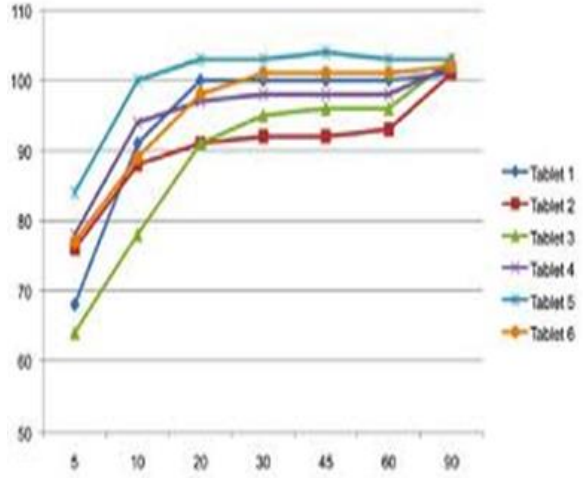
LIFE CYCLE MANAGEMENT
Dissolution Characteristics



Vijay Kshirsagar
Director-TRAC Pharma Consulting

At Disso India 2023, 27th June 2023

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Every care is taken to base all presentations/ discussions on current regulatory guidelines & own experiences but finally these are presenters thoughts & can not be construed as an organizer's or regulatory opinion.

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Contents

- Introduction (First time, such discussion)
- Logistics
- Panel Discussion Contents for all
- Presentation on subtopics allotted to me

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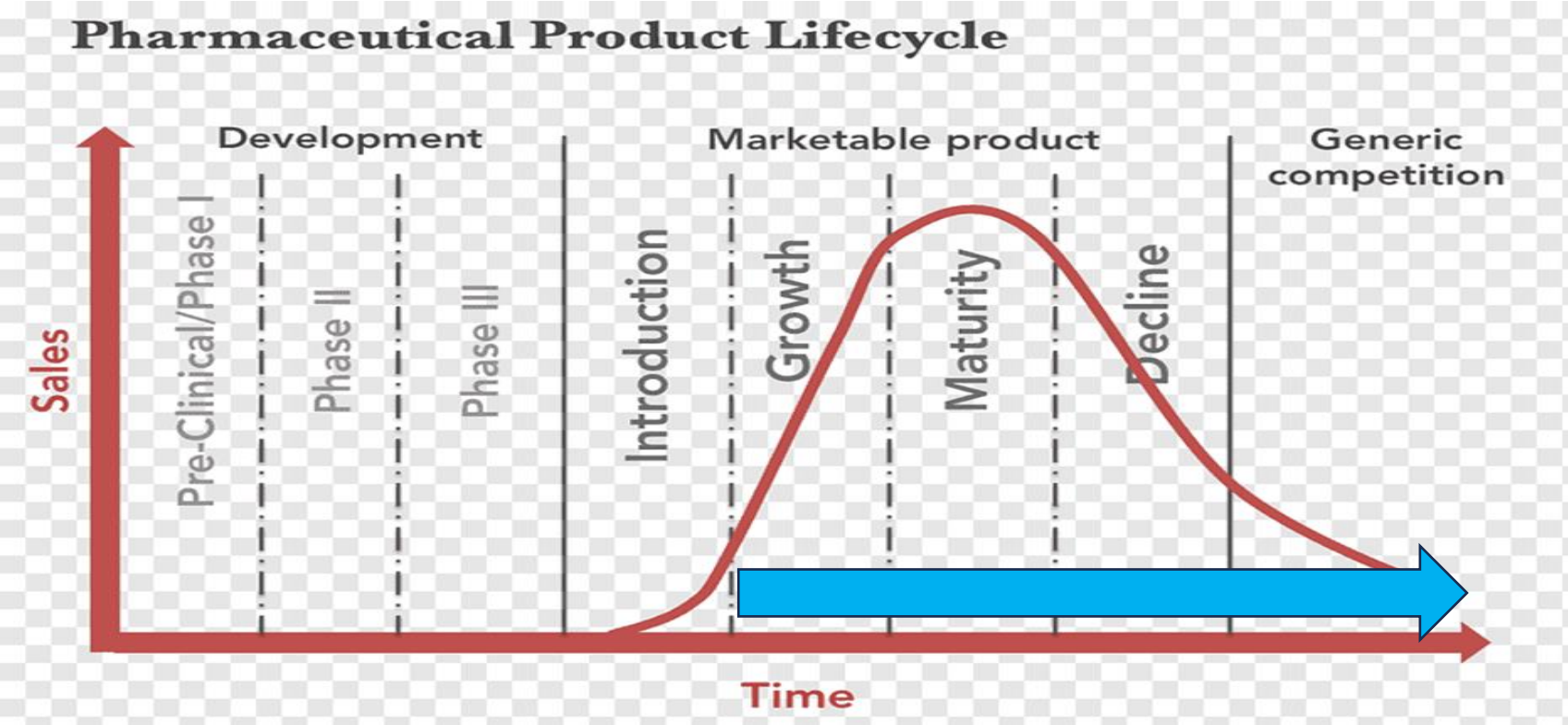
What is Product Lifecycle?

Everything from start till product discontinuation



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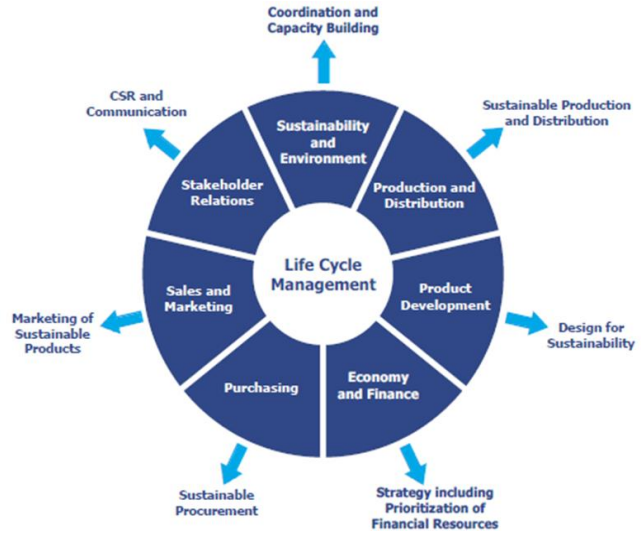
LCM for Each Stage



- Product Conceptualisation, Research on Paper
- Product & Method Development (QbD)
- Regulatory Approval
- Manufacturing/Testing
- Marketing
- Post Approval Changes
- Product Discontinuation

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Useful References

ICH HARMONISED GUIDELINE

TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT

Q12

Final version

Adopted on 20 November 2019

Status: Currently Official on 20-Jun-2023 Official
Date: Official as of 01-May-2022 DOI Ref: 46nba

Add the following:

▲⟨1220⟩
ANALYTICAL PROCEDURE LIFE CYCLE

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What are we going to cover?

Mr Vijay Kshirsagar: Emerging issues related to dissolution, Changes required, / Impact of Change in API/ formulation/ Excipients/Discriminatory Dissolution Studies

Dr Rajeev Desai: Stability Studies during the life cycle of the product /Ensuring data integrity on real time basis & before batch disposition/ shelf life extension

Dr Sajeev Chandran: Product development Life Cycle/ BA-BE studies/Adverse drug reaction monitoring/IV-IVC/Product extension e.g. IR to MR to TD/Supra bioavailable products

Dr. Rupesh Kelaskar : Electronic data management across life cycle/Data Back ups & Data Protection/Data Availability during regulatory inspections/ / Elements of 21CFR part 11 as applicable to dissolution data

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*Some overlap is unavoidable

Some Logistics

- About 30/20 mts presentation from each panellist
- Note down your questions
- Q&A session
- General Discussion
- We have so many SME’s here
- We will also invite Dr Vinod Shah for panel discussion
- Any body can participate & do the value addition
- Will take follow-up as needed

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Analytical Procedure Life Cycle USP <1220>

- Chapter 1220 is titled "The Analytical Procedure Lifecycle
- Became official on 1st May 2022
- Stages involved,
  - These stages include method development
  - Method validation across life cycle
  - Method Transfer
  - Ongoing Procedure Performance Verification (**OPPV**) i.e. Ongoing monitoring and maintenance

Procedure Performance Verification

- USP <1220> emphasizes **periodical monitoring and verification of method performance**
- Procedures to ensure required standards on continued basis i.e. ATP (Analy. target profile)
- **Modify the procedure if needed going back to Stage I (method design) & Stage II (method PQ)**
- Discusses system suitability testing, revalidation, and **trending of data** as part of this process

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Suggested checks for LCM

Current Dissolution Method

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Current Status

Survey in 2020

Have you implemented QbD principles for dissolution method development? If yes, to what extent? Software/Multivariate?

Response

Response was sought from more than 250 pharma professionals representing about 40 Indian Pharma companies

Findings

- Most of the companies follow very limited QbD principles
- Variation in speed/RPM/hardness/Surfactant
- Restricted largely to Type I & Type II apparatus, Univariate experiments
- Very few companies have implemented in toto

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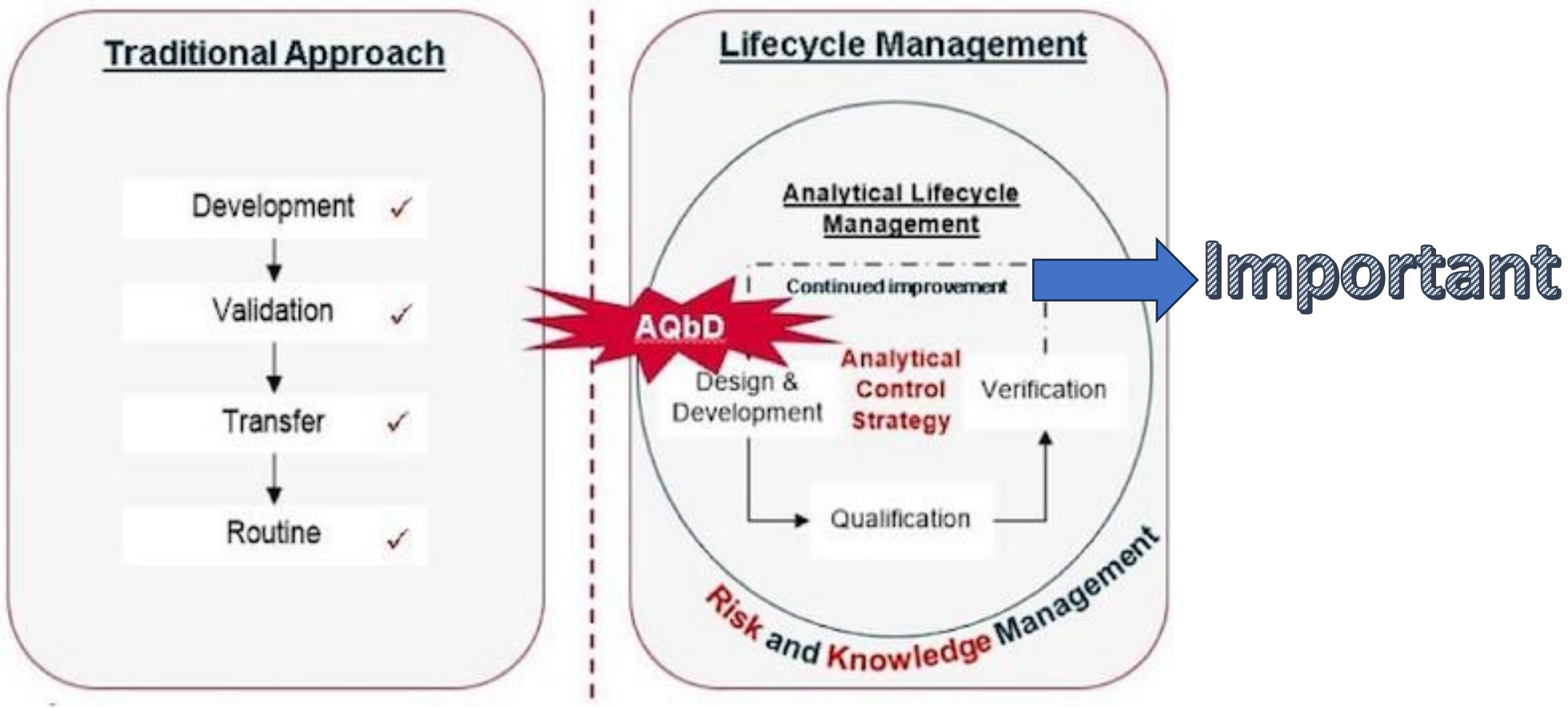
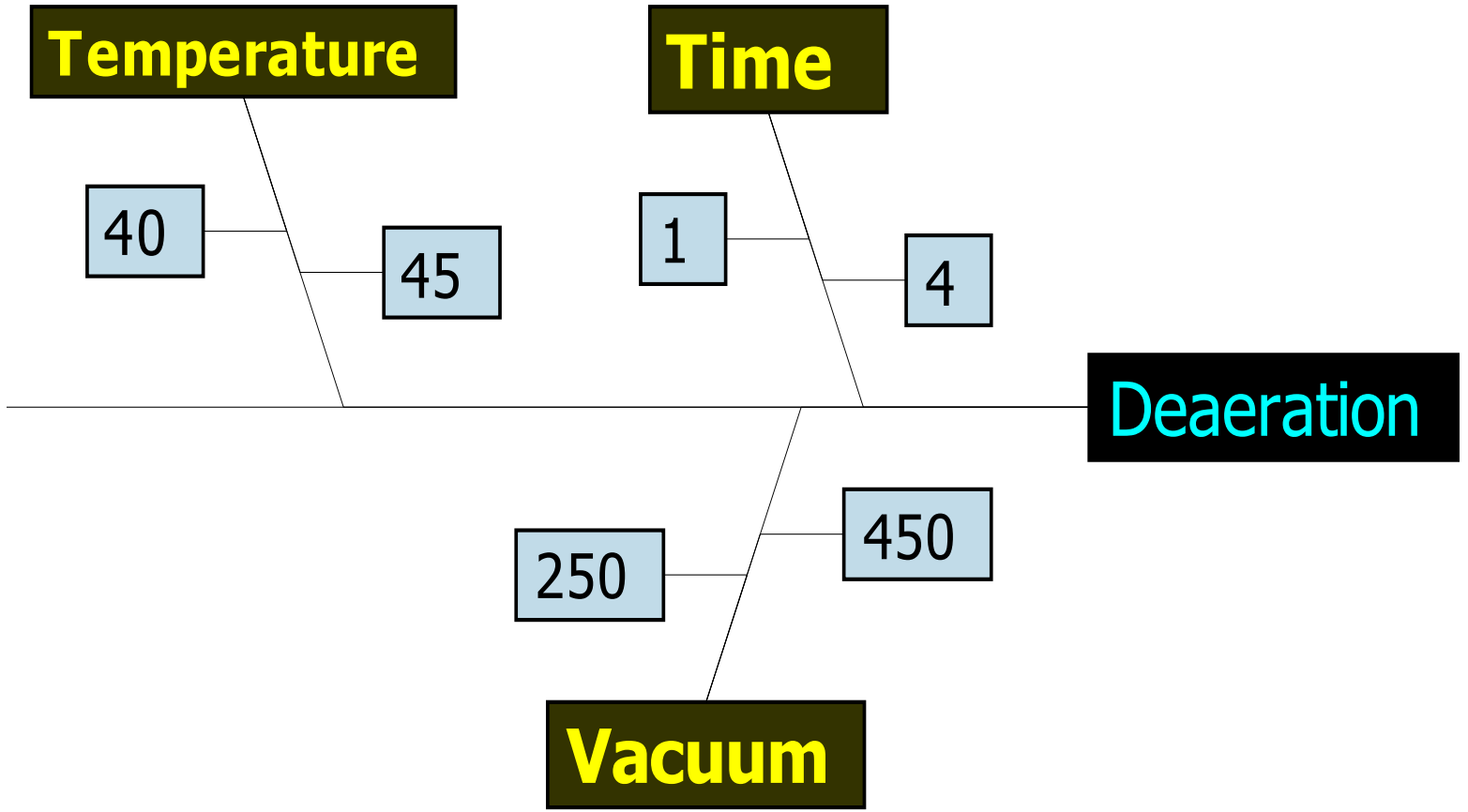
QbD must for Analytical LCM



*So challenge your existing methods from QbD angles including limits?

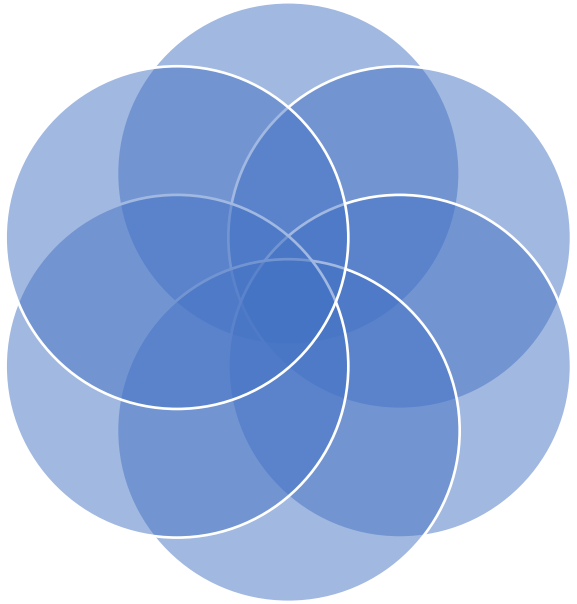
Optimization of Deaeration Procedure



Dissolution Dilemma

Experiments

Variation from batch to batch (Innovator)



Interpretation

Did innovator use QbD?

Automation

Reporting

*Study multimedia dissolution profile of 3 batches of innovator

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Results with & without & deaeration

Product: Piroxicam Capsules
Storage Condition: Long Term
Test: Dissolution by UV Apparatus I
Specification limit: NLT 75% (Q) of the label claim in 45 minutes

Results **with degassing** of dissolution media.

	Batch X	Batch Y	Batch Z
Capsule No.	% Release	% Release	% Release
1	78	70	67
2	75	66	71
3	72	73	64
4	73	66	68
5	69	69	74
6	71	67	62
Min	69	66	62
Max	78	73	74
Avg	73	69	68

Observation: The capsule shell opening pattern and granular powder release is same to that observed when media is not degassed however granular powder settles at bottom of dissolution vessel till end of dissolution testing.

Results **without degassing** of dissolution media

	Batch X	Batch Y	Batch Z
Capsule No.	% Release	% Release	% Release
1	82	88	90
2	87	83	89
3	88	84	87
4	90	87	82
5	84	85	90
6	89	89	85
Min	82	83	82
Max	90	89	90
A	87	86	87

spM

Observation: The capsule shell ruptures & the granular powder is released and it remains in the media till end of dissolution testing

***Do the dissolution study on your legacy products with & without deaeration of media.**

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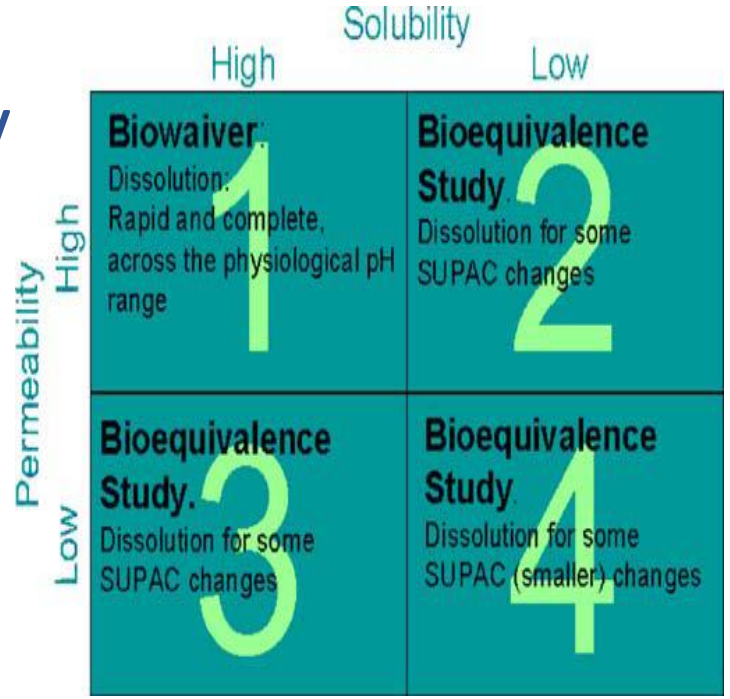
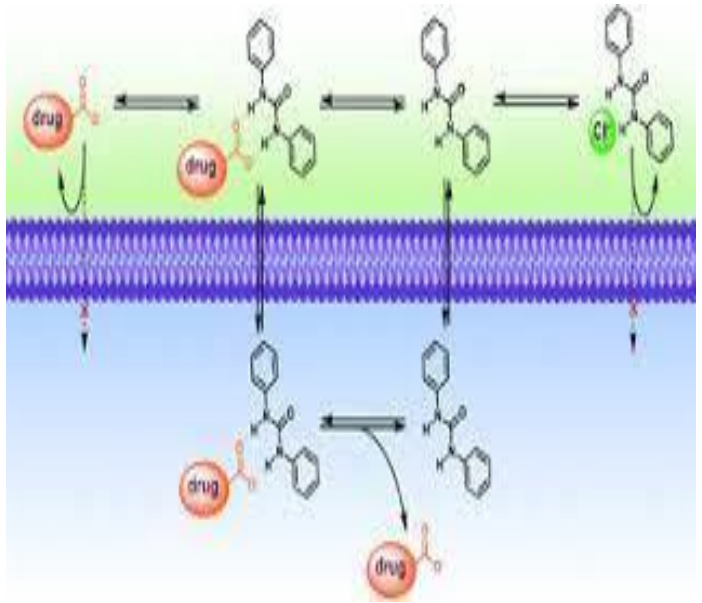
Biowaiver, Relook into legacy products

Revaluation of approved biowaiver may be necessary due to emerging knowledge especially for BCS Class III





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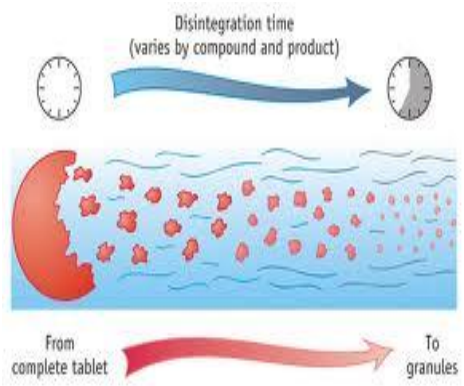
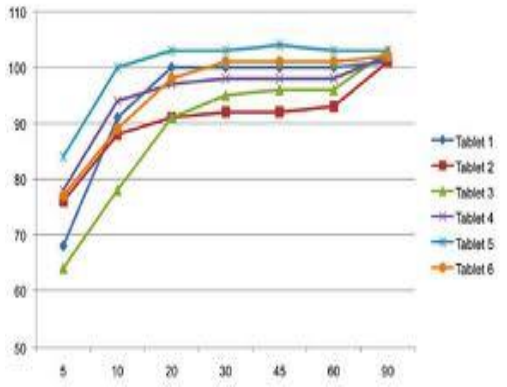
Monitor all 3D's on continued basis

- Disintegration
- Dispersion
- Dissolution





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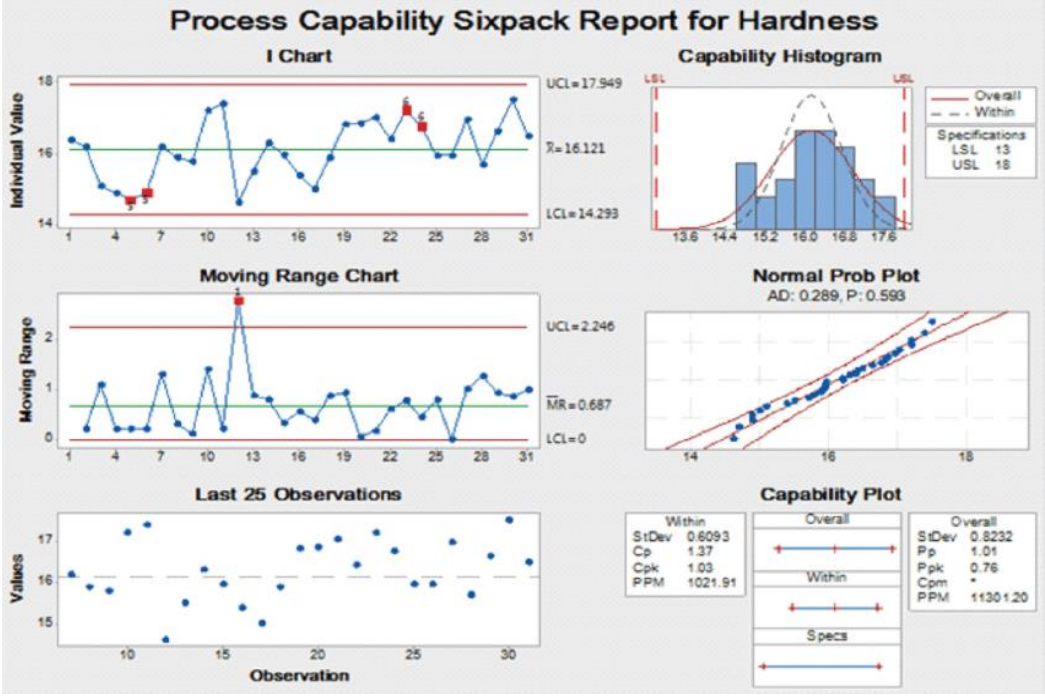
Continued Method Verification (CMV)

- **Need to introduce CMV like CPV**
- Monitor parameters that can affect dissolution from batch to batch (do trending)
  - Disintegration time
  - Dispersion time/pattern
  - Hardness
  - Monitor % undissolved



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Score Line

- Tablets with break line (divisible by design)
- Approved long back
- Compare & confirm the dissolution of 2 halves
- If necessary, bring in necessary changes

Reference:

Analysis of in vitro dissolution of whole vs. half controlled-release theophylline tablets, Comparative Study Pharm, 1987 Oct;4(5):416-9

***V P Shah**, L A Yamamoto, D Schuirman, J Elkins, J P Skelly

The dissolution of halved tablets was slightly faster compared to that of intact (whole) tablets. However, these small differences were not large enough to cause concern or to require bioavailability studies.

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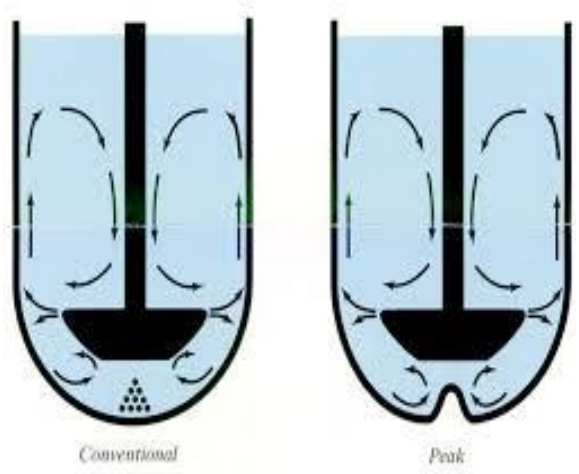
Coning Phenomenon

- Coning is a normal and expected occurrence for disintegrating dosage forms but not addressed at initial stages.
- Cone should move otherwise it hinders the dissolution
- If severe, **Peak Vessel can be used with justification though not official especially for investigation/method development purpose**



USP.APPARATUS	DESCRIPTION	ROT.SPEED	DOSAGE FORM
TYPE 1	Basket apparatus	50-120 rpm	IDR,DR,ER
TYPE 2	Paddle apparatus	25-50 rpm	IDR,DR,ER
TYPE 3	Reciprocating cylinder	6-35 rpm	IDR,ER
TYPE 4	Flow through cell	N/A	ER,Poorly soluble API
TYPE 5	Paddle over disk	25-50 rpm	TRANSDERMAL
TYPE 6	Rotating cylinder	N/A	TRANSDERMAL
TYPE 7	Reciprocating holder	30 rpm	ER

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Cross Linking Phenomenon

- Cross-linking of capsule shells can result in hardened and chemically resistant shells.
- May not be seen during initial 6 month study but can occur during long term stages
- Delays opening of capsule & traps DP
- Pellicle Formation If *Cross-Linking is seen, introduce testing with pepsin or pancreatin

*Bridge formation across the peptide backbone of the gelatin molecule which creates water insoluble membranes or pellicles during dissolution testing.

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FDA: Have your own discriminatory dissolution method

Note to Reader: A pharmaceutical development report should document the selection of the dissolution method used in pharmaceutical development. This method (or methods) may differ from the FDA-recommended dissolution method and the quality control method used for release testing.

Ref: Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms ,US FDA Guideline, 2012

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Discriminatory Vs Indiscriminatory

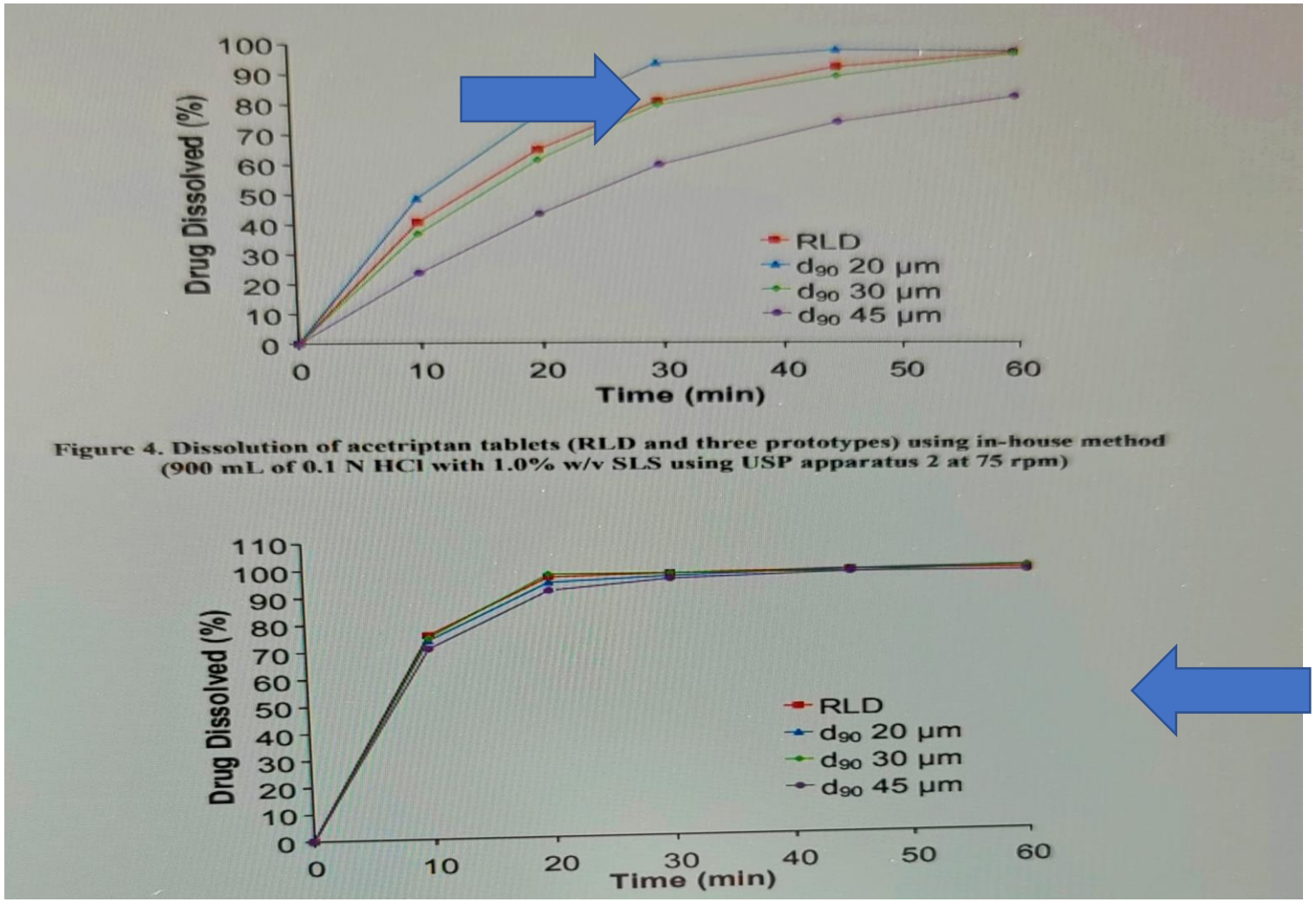

Figure 4. Dissolution of acetriptan tablets (RLD and three prototypes) using in-house method (900 mL of 0.1 N HCl with 1.0% w/v SLS using USP apparatus 2 at 75 rpm)

Dissolution of Acetriptan tablets (RLD and three prototypes) using FDA-recommended method (900 mL of 0.1 N HCl with 2.0% w/v SLS using USP apparatus 2 at 75 rpm)

Your method may be pharmacopeial. But is it discriminatory? Needs to be verified for legacy products.

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Mean PK profiles from Pilot BE

The pharmacokinetic results are presented in Figure 3 and Table 8.

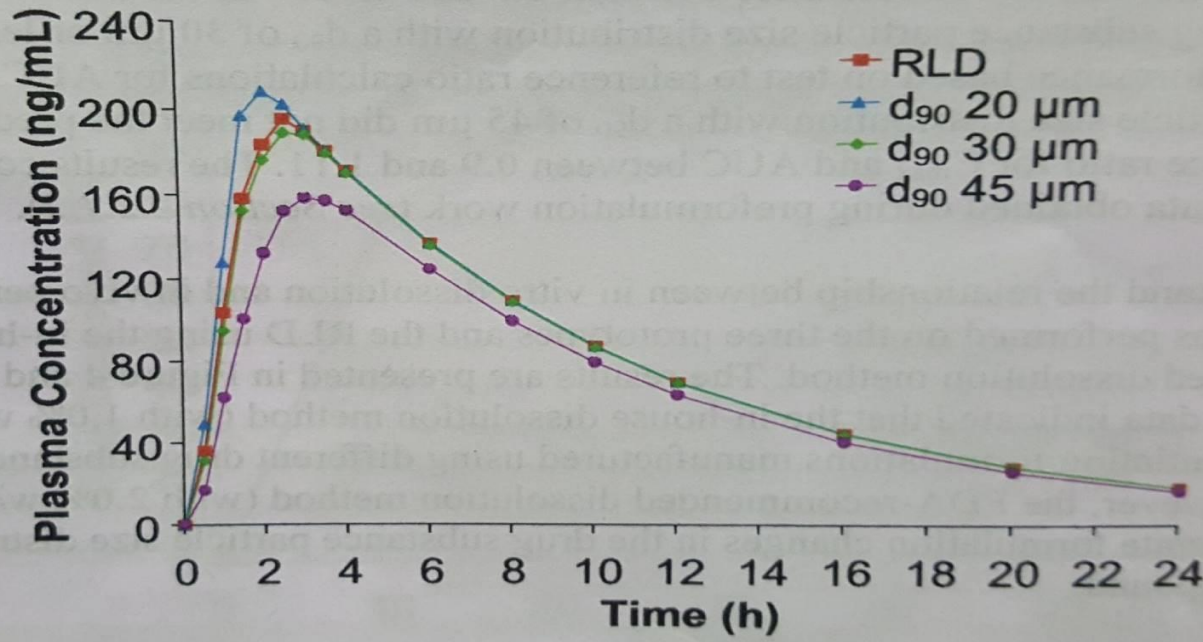
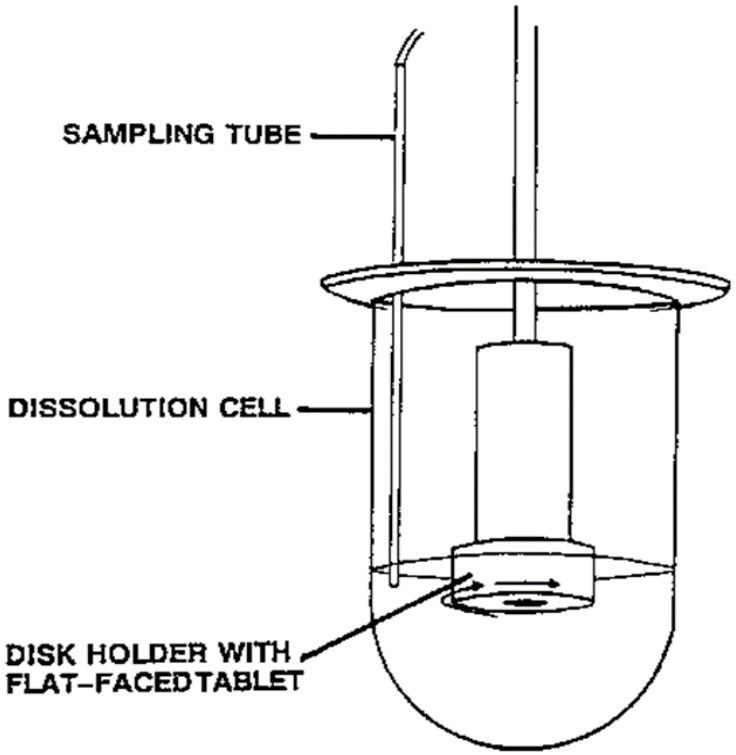


Figure 3. Mean PK profiles obtained from Pilot BE Study #1001

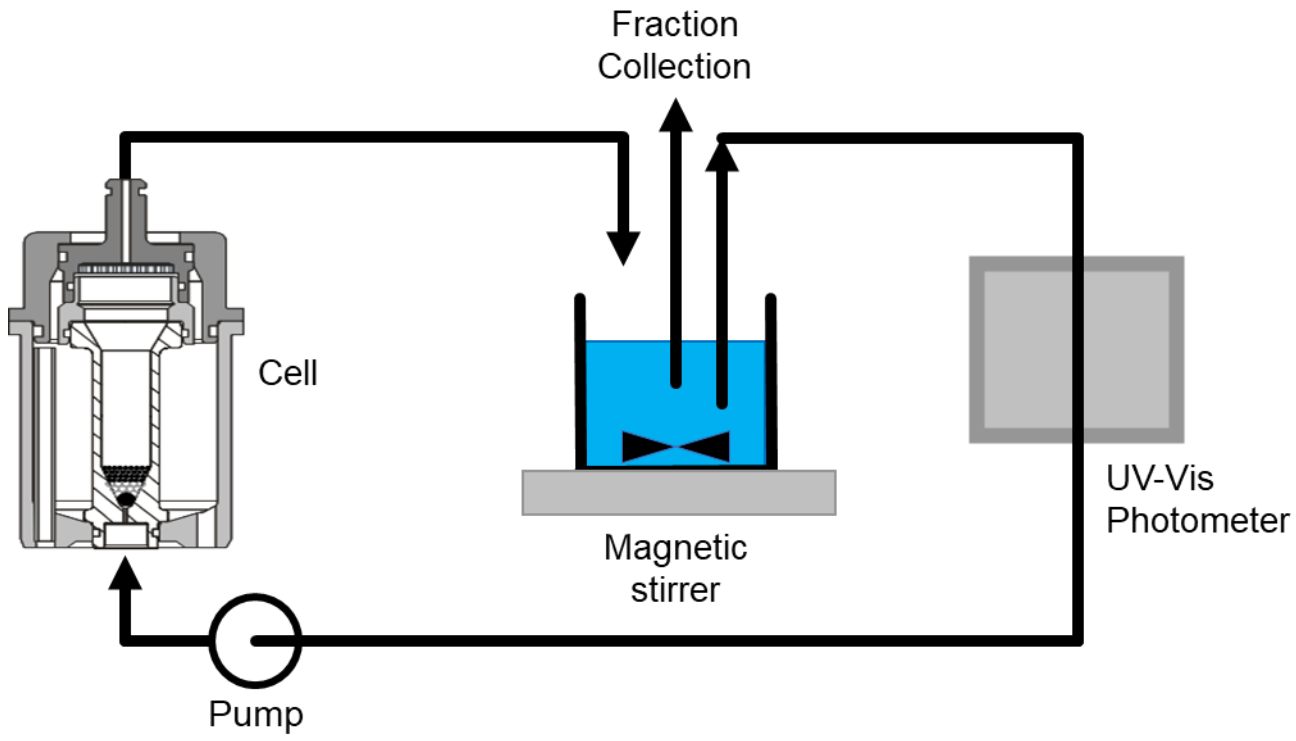
Intrinsic/Apparent Dissolution

Important but unexplored tool for API Characterization

USP <1087>



→ *Eur. Ph. § 2.9.43*



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Benefits as per response received

- Evaluation of drug solubility
- Setting particle size specification
- **Comparison of different forms/salts of the same molecule/solvates**
- Dissolution rate of API
- **Convert design from crystalline to amorphous form or vice versa or having a mix of both of them**
- **Determine BCS class of the compound**
- Solubility determination of compound as an alternative method to equilibrium solubility
- Solid dispersions of the API

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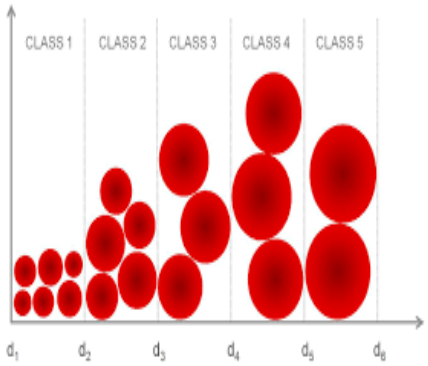
Regulatory Query Management



2006	2014
Your API specification has the particle size specification of 85% less than 40 micron. What is the permitted size for remaining 15% particles? A: Remaining 15% is between 40-100 micron.	Your API specification mentions the particle size specification of 85% less than 40 micron & 15% between 40 to 100 micron. Considering the low solubility of the molecule establish particle size distribution pattern & provide the results of experiments carried out to prove the entire specified design space.

What could be the nature of similar queries in future?

***Six tablets tested cant give idea about the dissolution profile of entire batch**.

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Managing Changes - Supporting Data

Level of Change

- Level I (Minor) change
- Level II (Moderate) change
- Level III (Major) change

Tests

- Chemistry (Tests, Stability)
- In Vitro dissolution/release
- In Vivo bioequivalence test / IVIVC

Filing

- Annual report
- Change being effected supplement
- Prior approval supplement

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SUPAC-MR Excipient Levels

- For the release controlling excipients, the SUPAC-MR guidance defines change in quantity as percentage (weight / weight) of total release-controlling excipients (RCE).
- Level 1 change: total additive effect of all RCE should not be more than ±5%.
- Level 2: allows a range of ±10%
- Level 3: > ±10%

What interference change creates, especially if current method is UV? Needs to be additionally verified.

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Summary of LCM points

- Reverify the method (QbD, Discrimination, Deaeration)
- Reverify the limits (relaxed/tighter)
- Introduce Intrinsic/Apparent Dissolution
- Check on the cross linking phenomenon
- Introduce CMV
- Challenge dissolution in case of change in excipients/ formulation as applicable
- % undissolved like mass balance
- UV to HPLC

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Acknowledgements

- M/s Unichem (Mr Jalesh Burye, CCO-CQA/RA)
- All respondents to the survey
- M/s Sotax (Dr Ramaswamy)

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THANK YOU

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