FDA Regulation of Drug Quality: New Challenges

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April 9, 2002

Regulation of Drug Quality: Current Status

- Pharmaceutical industry manufacturing sector highly regulated
- FDA review and approval of process, documentation, and facility required prior to approval
- Many process changes require FDA review and approval prior to institution
- Ongoing manufacturing subject to FDA inspection and GMP standards conformance

Current Status of System for Ensuring Drug Quality

- US Drug products are of high quality, BUT
- Increasing trend toward manufacturing-related problems
  - Recalls
  - Disruption of manufacturing operations
  - Loss of availability of essential drugs
  - Negative impact on new drug approvals

Current Status System for Ensuring Drug Quality, cont

- **US drug products are of high quality, BUT**
- **Low manufacturing process efficiency--cost implications**
- **Innovation, modernization and adoption of new technologies slowed**
  - **Introduction of new technologies in facilities not for US market**

Current Status System for Ensuring Drug Quality, cont

- **US Drug Products are of high quality, BUT**
- **High burden on FDA resources**
  - **About 4,000 manufacturing supplements submitted yearly**
  - **FDA inspectors unable to meet statutory biennial GMP inspection requirement**
  - **Lower scrutiny of non-domestic industry**
  - **Expensive & time-consuming litigation & legal actions**

Regulation of Drug Quality: Analysis of Industry Factors

- Reluctance to innovate/invest in manufacturing sector--poor stepchild compared to R&D?
- Emphasis on getting product out discourages early work on process and changes after marketing
- Possible role of regulatory oversight--unintended consequences

Regulation of Drug Quality: Analysis of Regulatory Role

- Thirty years ago--FDA's emphasis was on institution of basic procedures and recordkeeping--evolved to cGMP
- Currently: FDA attempting to drive innovation and investment in manufacturing sector via compliance/enforcement actions

Regulation of Drug Quality: Opportunity

- Empirical methods are probably approaching their theoretical maximum effectiveness
- New scientific understanding & new technologies can provide science-based approaches
- Plan: Use PAT as model

11/2000 Science Board Presentation on PAT

- Presented inefficiencies & problems in current manufacturing processes
- Presented examples of current industrial use of PAT (“Don’t tell”)
- Potential benefits of adoption of PAT

Challenges for FDA

- How to encourage innovation while ensuring high quality
  - Successful adoption of new technologies will IMPROVE overall quality
- How to successfully shift from empirical to science based standards for manufacturing process quality

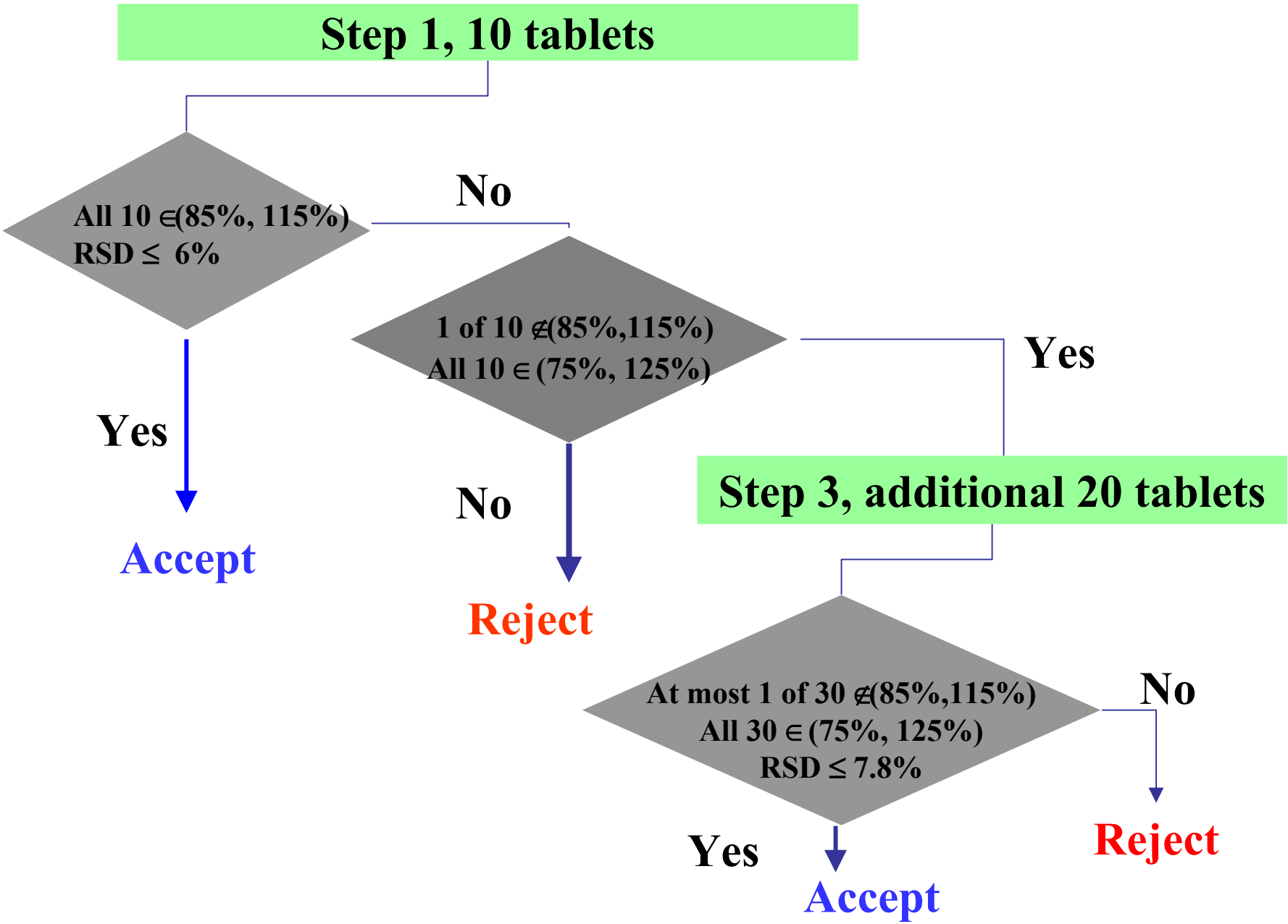
Major Barrier to Adoption:

- Industry Concern About Regulatory Implications of Results
- Closer scrutiny will reveal variations in existing products missed by sampling
- Delay in approval of new product

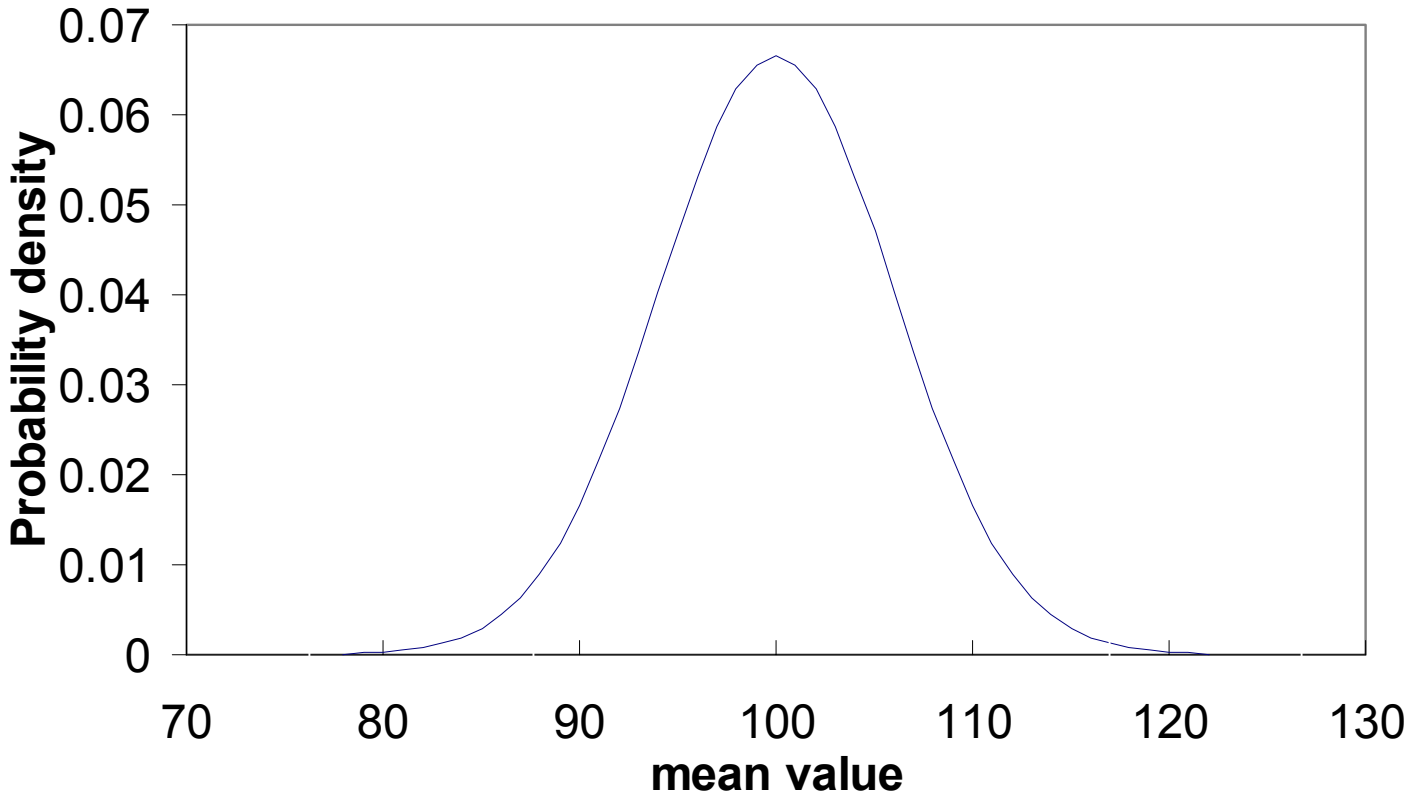
Example: Content Uniformity

- Quantity of active ingredient in a tablet/stated quantity-expressed as a percent
- USP has a standard algorithm
- Analysis: Stella Machado, Ph.D.
  Meiyu Shen, Ph.D.
  Charles Anello, Sc.D.

USP testing procedure



Content Distribution for typical batch for USP testing



EXAMPLE

- Assuming normal distribution, with mean 100% and sigma = 6%,
- Probability (batch passes USP) = 0.957
- Means about 4% of batches fail although they are no different than the passing batches

Consequences of 100% testing

- Use PAT to measure content uniformity of every tablet
- Assume batch of $1x10^6$ tablets
- Assume mean - 100% and sigma - 6%
- Will find 30 tablets outside (75, 125)
- Will find 12,419 tablets outside (85, 115)

LINKAGE BETWEEN 100% TESTING RESULT AND USP TEST

Example: Batch size = 1,000,000

Number of tablets, out of range {75,125}	**Probability Range of passing USP test* with 30 tablets**
2000	0.39 – 0.45
1000	0.54 – 0.57
500	0.66 – 0.69
100	0.83 – 0.90
50	0.88 – 0.94
30	0.91 – 0.96

* corresponding to a range of (mean,sigma) pairs that give desired N, for means between 95% and 105%.

Numbers of tablets found outside range 75-125% among a batch of 1,000,000 tablets for different means, sigma's

	Mean		
Sigma	95%	100%	105%
6%	430	30	430
7%	2150	360	2150
7.8%	5232	1350	5232

Numbers of tablets found outside range 85-115% among a batch of 1,000,000 tablets for different means, sigma's

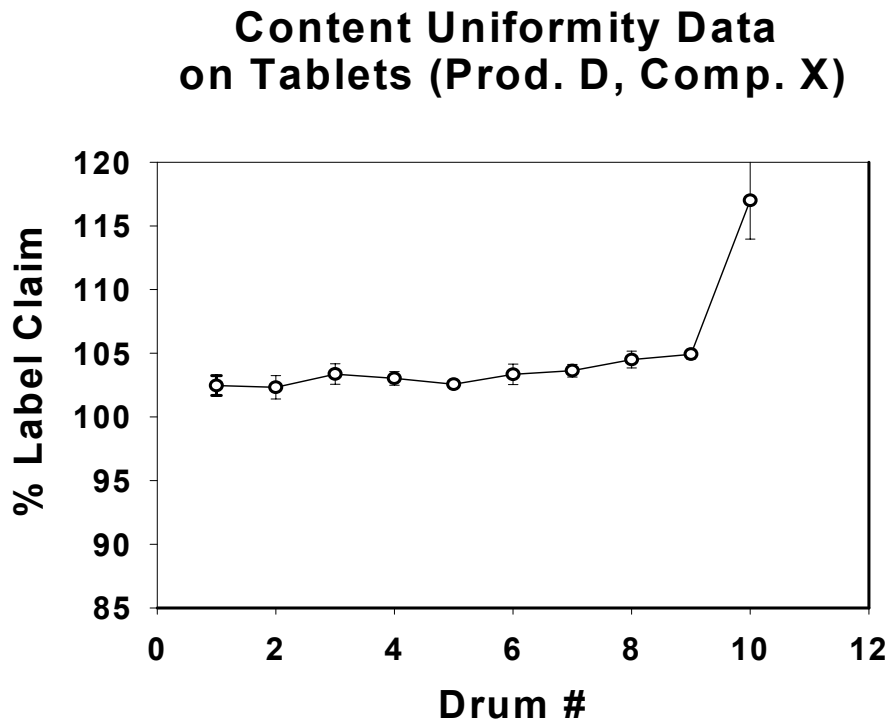
	Mean		
Sigma	95%	100%	105%
6%	48219	12419	48219
7%	78701	32124	78701
7.8%	105084	54470	105084

What about Normality Assumption?

Likely incorrect for some processes

An Example: Content Uniformity Test

Increasing test frequency may identify problems in currently "validated" process



PHARMACEUTICAL MANUFACTURING CASE STUDY:

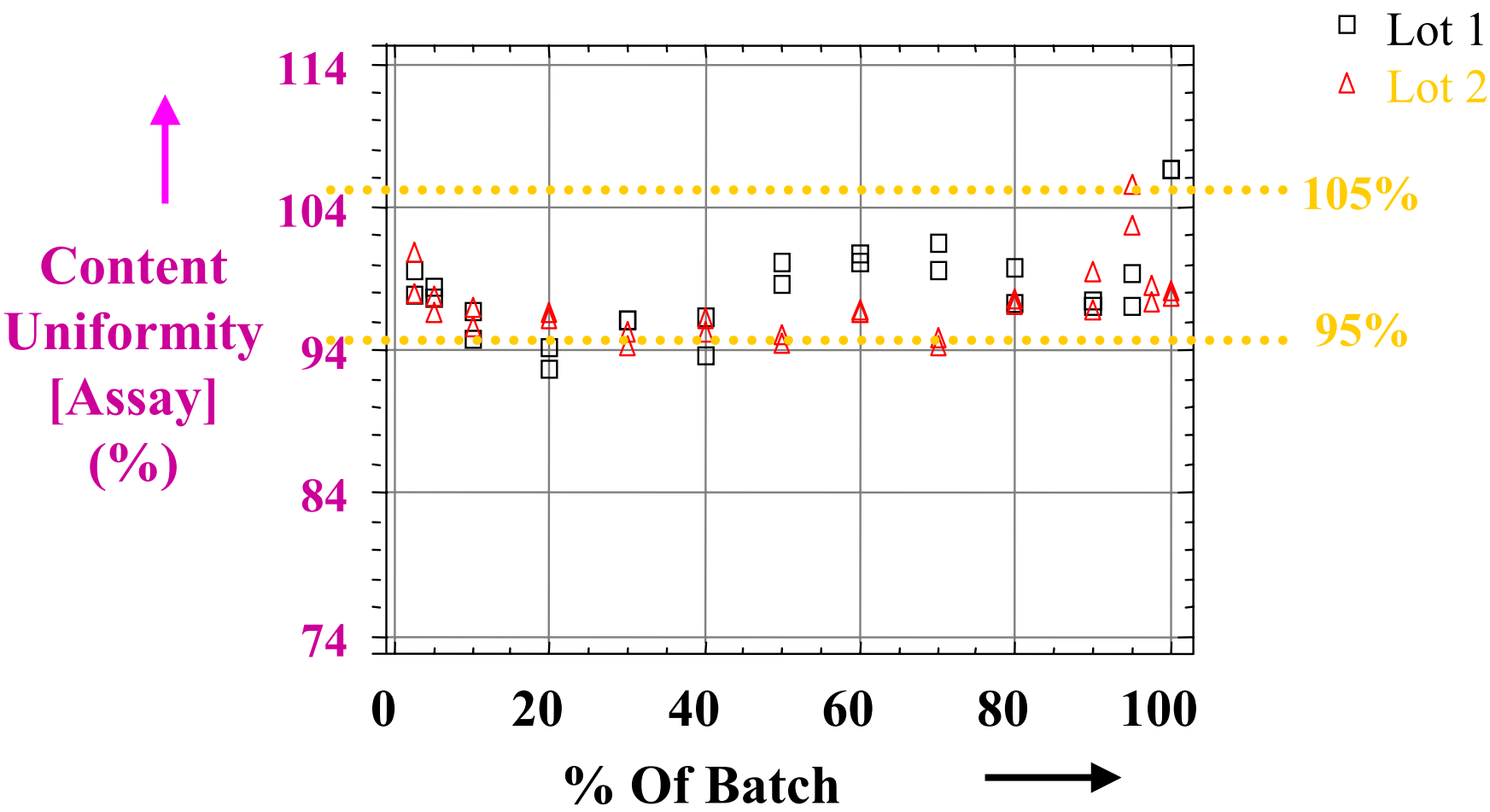
BACKGROUND

- Approved Product on The Market Today
- Product Provides Excellent Benefit to Patient
- Commercial Lots Meet All Final Product Specs
- In-Process Testing During Validation Showed Content Uniformity To Be Within Range (95-105%)
- The Company Would Like to Now Use PAT to Enhance Process Understanding & Efficiency..

Early Results from Additional Uniformity Testing In Developmental Mode

In-Process Content Uniformity

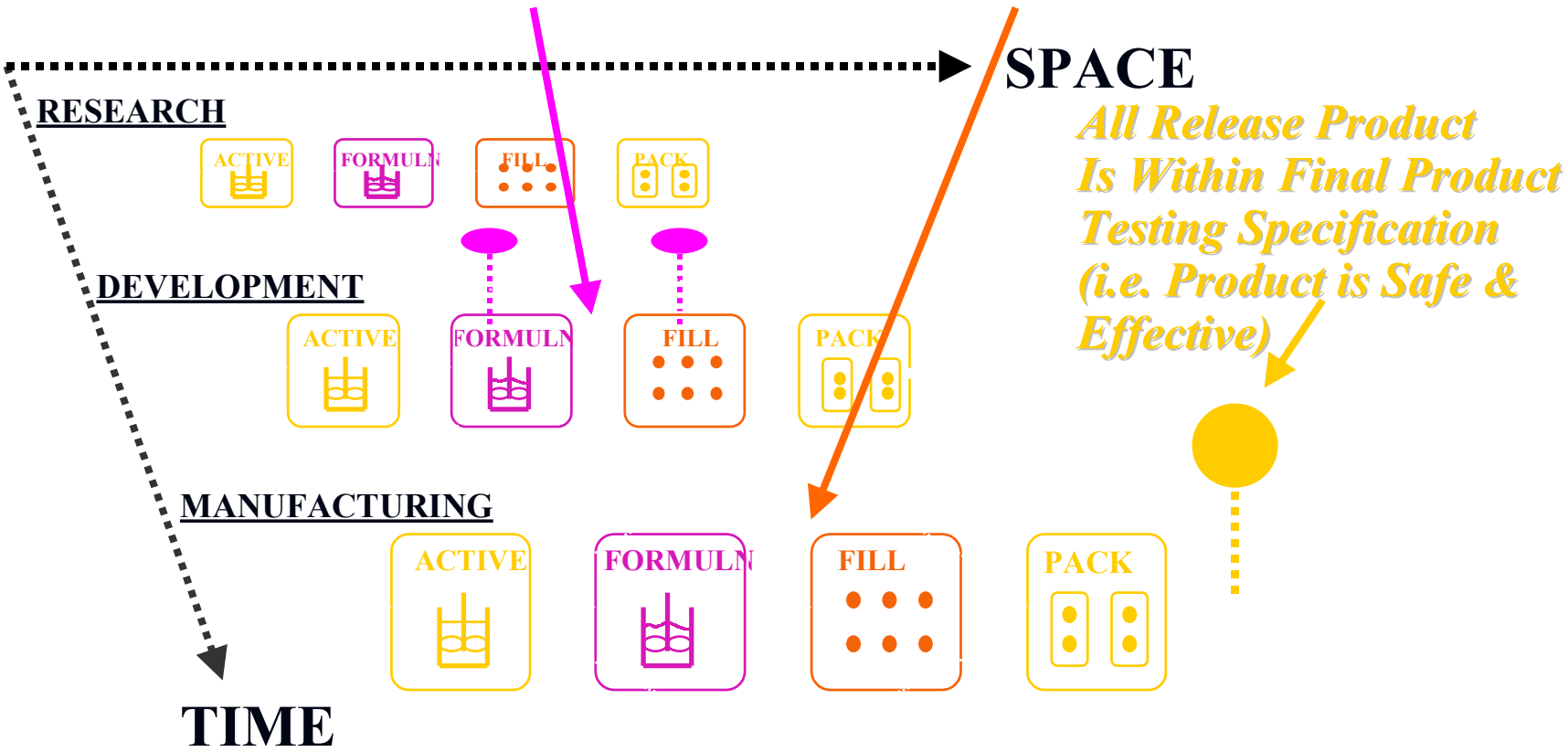
(During The Course Of A Batch)



PHARMACEUTICAL MANUFACTURING CASE STUDY: CONTEXT

Additional Content Uniformity Testing In Development Mode Revealed Some Potential Non-Random Patterns

How Do We Plan For What This Pharmaceutical Company Might See When They Attempt To Use PAT At Commercial Scale?



PHARMACEUTICAL MANUFACTURING CASE STUDY:

- **Pharmaceutical Company Wants to Do the Right Thing**
- **Wants To Better Understand Its Process & Enhance Efficiency**

CONCERNS

- ***BUT,*** **Are They Ready To Put PAT On The Actual Commercial Line for This Product?**
- ***BUT,*** **What If They See the Same (or Different) Kind of Content Uniformity Pattern on Commercial Batches That They Just Saw In Developmental Mode?**

PHARMACEUTICAL MANUFACTURING CASE STUDY:

GETTING TO *"WIN-WIN"*

- The Increased Ability to Measure Brings With It An Increased Responsibility To Understand/Explain
- What Happens In The Interim Period When The Companies Can Measure More But Are Still Working On Being Able to Explain More?
- How Can The FDA Work With The Pharmaceutical Companies To Help Address This Concern?
- Can The Pharmaceutical Industry Be Reassured In Some Way During This Interim Period?

Application of PAT may reveal facts about currently acceptable products that could jeopardize the cGMP compliance status of the firm.

PAT is likely to improve our understanding of current processes - identifying "critical" process variables that should be controlled and highlighting variability that was less visible with sampling techniques.

- **Need to develop risk based approach for addressing this new information without penalizing firms**

Need to provide a “safe harbor” during R&D related to PAT application on existing lines

Scientific (statistical) approach to control tests needed

Summary

- Application of new technologies to pharmaceutical manufacturing can improve quality and increase efficiency
- There are major (perceived) regulatory barriers to this happening
- We seek Board input on our approach
- Dr. Hussain: Accomplishments and next steps