



The application of Quality by Design to Excipient supplies: A Customer Perspective

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Quality by Design

- Review recent developments in the approaches used for drug product development
- Identify how understanding materials science, physical properties and the functional attributes of excipients will contribute to Quality by Design
- How working in partnership with excipient suppliers will provide the detailed understanding necessary to achieve Quality by Design.

The Changing Regulatory Environment:

Risk Management/ Quality systems approach to Pharmaceutical Development

- FDA Guidance for Industry
 - *Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach: Final Report* (Sept 2004)
 - *PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* (Sept 2004)
 - *Quality Systems Approach to Pharmaceutical CGMP Regulations* (Sept 2006)
- ICH Quality Guidelines
 - *Q 8: Pharmaceutical Development* (Nov 2005)
 - *Q 9: Quality Risk Management* (Nov 2005)
 - *Q10: Pharmaceutical quality system* (Final Draft [Step 4] version 4th June 2008)
- European Pharmacopoeia 6th Edition
 - *5.15: Functionality-Related Characteristics of Excipients*

A Drug Quality System for the 21st Century

- Pharmaceutical manufacturing is evolving from an **art** form to one that is now **science** and engineering based.
- Effectively using this **knowledge** in regulatory decisions in establishing specifications and evaluating manufacturing processes can substantially improve the **efficiency** of both manufacturing and regulatory processes.
- This initiative is designed to do just that through an **integrated systems approach** to product quality regulation founded on **sound science and engineering principles** for **assessing and mitigating risks of poor product and process quality** in the **context of the intended use** of pharmaceutical products.

*Ajaz S. Hussain, B.Pharm., Ph.D. Deputy Director
Office of Pharmaceutical Science, CDER, FDA. 2003
<http://www.fda.gov/cder/gmp/21stcenturysummary.htm>*

Desired State:

- Product quality and **performance achieved and assured by design** of effective and efficient manufacturing processes
- Product **specifications based on mechanistic understanding of how formulation and process factors impact product performance**
- Continuous "real time" assurance of quality
- Regulatory policies tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability
- **Risk based** regulatory scrutiny relate to
 - level of **scientific understanding of how formulation and manufacturing process factors affect product quality and performance**, and
 - the capability of **process control strategies to prevent or mitigate risk of producing a poor quality product**

“Effective innovation in development, manufacturing and quality assurance would be expected to better answer questions such as the following:

- What are the mechanisms of degradation, drug release, and absorption?
- What are the effects of product components on quality?
- What sources of variability are critical?
- How does the process manage variability?”

FDA Guidance for Industry

PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance – Sept. 2004

Quality by Design concepts

Knowledge Space

Design Space

Control Strategy

Knowledge Space

The multi-dimensional region which encompasses the combination of formulation design, process operating conditions, quality of raw materials and type of process which have been explored and/or modelled.

Design space

The multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the space is considered to be a change and would normally initiate a regulatory post approval change process. Design Space is proposed by the applicant and is subject to Regulatory assessment and approval. [ICH Q8]

Control Strategy

A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The *controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.* [ICH Q10]

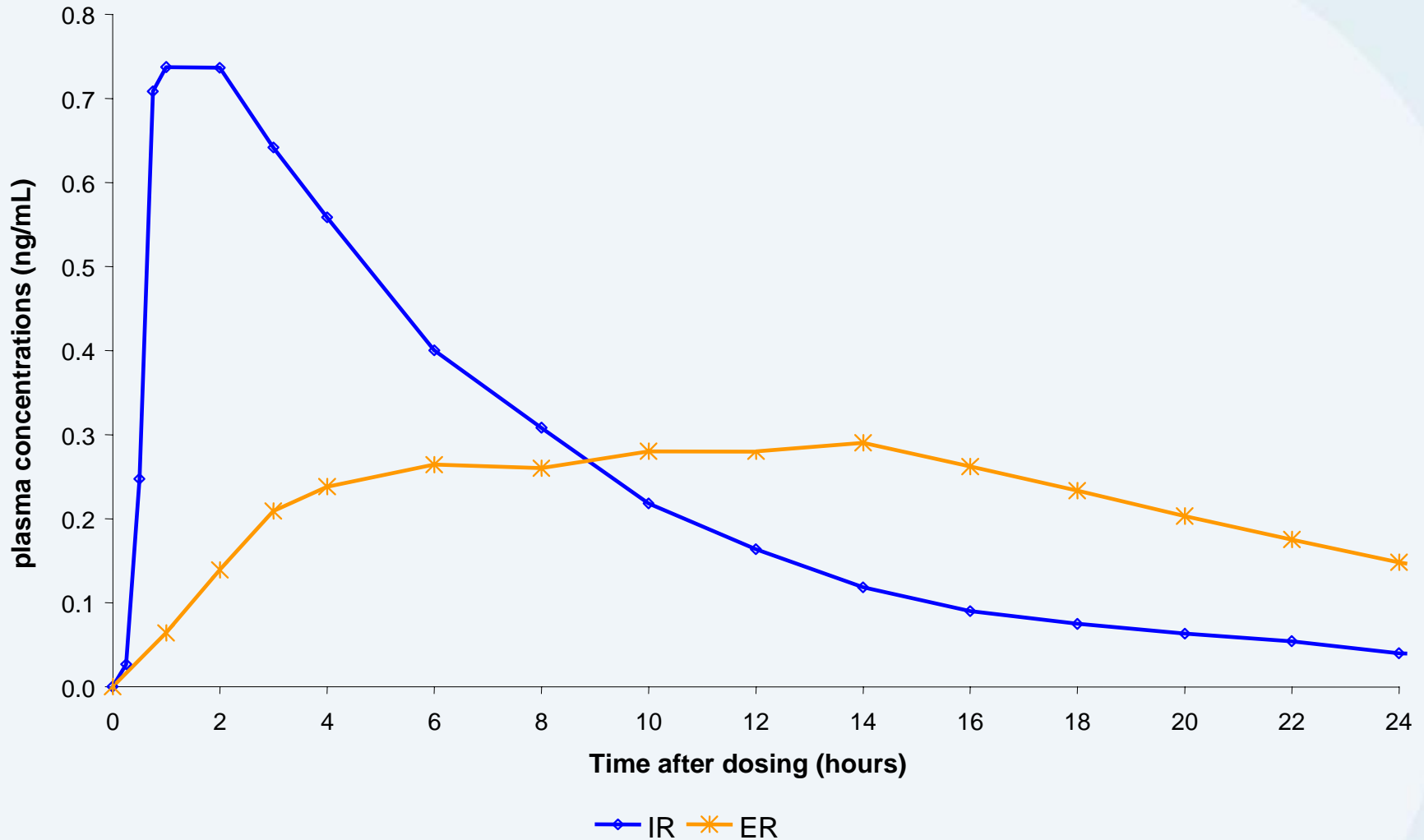
Excipients: inert, inactive ingredients?

- **High impact component of most drug products**
 - In some instances >99% by weight of the formulation
- **Functional role may be critical to Drug Product performance**
 - Efficacy and safety (biological activity)
 - Dissolution rate
 - Inhaled Fine Particle Mass
 - Quality (Manufacturability & patient confidence)
 - Content uniformity, tablet hardness, appearance, stability
- **Compendial specifications**
 - Ph.Eur, USPNF etc. historically focused on minimum (safety) standards
 - Identity, chemical purity and microbiological safety
 - Starting to introduce *Functionality-Related Characteristics*
 - Intended to permit wide range of applications
- **Excipient Handbook and the scientific literature**
 - Identify other variables which may be important
 - Not product, batch or supplier specific

Imagine ER:

A novel once daily hyperbole antagonist

Hypromellose matrix to control the rate of drug delivery



Imagine ER: A simple formulation Hypromellose matrix for controlled delivery

- **Development team have explored the effects of composition, granulation, lubrication, compression and film coating**
 - to create a process Knowledge Space
 - Agreed the process Design Space and established a control strategy...
- **Explored and understand changes to the drug substance**
 - Free base, water soluble and very permeable with moderate dose of 25mg (BCS class1)
 - excellent *in vitro in vivo* model that can predict oral absorption and clinical performance using a simple dissolution test
 - **Bioavailability is not affected by drug particle size/physical properties**
 - **Neither is the manufacturing process**
- **But what about the other product components/raw materials/excipients?**
 - Risk assessment has identified Hypromellose as potentially important

Hypromellose 2208; 4000 mPa s

● European Pharmacopoeia 6th Edition

- *Identification*
- *Appearance of solution*
- *pH (1% ^w/_w solution)*
- *Heavy metals*
- *Loss on drying*
- *Sulphated ash*

Functionality-Related Characteristics

With limits

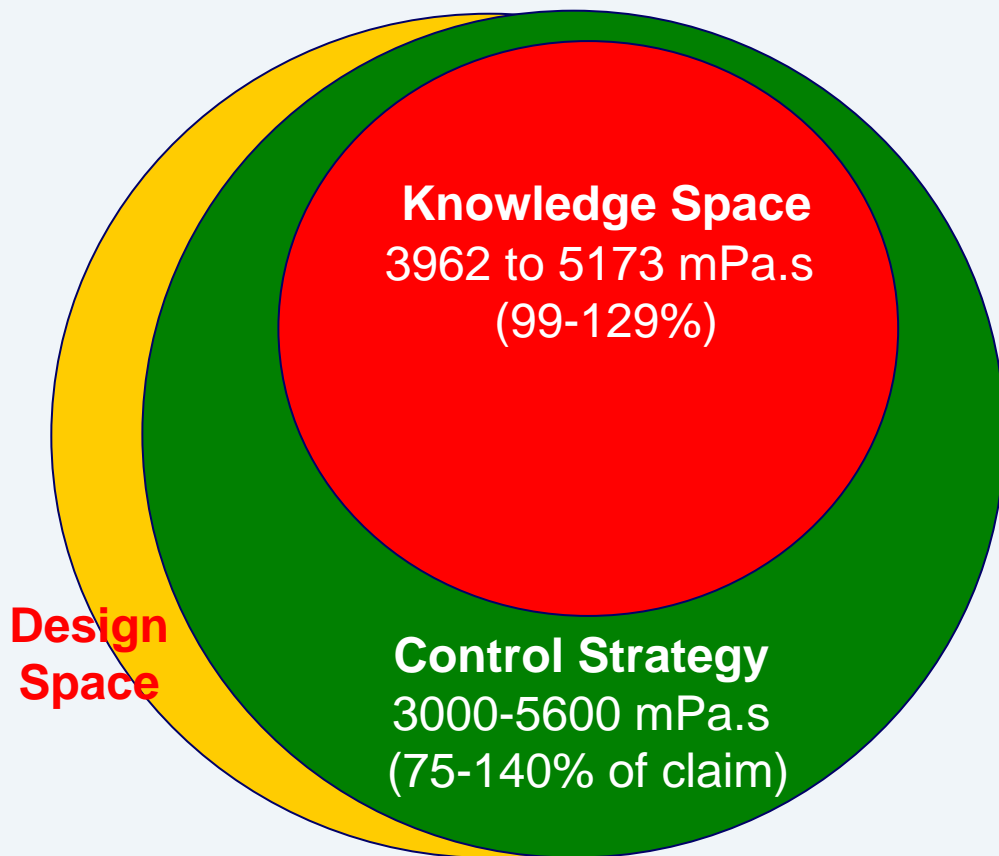
- *Apparent viscosity (75-140% of label claim; 3000-5600 mPa.s)*
- *Degree of substitution*
 - *Methoxy (19 to 24%)*
 - *Hydroxypropoxy content (4.0 to 12%)*

Without limits

- *Molecular mass distribution* (size-exclusion chromatography)
- *Particle-size distribution* (laser light diffraction or analytical sieving)
- *Powder flow* (angle of repose, compressibility index or Hausner ratio, flow rate through an orifice or shear cell)

Imaginate ER

Performance related to Hypromellose viscosity?
Batches used in development 3962 to 5173 mPa.s

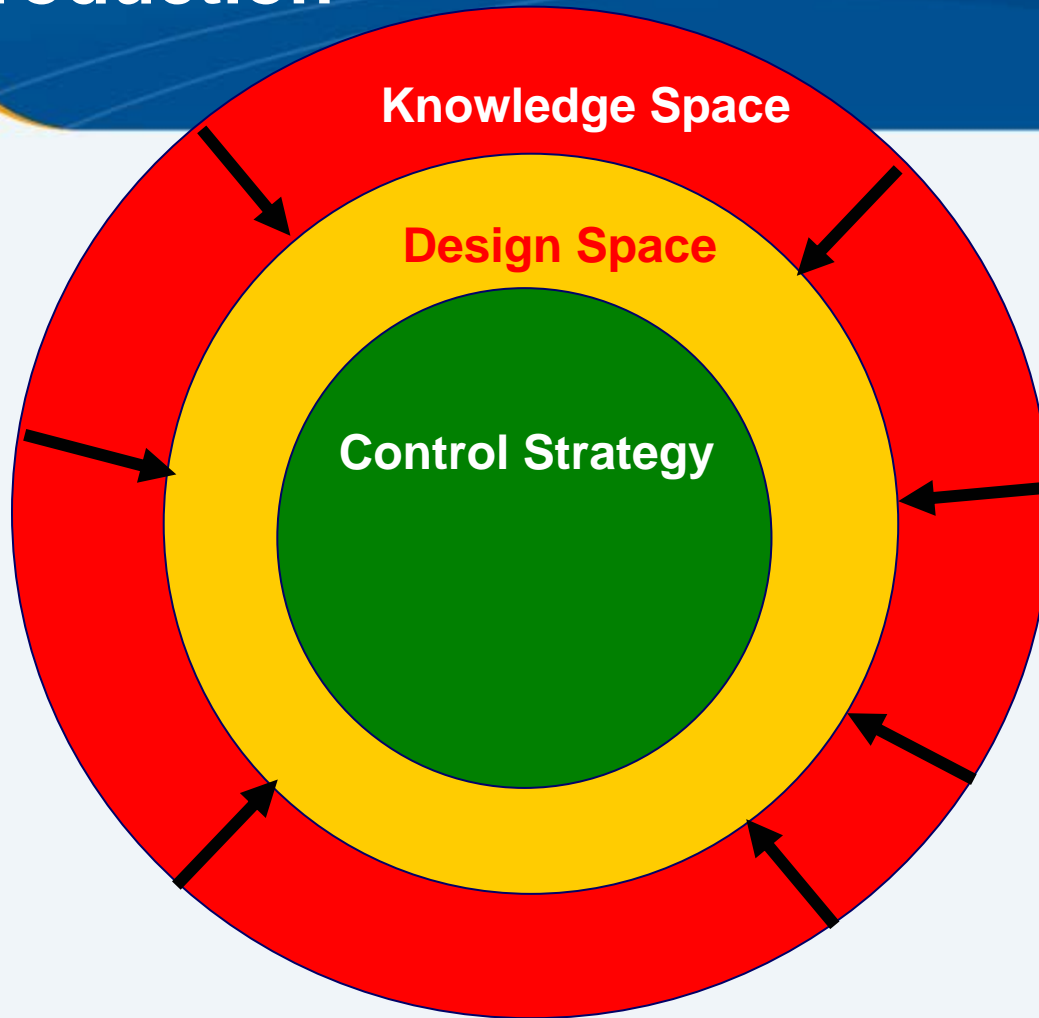


- Knowledge space
5 batches used in development
smaller than
- **Design Space** & **Control Strategy**
Set by the EP monograph

Where we need be is:

- Knowledge space
Greater than
- **Design space**
Greater than
- **Control strategy**

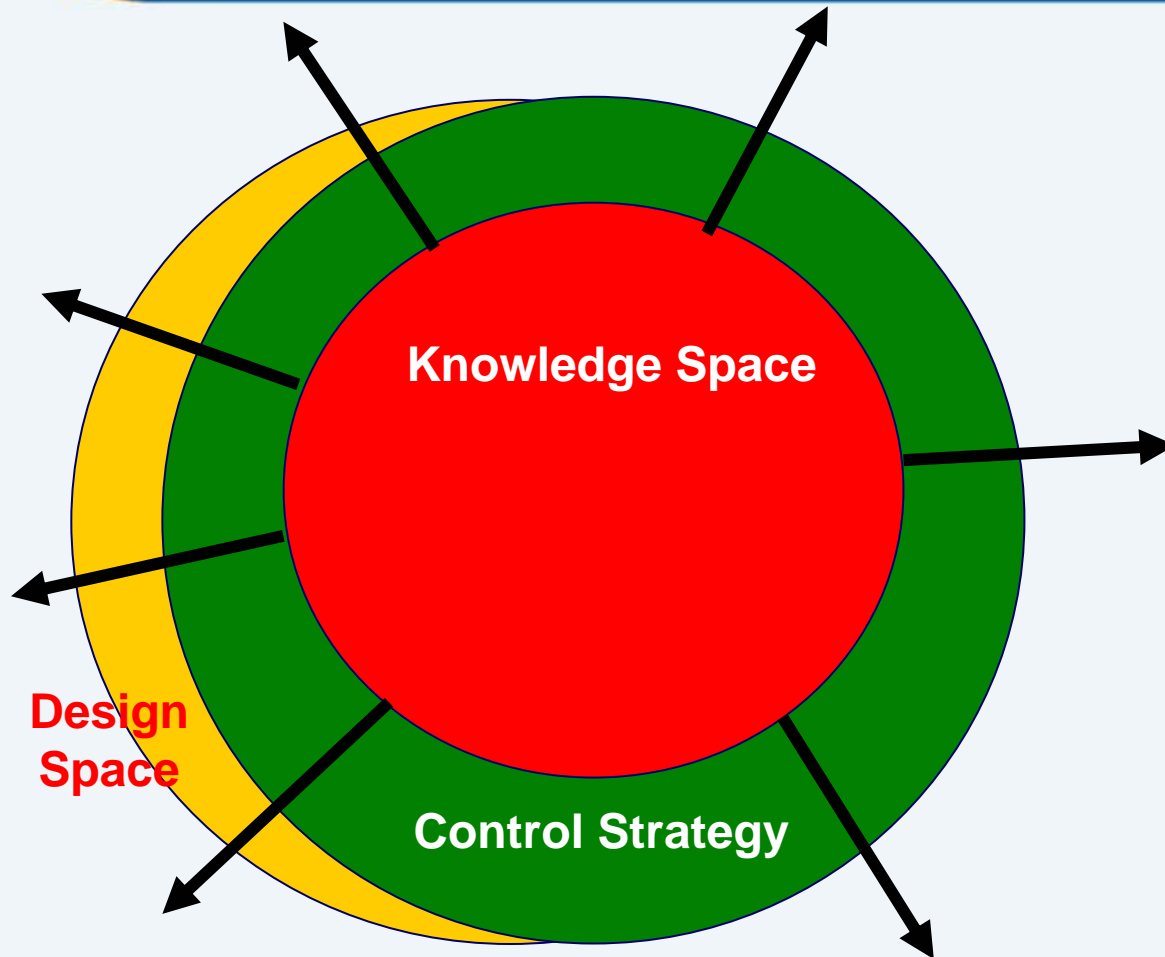
How do we resolve the situation?



- Interpolation from a large data set
- Multivariate, empirical and statistical model
- To define the Design Space & Control Strategy
- Single Design Space per product/CQA

- Most excipients are established products, manufactured at production scale
- In practice the Knowledge/Design space is multi-dimensional with 10 to 20 chemical, physical or process parameters.

Pharmaceutical Development



- Extrapolation from a small data set
- Expand the knowledge space
 - inferred from similar products
 - process and product stretching
 - uni-variate expts
 - DOEs
- May be several design spaces per product/CQA

What happens in reality?

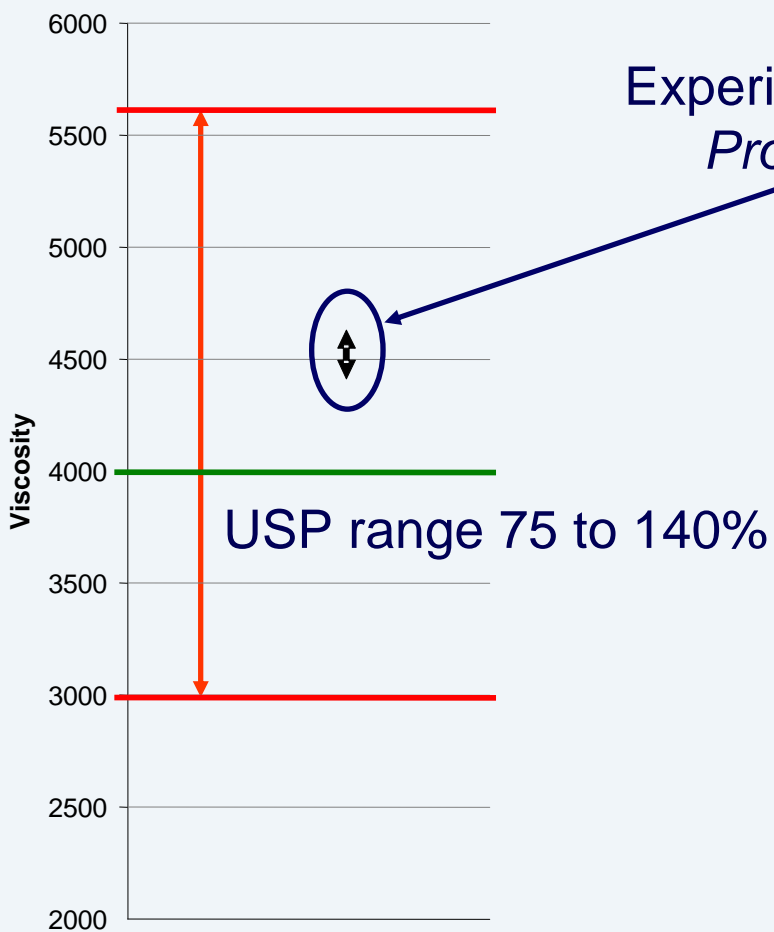
Product X: Regulatory Question

“Excipients: Comment on the effects of *variations in hypromellose polymer hydroxypropoxy content, degree of substitution or viscosity on release rate. Describe any additional control limits for the hypromellose polymers, such as hydroxypropoxy content, methoxy content and viscosity that are in addition to the USP specifications.*”

In this instance two grades Hypromellose were used:
2910 4000cPs and 2208 100cPs

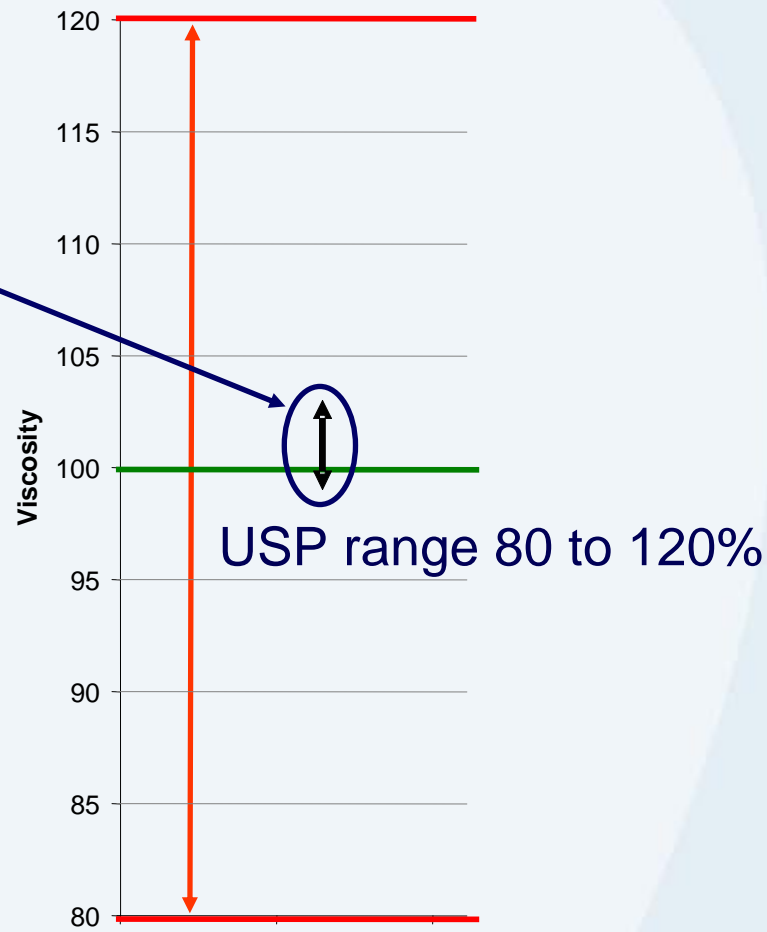
Product X: Viscosity experience

Hypromellose
2910 4000cPs



Experience with
Product X

Hypromellose
2208 100cPs



We obtained HPMC closer to the Viscosity extremes...

Property of Hypromellose 2910 4000 cPs	USP Specification	Batch 1 Low Viscosity	Batch 2 Target Viscosity	Batch 3 High Viscosity
Viscosity (cPs)	3,000 – 5,600 75-140%	3131 78.3%	4129 103.2%	5087 127.2%
Hydroxypropyl content (%)	7.0 – 12.0	9.5	9.6	9.4
Methoxyl content (%)	28.0 – 30.0	28.7	29.0	28.5
Property of Hypromellose 2208 100 cPs	USP Specification	Batch 1 Low Viscosity	Batch 2 Target Viscosity	Batch 3 High Viscosity
Viscosity (cPs)	80 – 120	82	101	113
Hydroxypropyl content (%)	4.0 – 12.0	8.7	8.0	8.1
Methoxyl content (%)	19.0 – 24.0	22.6	23.0	22.5

“CONCLUSION

There are no significant differences in the dissolution profiles, the amount dissolved at intermediate time point or the total amount dissolved at the final time point between batches manufactured from low, target and high viscosity Hypromellose 2208 and 2910 for *Product X* tablets”

Lessons learnt...

- As expected regulatory authorities have asked about the impact of excipient variation covering the full extent of pharmacopoeial specification
- Resolution requires close collaboration with the supplier
- Trending data allowed us to understand how each of the parameters varied over a longer period of time and how they interact
- Hypromellose batches to stretch the drug product were obtained
 - Difficult to go right up to the limit: but we have obtained a reasonable spread within the USP limits.
 - Difficult to vary more than one parameter at a time
- A new expectation of good suppliers
 - Trend batch data to provide an understanding of how the excipient varies
 - Be prepared to provide data for *Functionality-Related Characteristics* and potentially other parameters, after discussion with customer
 - Make available Batches at/close to the extremes