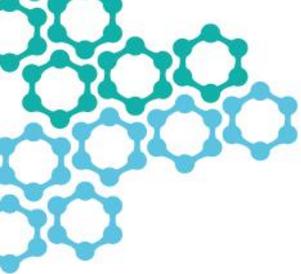


# A personal perspective on the use of models in Module 3

Dr Nick Lee  
HPRA, Ireland

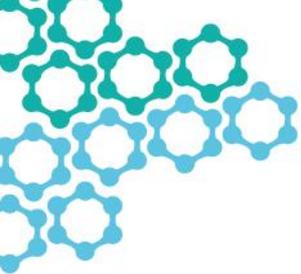
---

***The contents of this presentation are  
personal observations and are not  
necessarily representative of the HPRA or  
any other agency***



# Overview

- I. Basic considerations
- II. Models
  - Type
  - Current and future states
- III. Models in regulatory submissions
  - Models: product/process design
  - Models: analytical procedures
  - Models: process monitoring and control
  - Models: life-cycle
  - Models: other considerations
- IV. Other considerations
  - Relative importance
  - "Passive" vs. "Active"
- V. Conclusions



## I. Basic considerations

It is important to classify a model as either...

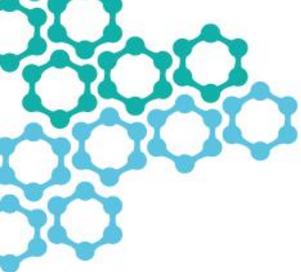
- Supportive (e.g., used during process development), or
- Not supportive (e.g., used during routine manufacture)

Assessors use a risk based approach for classification (ICH Q8-Q10 Points to Consider (PtC)), i.e. **low, medium or high** impact.

This risk-based approach may include consideration of information in the dossier and GMP.

Arguably, there is no definite or ultimately correct solution to the problem to which the model is applied, and so a scientifically sound justification for the approach taken by the applicant should be provided.

Explain fully!

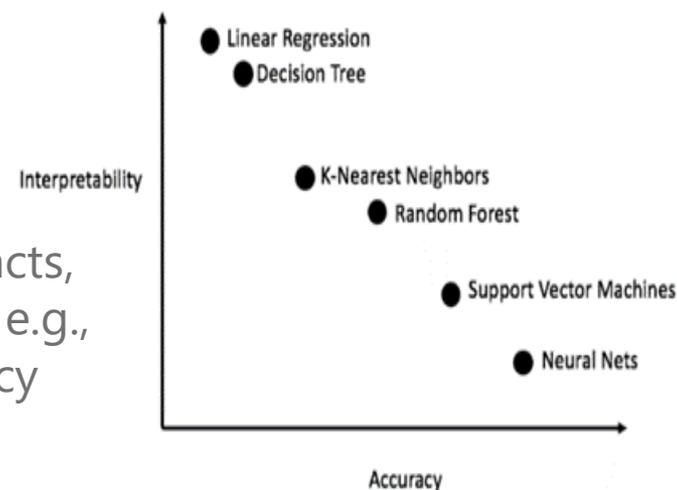


# I. Basic considerations

The most appropriate model is that which best predicts the desired parameter (e.g. control, measure, etc.) with the required degree of predictability/accuracy.

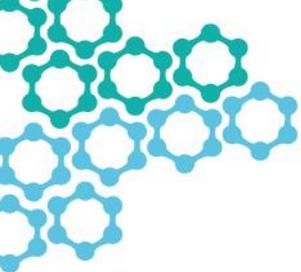
For a model, the risk (impact) to material quality depends on...

1. The intention of the model
2. Its relevance for routine production during commercial marketing, and
3. How the model is integrated into, and impacts, the overall control strategy for the material e.g., its interpretability and predictability/accuracy



Models can deliver explicit or implicit outputs.

This informs the scope of the assessment by the assessor.

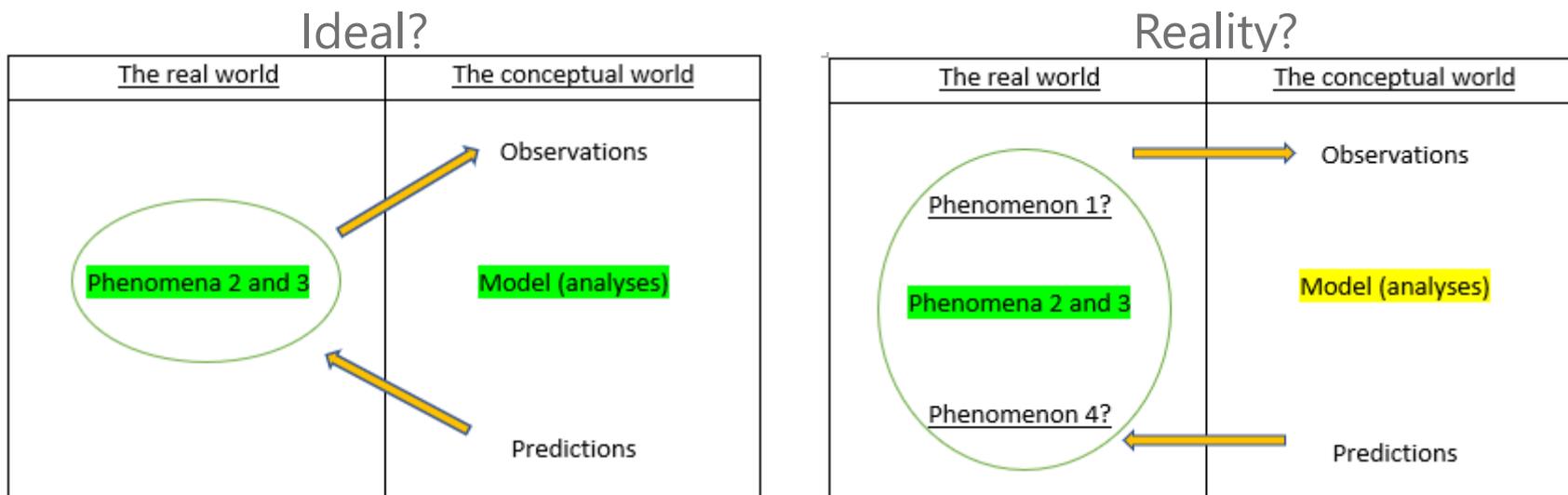


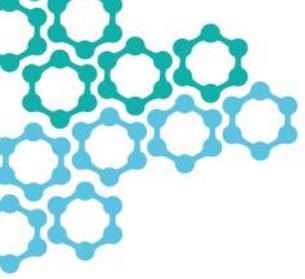
## II. Models: types

Models may be empirical, mechanistic, or hybrid, and may utilise small or large data sets to predict outcomes.

Their use should be justified.

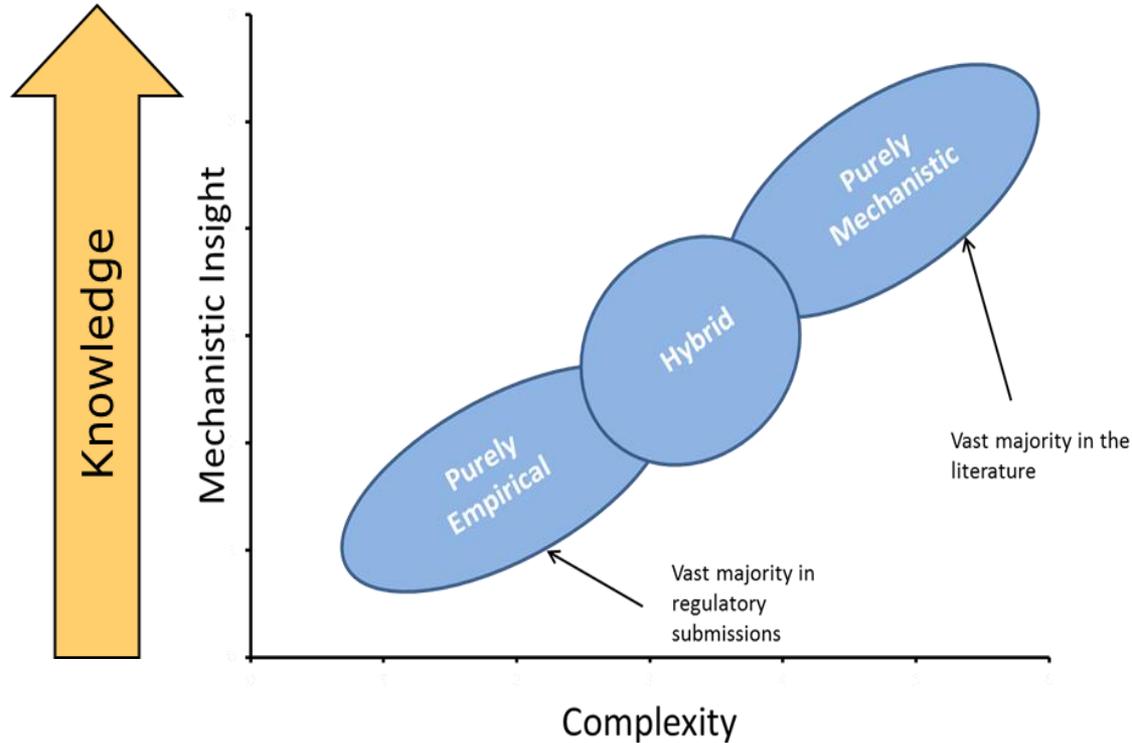
But *caveat emptor*...

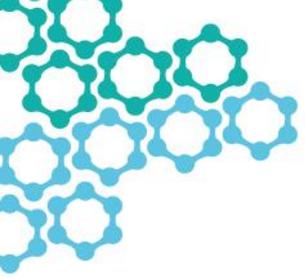




## II. Models: current state

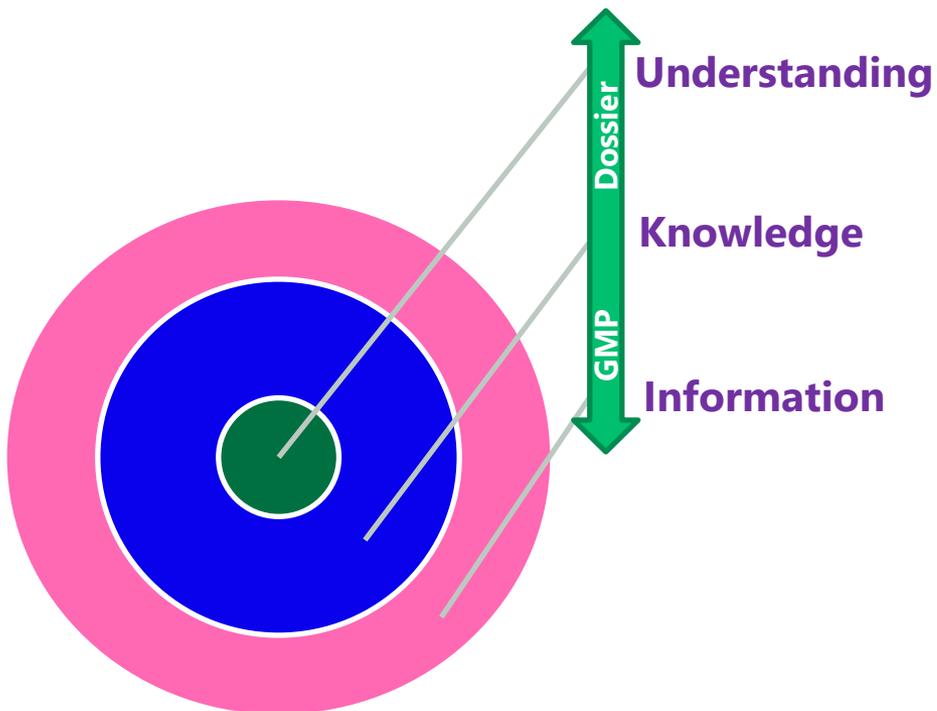
Model type depends on application, i.e. case specific

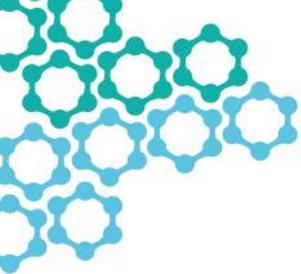




## II. Models: future state

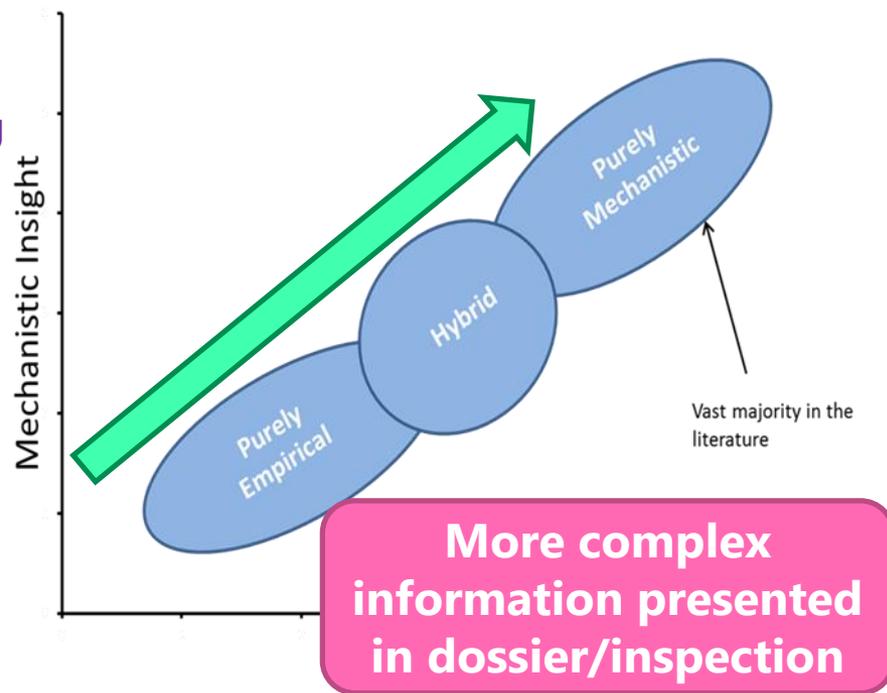
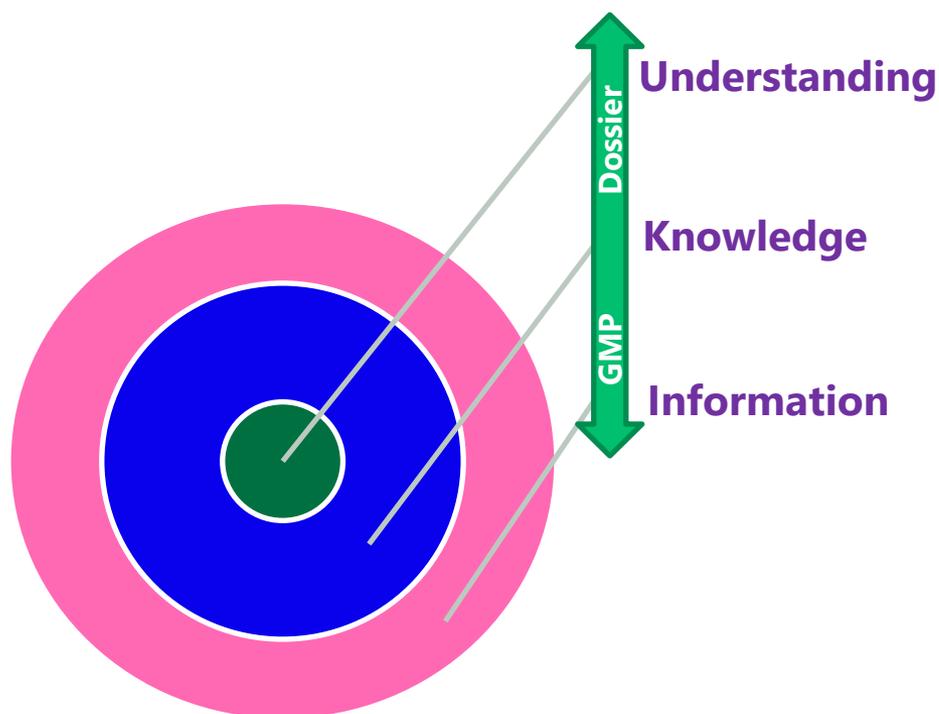
— Impact of Pharma 4.0 and Innovative Manufacturing? Impact of ICH Q12? Changes in Assessment – Inspection practices?





## II. Models: future state

- Impact of Pharma 4.0 and Innovative Manufacturing? Impact of ICH Q12? Changes in Assessment – Inspection practices?

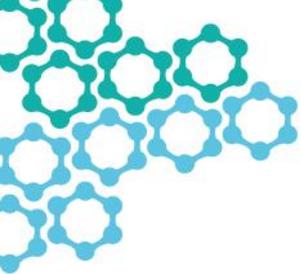




## II. Models: future state

As Pharma 4.0 accelerates, data lakes are created, containing information on materials, process parameters, equipment performance, etc.. ➔ multivariate data

- Real-time predictive modelling... e.g., equipment maintenance, process control/adjustments, process capability and process 'health'
  - ❖ Prediction underpins making decisions around uncertainty and hence product quality determination ➔ regulatory impact?
- Increased use of 'AI' (e.g. Machine Learning)
- Increased use of models under GMP and thus in MAs (e.g. enhancing a product's overall control strategy over its lifecycle)
- Increasing complexity - do we (NCAs) have the right experts / tools?



## II. Models: future state

### Knowledge

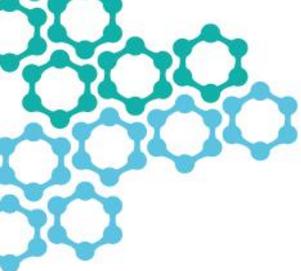
- Use of data analytics to create models
- Data management in accordance with GMP
- Supports GMP decisions (deviations etc.)

### Understanding

- Ability to apply knowledge in a specific manner
- Comprehension of the underlying principles behind data / models
- Supports future changes (e.g., control strategy)

### Control

- Application of knowledge and understanding
- Real-time process control
- Use of data analytics/models in MAA and LCM (e.g., defined control strategy elements)



### III. Models: product/process design

**Typical application:** formulation / process optimisation, process capability, design space determination and scale-up.

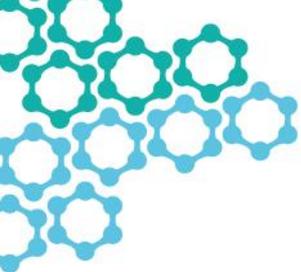
**Impact:** varies, e.g. design space determination typically medium-impact; formulation optimisation during development typically low-impact.

**Dossier (not exhaustive):**

$$F_i(x) - F_i(x + dx) + A_t dx \nu_i r = 0$$

Case and impact dependant; model description including rationale (e.g. literature references, quality of underlying data and applied statistical methods in case of an empirical model), use of models specific to equipment/system design/configuration.

Clear statement how the model was developed and validated, and how it was used to support product development. Any iterations?



### III. Models: analytical procedures

**Typical application:** empirical (i.e., chemometric), e.g. NIR calibration.

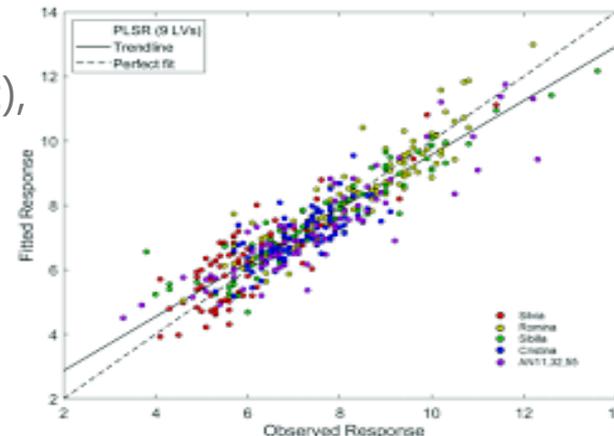
**Impact:** varies, typically high-impact.

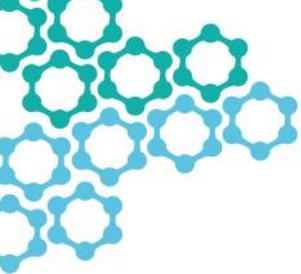
**Dossier (not exhaustive):**

Case and impact dependant; purpose of model clearly stated, e.g. used for process control only, part of the control strategy, etc.?

For medium/high impact models, the external analytical validation is a key element, where validation parameters should be similar to the reference test procedure (e.g. conventional HPLC)

Discussion regarding life cycle management of model validity.



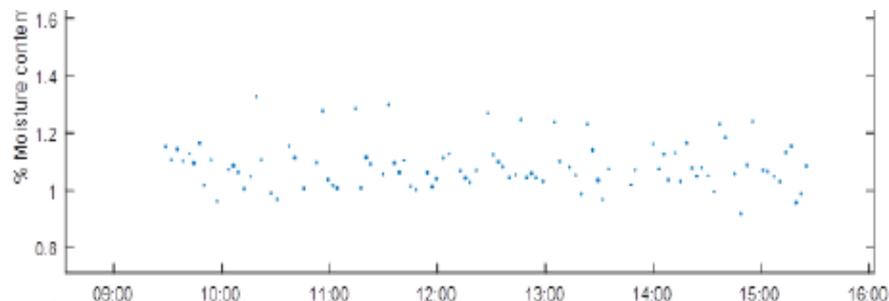


## III. Models: process monitoring/control

**Typical application:** univariate or multivariate process control to detect special cause variability, feedback/feedforward process control.

**Impact:** varies, e.g., if RTRT approach, then typically high-impact.

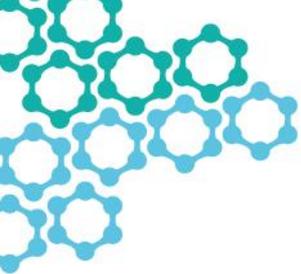
**Dossier (not exhaustive):**



Case and impact dependant; purpose of the model should be clearly stated, e.g. single decision point for product quality, part of a series of controls assuring product quality?

Data-driven models should be developed through appropriately designed experiments (e.g. DoEs), and should be validated.

Discussion regarding life cycle management of model validity.



## IV. Models: others (e.g. specifications)

**Typical application:** support shelf-life proposal

**Impact:** varies.

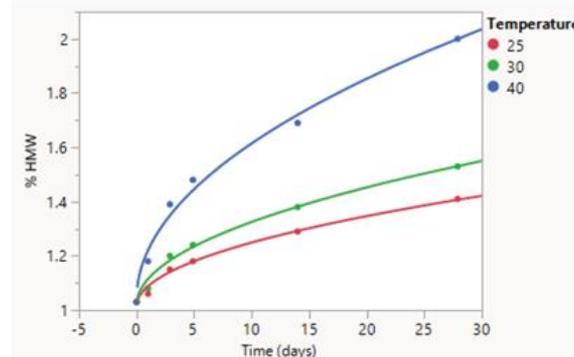
**Dossier (not exhaustive):**

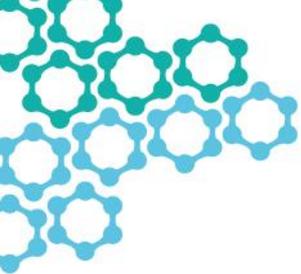
Case/impact dependant; model purpose should be clearly stated, e.g. single decision point, part of a series assuring product quality?

Different models can be used for different attributes. Assumptions made, equations should be defined.

Appropriately develop (e.g. DoEs) and validate data-driven models.

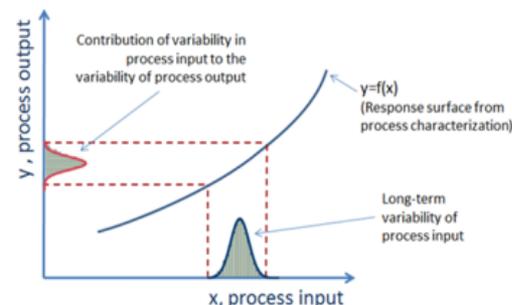
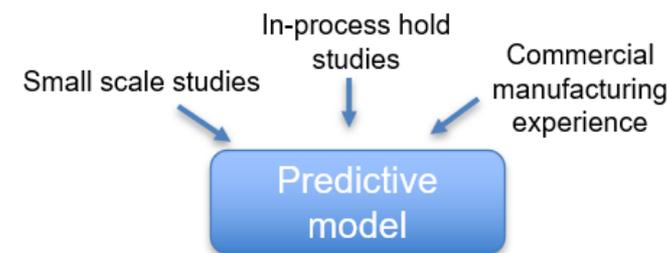
Discussion regarding life cycle management of model validity.





# III. Models: others (e.g. specifications)

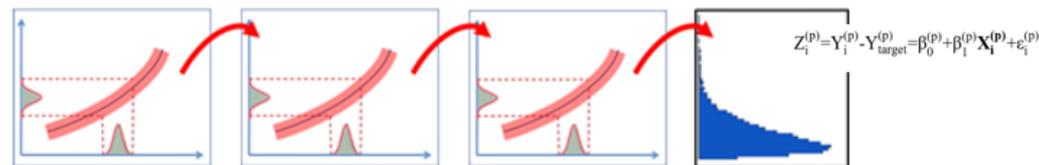
## Case study: using manufacturing data to build a predictive process model

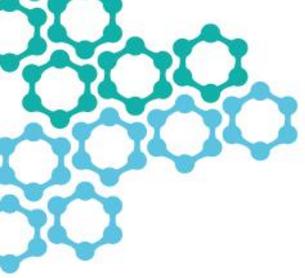


Response surface predicts the variability in process outputs (CQAs) from the variability in process inputs (process parameters)

Overall process variability estimated from combining individual steps using Monte Carlo simulations with a Bayesian model to generate a posterior predictive distribution

Model used to justify the specification limits





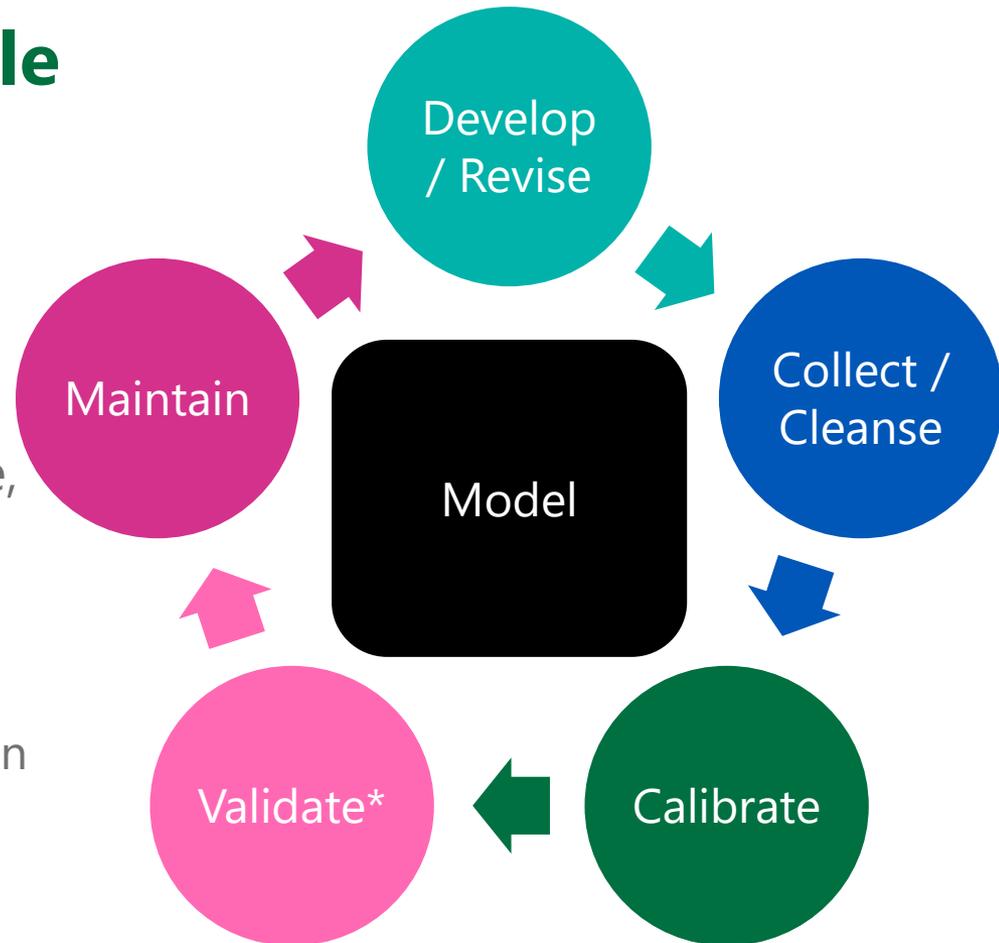
### III. Models: life-cycle

#### Dossier (not exhaustive):

Pre-defined scope and acceptance criteria

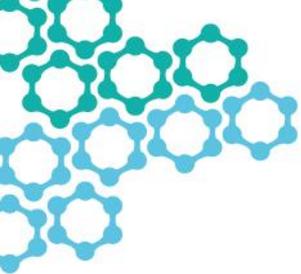
Depending on function / use, either...

- action under PQS alone, **or**
- notification to NCA and action under PQS



\* Depends on use

ICH Q14 proposes a life-cycle too...

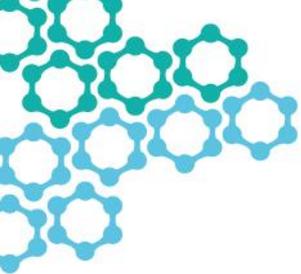


### **III. Models: other considerations (not exhaustive)**

Applicants have their preferred approaches, typically using a similar (or same) approach for different products.

Clarity is appreciated, e.g., Cpy X specifically defines their approach to QbD, models and derivation of CS in a separate section of P.2,

- Identifying relationships to define discrete elements
- Discussing behaviour of the defined, discrete elements
- Prediction of physicochemical properties
- Modelling systems / system dynamics
- Process control / defining control limits
- Chemometrics and statistics



### **III. Models: other considerations (not exhaustive)**

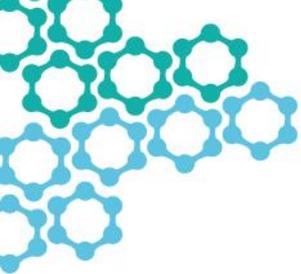
Degree of information in S.2.6/P.2.3 varies e.g., from simple statements to derived equations to comprehensive justifications.

- Consider the complexity, impact and reader... explain and justify clearly
- Use of diagrams, figures and examples helps comprehension
- Don't forget references used to support approach!

How does this translate into content of S.2.2/S.2.4 and P.3.3/P.3.4?

- Lack of (contextual) information, inadequate scope of model development, deficient justifications, lack of validation, non-compliance with EU guidelines, etc.

Applicability of current guidance to future modes of model use?



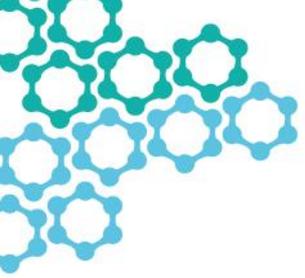
## IV. Relative importance (of models)

ICH PtC ranks models as either low, medium and high impact.

How can we understand the relative importance of models within these three categories important in the context of assessment?

1. Identify model use (e.g. IPC, end of process)
2. Consider model characteristics (e.g. type of algorithm, model and prediction, impact)
3. Consider risk criterion for each characteristic
4. Consider weighting for each risk criterion
5. Combine to yield a score

Can deliver clarity over relative ranking (importance) of models.



## IV. And finally...

Consider how to discriminate between models

### 'Passive' models

No active control (e.g. set-points within a DSp).

Data limited?

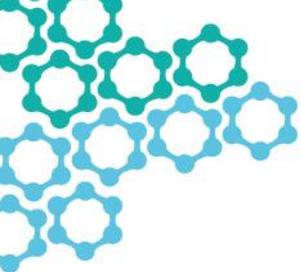
No potential to react to stimulus

### 'Active' models

Active control (e.g. feed-back to LIWF).

Data rich?

Potential to react to stimulus



## IV. And finally...

### 'Passive' models

No active control (e.g. set-points within a DSp).

Data limited?

No potential to react to stimulus

### 'Active' models

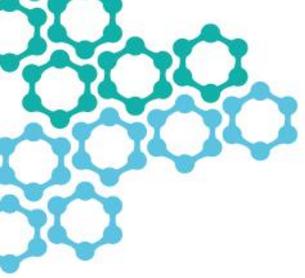
Active control (e.g. feed-back to LIWF in CM).

Data rich?

Potential to react to stimulus

### Risk to material quality

	High	Medium	Low
Passive	↻	Fixed risk	↻
Active	Potential to transform risk		↻ ↻



## V. Conclusions

Risk-based approach, scientific justification essential

Clear communication around assumptions, theory and rationale

More complex, hybrid models, facilitated by data analytics

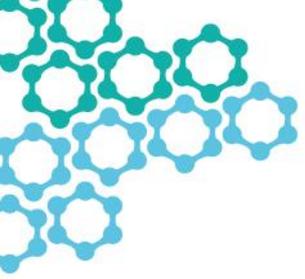
More models as an integral part of Module 3

Drive reduction in, and mitigation of, risks to quality

Platform processes = 'platform models'?

Regulators tools?

Guidance? Scope of Guidance?

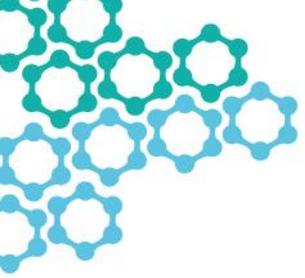


## Acknowledgements

Dr Jobst Limberg, BfArM

Dr Oisín Daly, EDQM (ex HPRA)

Dr Seán Barry, HPRA



# Thank you for your attention

