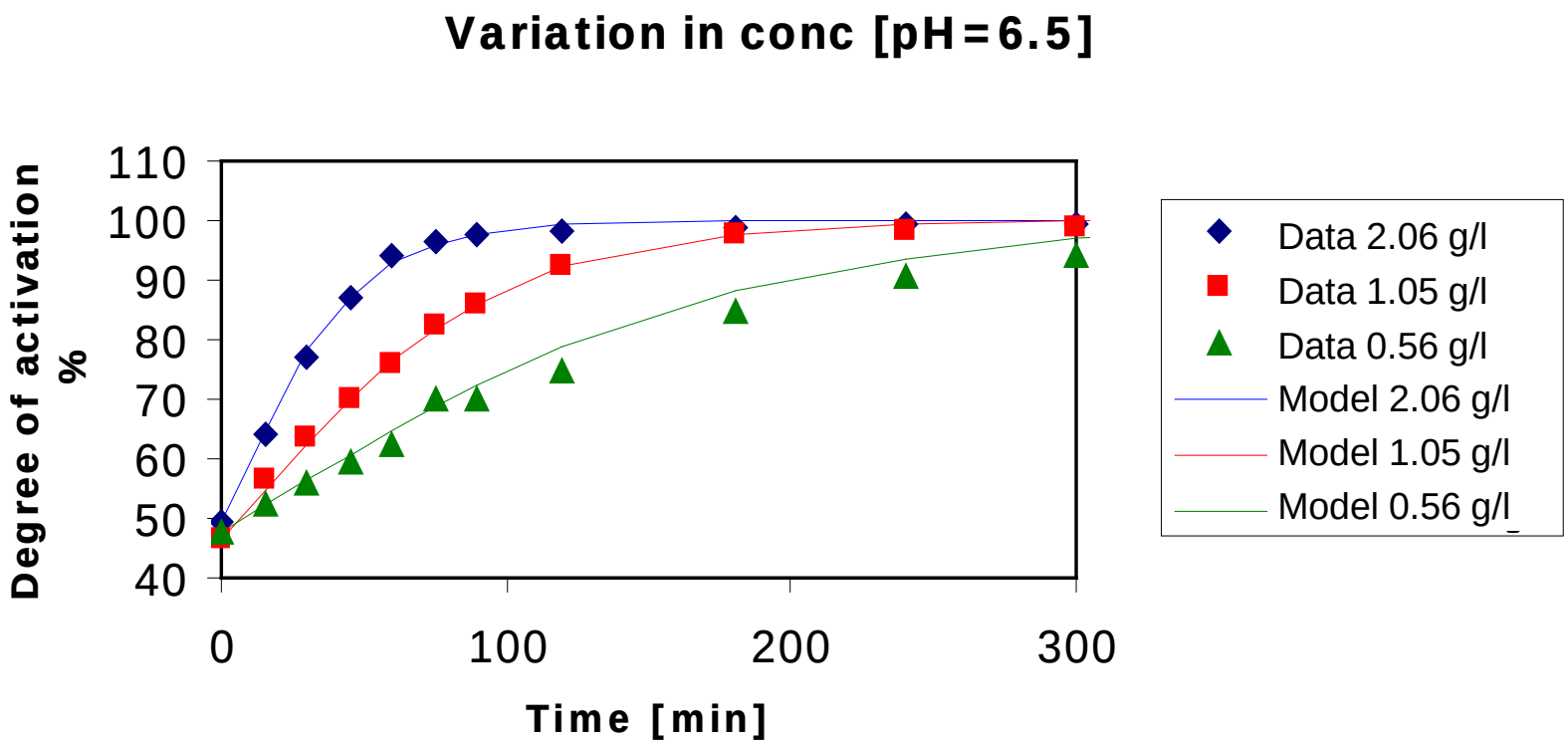
# The mechanistic model can be solved

$$akt = -\frac{akt0}{\exp(-t \cdot k \cdot xb \cdot F0) \cdot akt0 - \exp(-t \cdot k \cdot xb \cdot F0) - akt0}$$

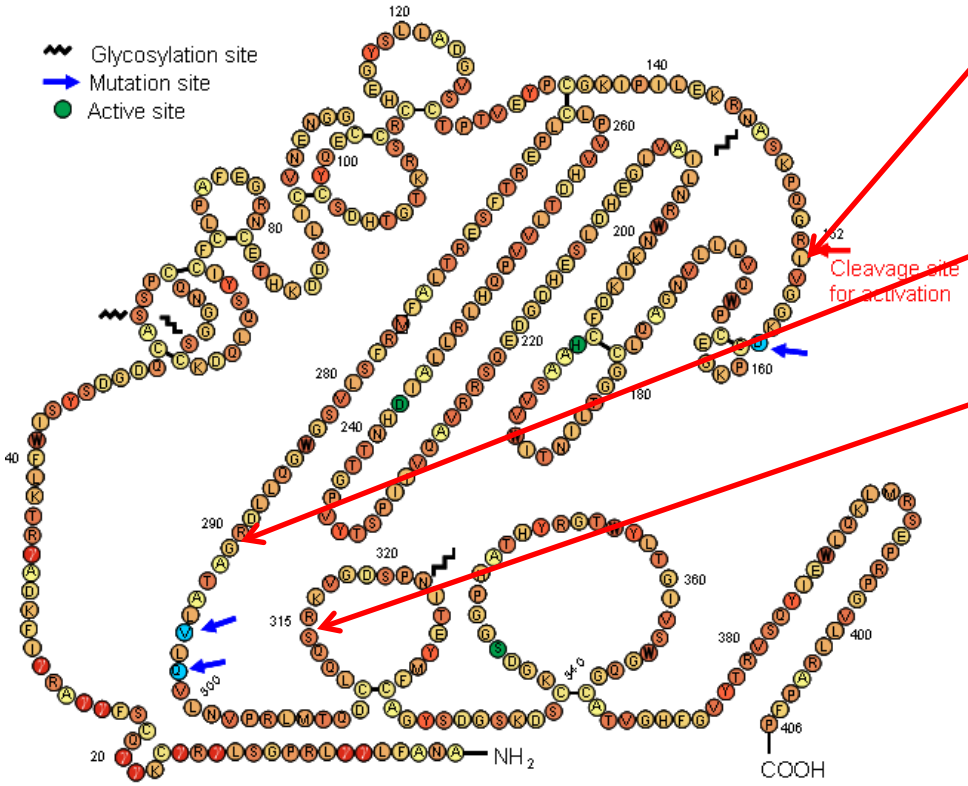
$$xb = \frac{10^{pH-7.61}}{1+10^{pH-7.61}}$$

| | |
|---|---|
| akt | Activation |
| akt 0 | Initial degree of activation |
| F 0 | Total amount of protein (activated and un-activated) |
| k | Concentration dependent rate constant – determined during calibration |
| 7.61 | pKa for dissociation of the histidine side chain – determined during calibration |
| *x*b | Molar fraction of histidines side chain, which is deprotonized – determine the pH dependency of the reaction |

# Laboratory data for calibration of model



# Clip forms of vatreptacog alfa

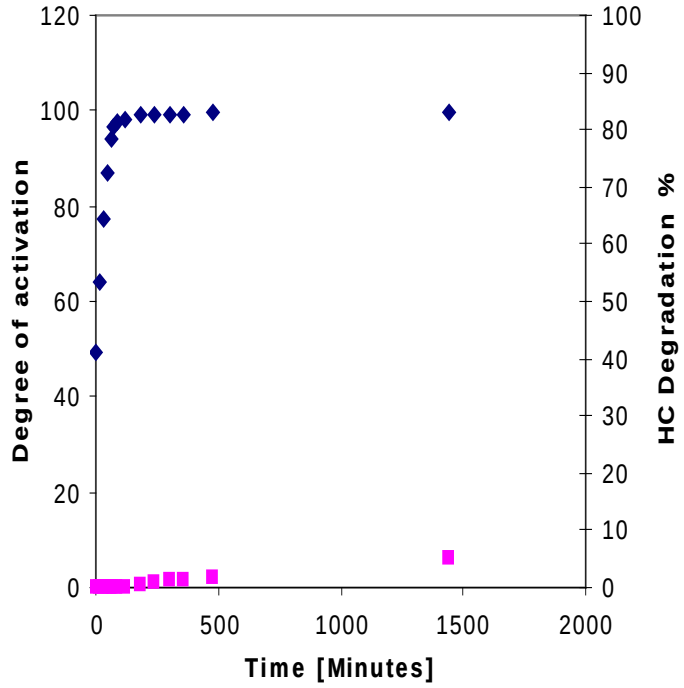


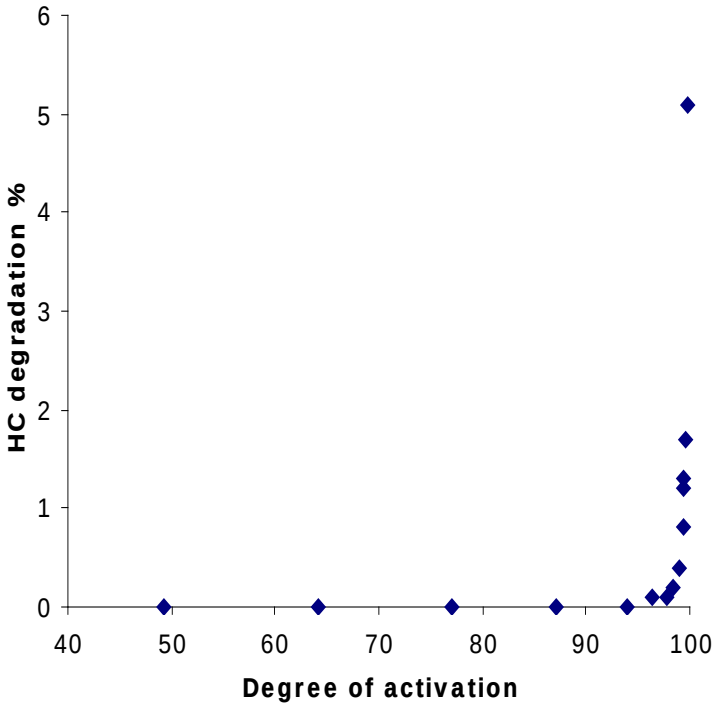

**Activation**:
Clip at AA 152 / 153
- Light chain: AA 1 – 152
- Heavy chain: AA 153 - 406

**Heavy chain degradation**:
Clip at AA 290 / 291
- Molecule disintegrates in AA 1 – 290 and AA 291 - 406

Clip at AA 315 / 316
- '3-chain' – molecule stays together held by disulphide bridges

# Prolonged activation leads to degradation



# Design Space for activation

– Any combination of parameters giving a final degree of activation of 90% - 99% given by

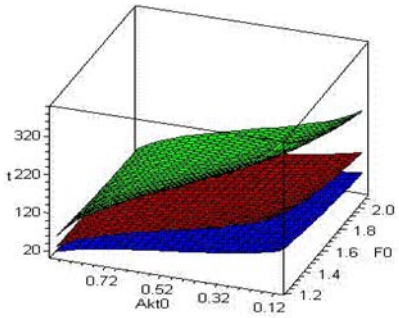
$$xb = \frac{10^{pH-7.61}}{1+10^{pH-7.61}}$$

$$t[\min] = \frac{-\ln\left(\frac{akt0\cdot(akt-1)}{akt\cdot(akt0-1)}\right)}{0.29\,\frac{L}{g\cdot\min}\cdot xb\cdot F0\,\frac{g}{L}}$$

Where “akt 0” is the initial degree of activation and,
“F 0” is the total amount of protein (activated and un-activated)

– Boundary conditions

| Parameter | Boundary conditions |
|---|---|
| Degree of activation at t=0 | 10 – 99 % |
| Concentration [g/l] | 1.4 – 2.1 g/l |
| pH | 6.2 – 6.8 |
| Reaction time | Calculated from the other values |
| Temperature | 20 - 24°C |

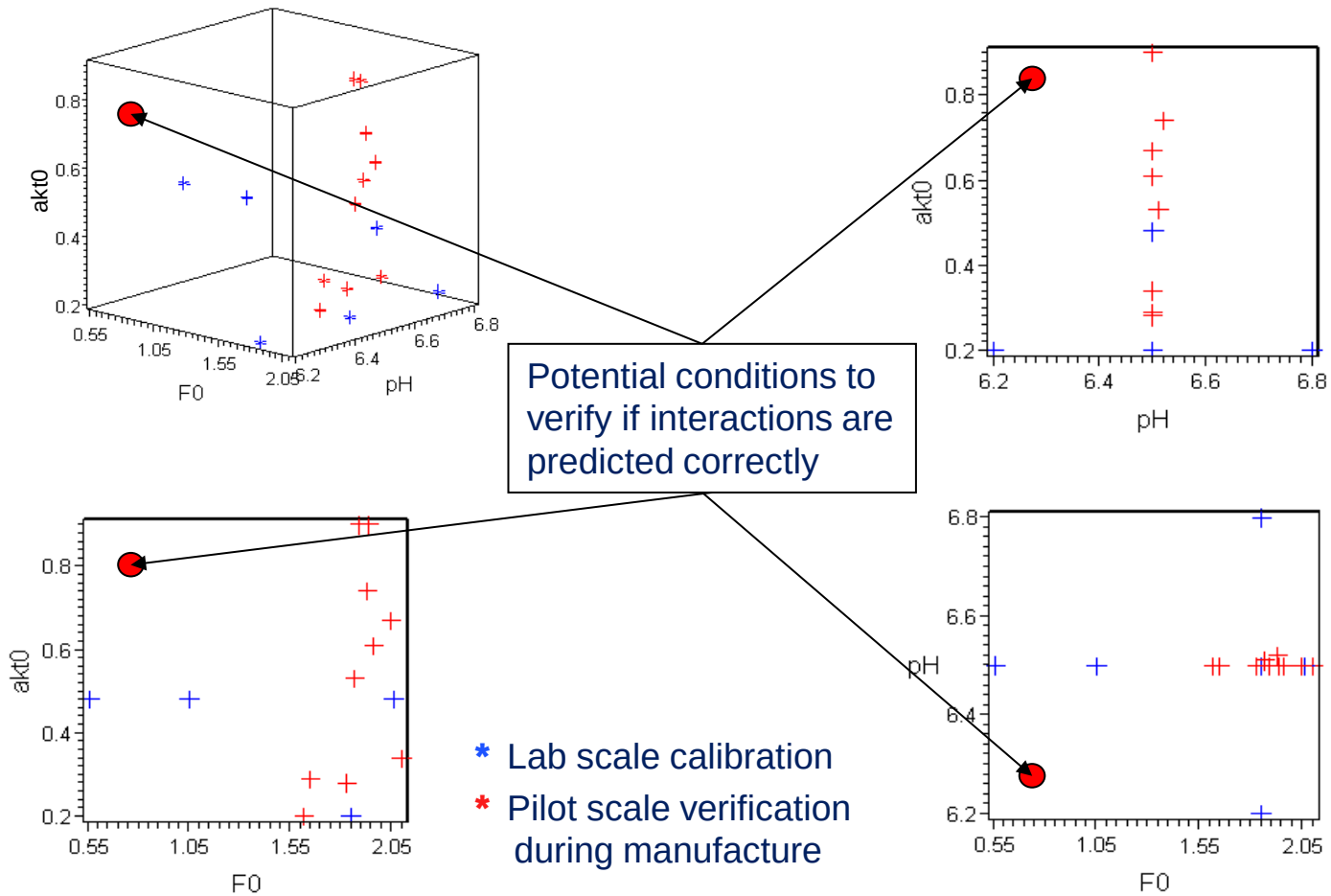



Green: pH = 6.2
Red: pH = 6.5
Blue: pH = 6.8

# Discussion Topic 1:
## Model verification in laboratory and commercial scale

- The number of verification studies required to confirm the design space
- To which extent can laboratory scale verification studies support the design space in commercial scale?

# Discussion Topic 1:
## Data for model calibration and verification

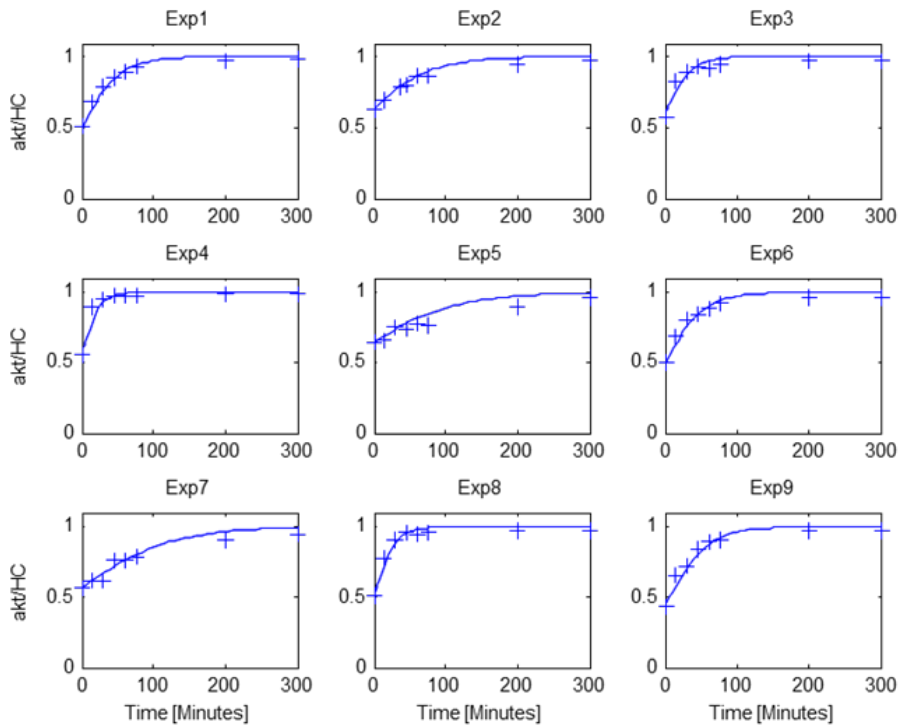


# Discussion Topic 1:
## Model verification based on authority feedback

| Experiment | pH | Conc | Temp | pH | Conc | Temp |
|---|---|---|---|---|---|---|
| | | | | Factor levels | | |
| 1 | 6.5 | 1.8 | 22 | 0 | 0 | 0 |
| 2 | 6.2 | 2.1 | 22 | -1 | 1 | 0 |
| 3 | 6.8 | 1.4 | 22 | 1 | -1 | 0 |
| 4 | 6.8 | 2.1 | 22 | 1 | 1 | 0 |
| 5 | 6.2 | 1.4 | 22 | -1 | -1 | 0 |
| 6 | 6.5 | 1.8 | 22 | 0 | 0 | 0 |
| 7 | 6.2 | 1.4 | 20 | -1 | -1 | -1 |
| 8 | 6.8 | 1.8 | 24 | 1 | 0 | 1 |
| 9 | 6.5 | 1.8 | 20 | 0 | 0 | -1 |
| 10 | 6.5 | 1.8 | 24 | 0 | 0 | 1 |
| 11 | 6.2 | 1.4 | 22 | -1 | -1 | 0 |
| 12 | 6.2 | 1.4 | 20 | -1 | -1 | -1 |
| 13 | 6.8 | 2.1 | 24 | 1 | 1 | 1 |
| 14 | 6.5 | 1.8 | 25 | 0 | 0 | 1.5 |
| 15 | 6.5 | 1.8 | 19 | 0 | 0 | -1.5 |
| 16 | 6.5 | 1.8 | 22 | 0 | 0 | 0 |

- Data from both laboratory and pilot (full) scale were used to verify model parameters
- Activation process is considered scalable as it takes place in a homogeneous solution
- Consequently, the model is primarily verified by experiments in laboratory scale
- Verification of the model at borders of the design space was done by a full factorial design for concentration and pH supplemented by worst case conditions for temperature

# Discussion Topic 1:
## Data from verification of model

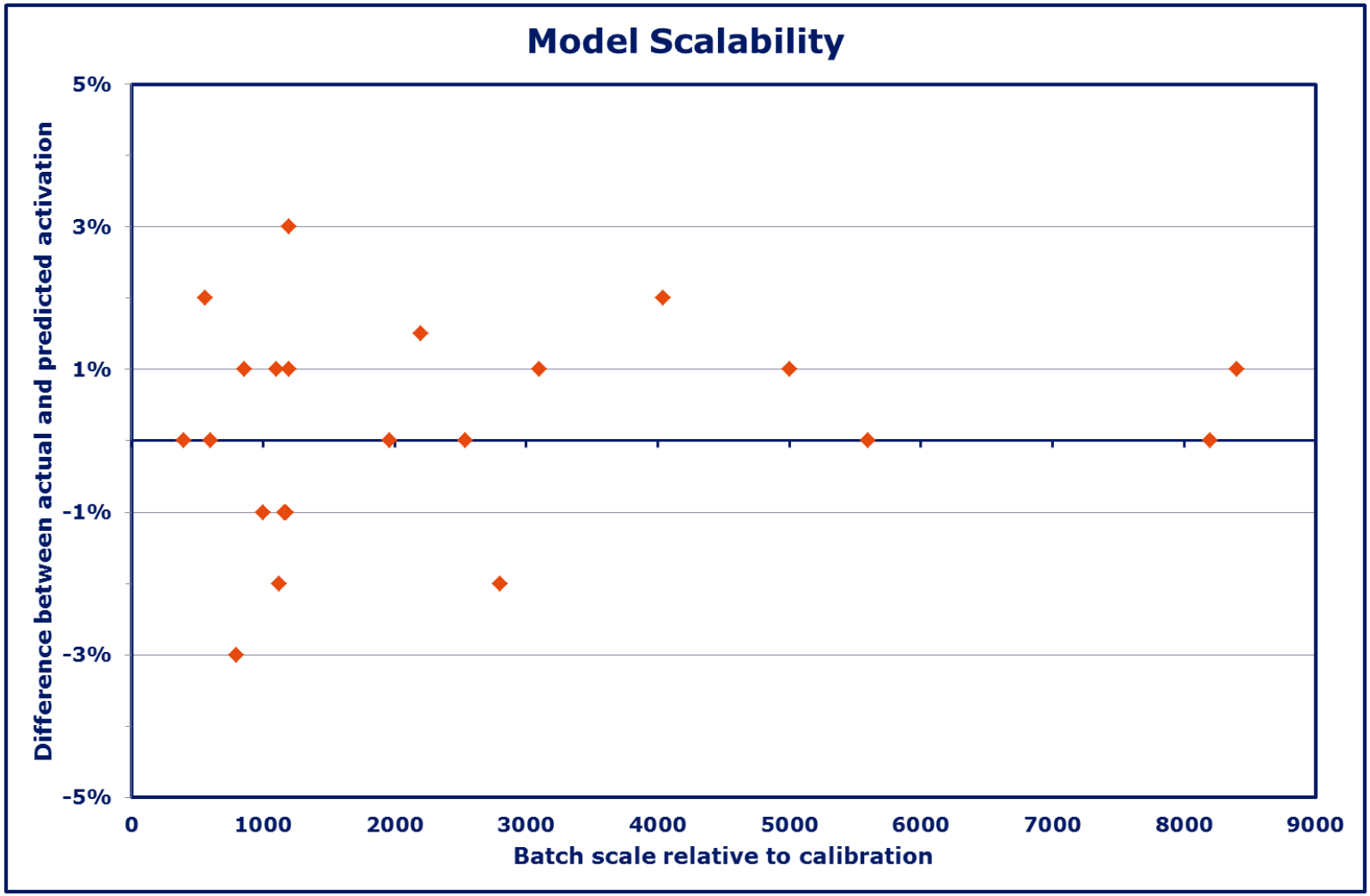



- Samples were taken at time intervals for determination of activation and heavy chain degradation
- Activation versus Time (minutes)
  - Lines are model prediction
  - Marks are measured value

# Discussion Topic 1:
## Scalability

- The activation process is evaluated to be scalable Only potential non scalable parameter is time for pH adjustment before and after activation – pH adjustment is done within a time period negligible compared to the activation time
- In commercial scale the model will consequently only be verified at normal operation set points (i.e. during manufacture of clinical batches and PPQ)

# Predictability in large scale confirms scalability of model



# DoE and Small scale studies/linkage studies
**(regulators position)**

- Knowledge of process performance when operated under worst-case conditions for each CQA.
  - Small scale studies are considered essential in order to address multivariate parameters
  - Provide scientific rationale for worst case
  - All DoEs to be provided?
  - Moving outside of worst-case conditions
- The Design Space is limited by the multivariate ranges for all critical process parameters (CPPs).

| Experiment | pH | Conc | Temp | pH | Conc | Temp |
|---|---|---|---|---|---|---|
| | | | | Factor levels | | |
| 1 | 6.5 | 1.8 | 22 | 0 | 0 | 0 |
| 2 | 6.2 | 2.1 | 22 | -1 | 1 | 0 |
| 3 | 6.8 | 1.4 | 22 | 1 | -1 | 0 |
| 4 | 6.8 | 2.1 | 22 | 1 | 1 | 0 |
| 5 | 6.2 | 1.4 | 22 | -1 | -1 | 0 |
| 6 | 6.5 | 1.8 | 22 | 0 | 0 | 0 |
| 7 | 6.2 | 1.4 | 20 | -1 | -1 | -1 |
| 8 | 6.8 | 1.8 | 24 | 1 | 0 | 1 |
| 9 | 6.5 | 1.8 | 20 | 0 | 0 | -1 |
| 10 | 6.5 | 1.8 | 24 | 0 | 0 | 1 |
| 11 | 6.2 | 1.4 | 22 | -1 | -1 | 0 |
| 12 | 6.2 | 1.4 | 20 | -1 | -1 | -1 |
| 13 | 6.8 | 2.1 | 24 | 1 | 1 | 1 |
| 14 | 6.5 | 1.8 | 25 | 0 | 0 | 1.5 |
| 15 | 6.5 | 1.8 | 19 | 0 | 0 | -1.5 |
| 16 | 6.5 | 1.8 | 22 | 0 | 0 | 0 |

# Model verification
**(regulators position)**

- In commercial scale the model will usually only be verified at normal operation set points

- Scalability of the model
  - Model verification at commercial scale under normal operating ranges vs. under worst case conditions?

# Discussion Topic 2:
## Movement within the design space

Can the following options be considered as part of the design space?

- Change of set point for pH within the boundary conditions
- Rearrangement of model to obtain constant process time – adjustable pH

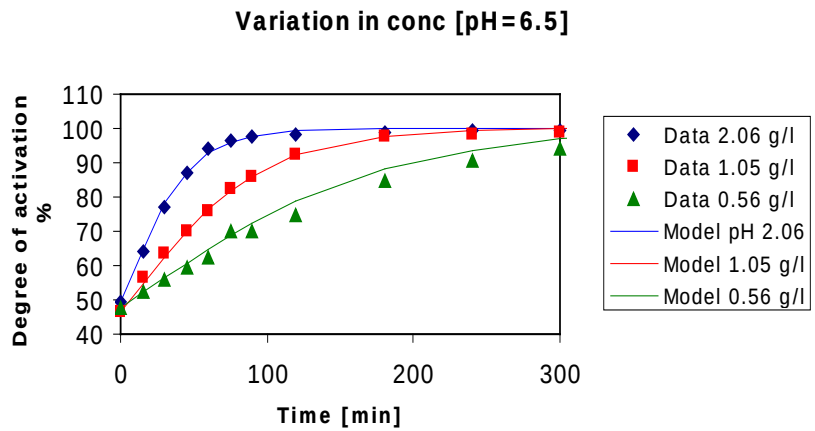
# Discussion Topic 2:
## Further operational freedom

The mechanistic model may be re-arranged in order to obtain constant process time by calculation of process pH for each batch

| **Model, solved for time** | **Model, solved for pH** |
|---|---|
| $xb = \frac{10^{pH-7.61}}{1+10^{pH-7.61}}$ <br> $t[\min] = \frac{-\ln\left(\frac{akt0\cdot(akt-1)}{akt\cdot(akt0-1)}\right)}{0.29\,\frac{L}{g\cdot\min}\cdot xb\cdot F0\,\frac{g}{L}}$ | $xb = \frac{-\ln\left(\frac{akt0\cdot(akt-1)}{akt\cdot(akt0-1)}\right)}{0.29\,\frac{L}{g\cdot\min}\cdot t\min\cdot F0\,\frac{g}{L}}$ <br> $pH = pKa + \log\frac{xb}{1-xb}$ |

# Regulator´s Opinion on rearrangement of modelling

Modification of the control of the activation step from fixed pH and variable reaction time to fixed reaction time and variable pH within the design space




| Original model | Re-organized model |
|---|---|
| $xb = \frac{10^{pH-7.61}}{1+10^{pH-7.61}}$ <br> $t[\min] = \frac{-\ln\left(\frac{akt0\cdot(akt-1)}{akt\cdot(akt0-1)}\right)}{0.29\,\frac{L}{g\cdot\min}\cdot xb\cdot F0\,\frac{g}{L}}$ | $xb = \frac{-\ln\left(\frac{akt0\cdot(akt-1)}{akt\cdot(akt0-1)}\right)}{0.29\,\frac{L}{g\cdot\min}\cdot t\min\cdot F0\,\frac{g}{L}}$ <br> $pH = pKa + \log\frac{xb}{1-xb}$ |

# Regulator´s Opinion on rearrangement of modelling

- Acceptable approach for <u>that</u> case
  - Correlation between pH and reaction time
  - Valid model (verified)
  - Seems to be a mathematic calculation

  - ? Notification of regulatory agency
  - ? Verification of rearranged model
    - At small scale/commercial scale
    - Continued verification

# Discussion Topic 3:
## Recalibration / adjustment of model constants

Can an optimisation of the model to obtain better agreement between predicted and actual activation be considered as a GMP related life cycle management activity not requiring regulatory actions?

# Discussion Topic 3:
## Refinement of Model

$$t = \frac{-\ln\left(\frac{akt0\cdot(akt-1)}{akt\cdot(akt0-1)}\right)}{k\cdot xb\cdot F0}$$

Recalibration of the constant *k* ?

$$xb = \frac{10^{pH-pKa}}{1+10^{pH-pKa}}$$

Recalibration of *pKa* ?

# Discussion Topic 3:
## Continuous optimisation of model

- Model performance is monitored by comparison of predicted activation with actual activation
  If a systematic deviation is observed several actions may be considered:
  - Adjustment of target activation in the mechanistic model while maintaining approved drug substance specifications
  - Recalibration of model constants
- These adjustments are considered to be within the scope of continuous verification and should be considered GMP

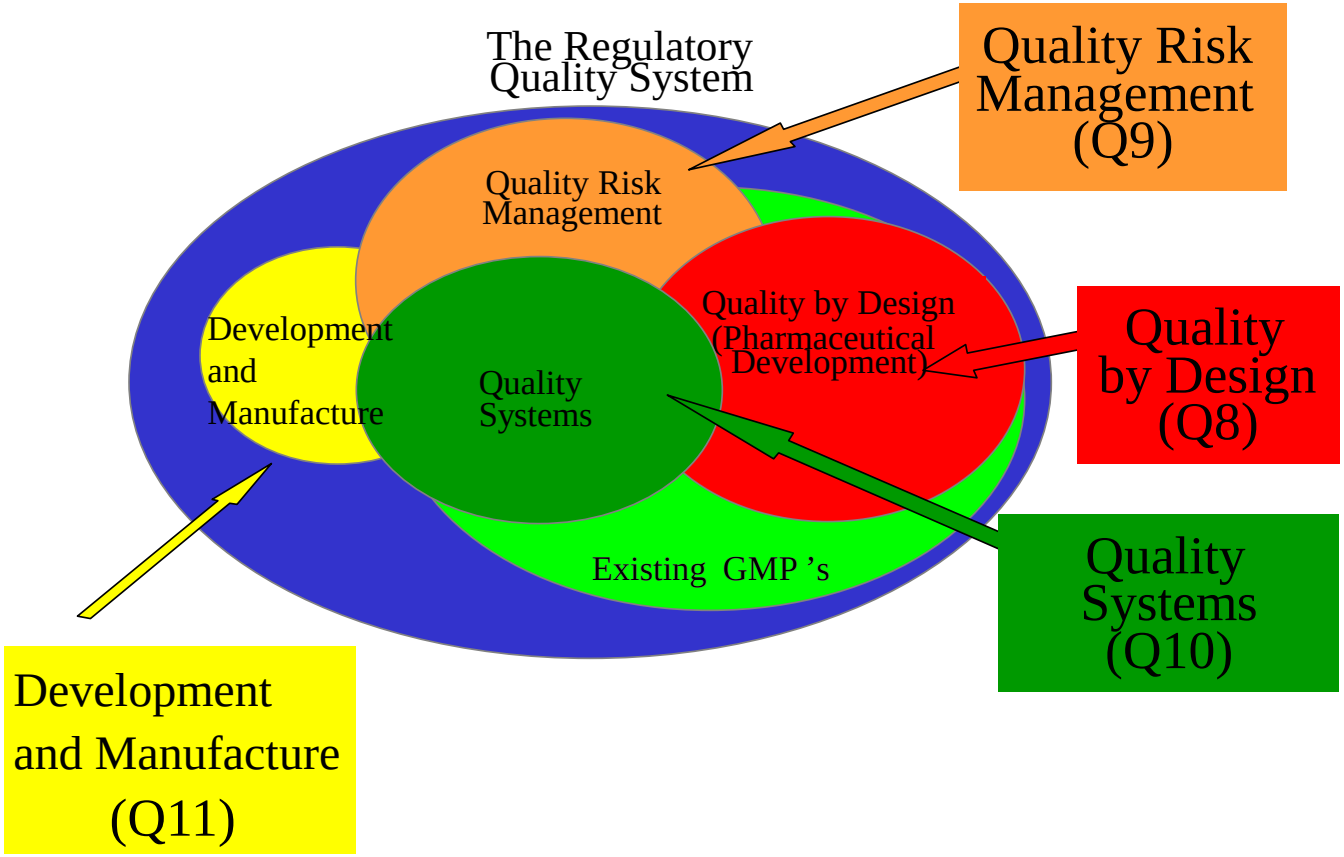
# Requirements for Notification of regulatory body

*Movement within design space*:
A movement within the verified design space does not require regulatory submission.

*Changed model*:
when the recalculated predicted values for the degree of activation for all previous data results in a better or unchanged fit with the actually achieved data, an improvement of the model for the design space is not considered a change requiring a regulatory submission.

- The model validity, criticality of quality attributes and process parameters, the Design Space, and the approach to attribute testing should be revised at certain time points (review period).

# GMP Inspections



# Refinement of models/Process PQR and APR?

Product Quality Review

- 1.10 Regular periodic or rolling quality reviews of all authorised medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
**Pharmaceuticals**

Brussels, 03 February 2010
ENTR/F/2/AM/an D(2010) 3374

# PALM Plan.

- Testing requirements for target and target range changes to **non-CPPs:**
- Changes to the acceptable range for non-CPPs for these steps require further justification. The possible outcomes of the assessment and studies are:
- a) If the outcome is acceptable then the acceptable range is extended and the Heath Authority is **notified**.
- b) If the product quality results are not acceptable, additional studies will establish a new acceptable range, or the acceptable range is not extended. If the acceptable range is extended, the Heath Authority will be **notified**.
- If the criticality of the non-CPP changes to a CPP, that information and the updated Design Space are also reported and require Health Authority prior approval.

# “Operational parameter” Design Space

**B.I.e) Design Space and post-approval change management protocols**

| **B.I.e.1 Introduction of a new design space or extension of an approved design space for the active substance, concerning:** | **Conditions to be fulfilled** | **Documentation to be supplied** | **Procedure type** |
|---|---|---|---|
| a) One unit operation in the manufacturing process of the active substance including the resulting in-process controls and/or test procedures | | **1, 2, 3** | **II** |
| b) Test procedures for starting materials/reagents/ intermediates and/or the active substance | | **1, 2, 3** | **II** |
| Documentation | | | |
| 1. The design space has been developed in accordance with the relevant European and international scientific guidelines. Results from product, process and analytical development studies (e.g. interaction of the different parameters forming the design space have to be studied, including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the active substance has been achieved. | | | |
| 2. Description of the Design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges. | | | |
| 3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate). | | | |

# “Operational parameter” Design Space

| B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance | Conditions to be fulfilled | Documentation to be supplied | Procedure type |
|---|---|---|---|
| a) Tightening of in-process limits | 1, 2, 3, 4 | 1, 2 | IA |
| b) Addition of a new in-process test and limits | 1, 2, 5, 6 | 1, 2, 3, 4, 6 | IA |
| c) Deletion of a non-significant in-process test | 1, 2, 7 | 1, 2, 5 | IA |
| d) Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the active substance | | | II |
| e) Deletion of an in-process test which may have a significant effect on the overall quality of the active substance | | | II |
| f) Addition or replacement of an in-process test as a result of a safety or quality issue | | 1, 2, 3, 4, 6 | IB |
| g) Change to the limits of non critical proce[illegible] parameters, where the process has been developed and optimised using an enhanced development approach for the particu[illegible] manufacturing step(s). | [illegible] 7, 8, 9 | 1, [illegible] | IA |

interaction of the different parameters forming the design space have to be studied, including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic mechanistic understanding of material attributes and process parameters to the

# Regulators viewpoint on additional discussion points

Model verification in laboratory and commercial scale

Movement within the design space
Recalibration / adjustment of model constants
Presentation of Quality Risk Assessments in regulatory file
Control Strategy

# Discussion Topic 5:

## Criticality of QA and process parameters from regulators viewpoint

- Quality attribute criticality
- approval of Critical Quality Attribute (CQA) is assured through formalised procedures, training, subject matter expert (SME), team review and management
- Impact Scale is developed for designation of CQAs (low (?)- Very high (?).
- CQA Risk Ranking and Filtering (RRF) assessment needs to be reviewed and endorsed by a cross functional committee.
  - Uncertainty scale;
  - Impact scale (activity, PK, Immunogenicity, safety)
  - Risk score (U (1-?) x I(1-?), can it be zero?

# Identification of CPPs

- Considers knowledge gained from multivariate studies
- Statistically designed studies conducted on individual unit operations
- Overall process worst-case linkage studies
- Acceptable values for CQAs

# Parameter Definition

- Critical:

An adjustable parameter (e.g. pH) of the process that should be maintained within a narrow range so as not to affect critical product quality attributes

**CPP = Parameter which variation has a practically significant impact on a CQA**

# Discussion Topic 6: Control strategy

- A “minimum” control system for a QbD product is employed because in some instances, the lack of high criticality quality attributes or overall high process capability may result in the recommendation that control system testing for a product would not include any tests which are useful in **monitoring product consistency and for further mitigation risk to patients due to unanticipated source of variation.**

# Control strategy

- The Control Strategy comprises several elements including:
  - Raw material control
  - Process control via procedural and process parameter control
  - In-process, lot release, and stability testing
  - Testing done as part of process monitoring
  - Testing to demonstrate comparability

# RTRT as part of a Control Strategy?

- system of release that gives assurance that the product is of intended quality, based on the information collected during the manufacturing process, through product knowledge and on process understanding and control
- product knowledge and process understanding, the use of quality risk management principles and the application of an appropriate pharmaceutical quality system, as defined within ICH Q8,Q9 and Q10 provide the platform for establishing RTRT mechanisms
- combination of a RTR approach for certain critical quality attributes (CQAs) and a more conventional evaluation for other CQAs (partial RTR).
  - already authorised for use as an optional alternative to routine sterility testing of products terminally sterilised in their final container
  - residual host cell DNA or host cell proteins (HCP), which are typically tested on a routine basis on the active substance, may be evaluated using a routine testing approach and/or a validation approach.

# Summary Discussion points

1. Model verification in laboratory and commercial scale
2. Notification of regulatory bodies
   1. Movement within the design space
   2. Recalibration / adjustment of model constants
   3. Changes to non-CPP…
3. Presentation of Quality Risk Assessments in regulatory file
4. Criticality of process parameters from regulators viewpoint
5. Control strategy/Review period
6. Glossary/Terminology
7. Others……..