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PAT, QbD and Continuous Process Verification – The 21st Century Opportunity

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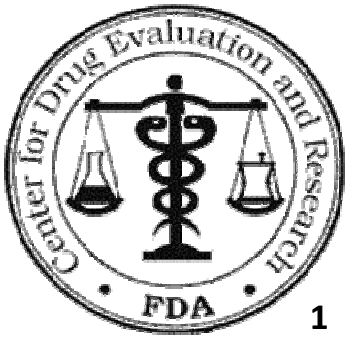


Outline

- **Pharmaceutical Manufacturing**
  - Public Health and Product Quality Expectations
  - Quality Issues and Trends Overview
  - Desired state
- **Scientific Principles and Regulatory Tools**
  - Pharmaceutical CGMPs for the 21st Century
  - Process Analytical Technology & Quality by Design
  - Process Validation
    - Continuous Process Verification
    - Utility of Consensus Standards - ASTM
- **Closing Remarks**

Public Health - Shared Vision

- **Patients/Consumers**
  - Access to safe, efficacious, high quality, stable & cost effective pharmaceuticals
- **Manufacturers**
  - Viable and secure supply chain
  - Risk mitigated manufacturing operations
  - Safe, efficacious and high quality products
- **Regulators**
  - Stand in for the consumer to ensure quality
    - Risk-commensurate regulatory oversight

Product Quality Expectation:
Every unit, Every batch, Every day…

"We **rely** upon the **manufacturing controls** and **standards** to ensure that *time and time again*, *lot* after *lot*, *year* after *year* the same clinical profile will be delivered because the product will be the same in its **quality**…

We have to think of the primary customers as **people** consuming that medicine and we have to think of the **statute** and what we are guaranteeing in there, that the drug *will* ***continue*** *to be* ***safe*** *and* ***effective*** *and* ***perform*** *as described in the label*."

- Janet Woodcock, M.D., CDER

The Risk-Benefit Equation

- Drugs have side effects, and sometimes significant adverse side effects
- Consumers, patients, & healthcare professionals **accept** that risk because the **benefit** of treatment, cure, prevention, diagnosis and/or mitigation is deemed **greater than** the possible adverse effects.
- Healthcare professional and consumers **do NOT expect** or consider there may be **risks from manufacturing**, i.e., manufacturing problems or poor component quality resulting in unsafe or ineffective drugs.

Pharmaceutical Manufacturing
"Desired State"

A mutual goal of Industry, Society, and Regulators:

> ***A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.***
>
> **- Janet Woodcock, M.D.**
> **AAPS-FDA-ISPE Workshop, October 5, 2005**

In Other words:

- Manufacturers have extensive knowledge about critical product and process parameters and quality attributes
- Manufacturers strive for continuous improvement through operational Excellence
- **FDA role**:
  - Initial verification
  - subsequent audit

Pharmaceutical Manufacturing
"Desired State Expectations"

- Product specifications based on
  - mechanistic understanding of how **formulation** and **process factors** impact **product performance**
  - understanding the causation and not just correlation
- Product quality and performance achieved and assured by
  - design of effective and efficient manufacturing processes

Quality Issues and Trends Snapshots

- Drug Quality Reporting System Databases
  - MedWatch Reports
  - Field Alert Reports
  - Consumer Complaints
- Trends in Product Quality Issues
  - Across 5 Year Range: 05/2006 – 05/2011
  - Across Dosage forms
    - Solid oral (tablet capsules), parenteral, inhalation, transdermal
    - Miscellaneous: Solutions, suspensions, emulsions, ointments, etc
  - Across Prescription Vs. Generic Drugs
- CGMP citations

Quality Issues: Examples

- Potency questioned
- Oversize tablet
- Capsule Fill varies
- Volume/Quantity questionable
- Dosage units missing
- Empty capsule units

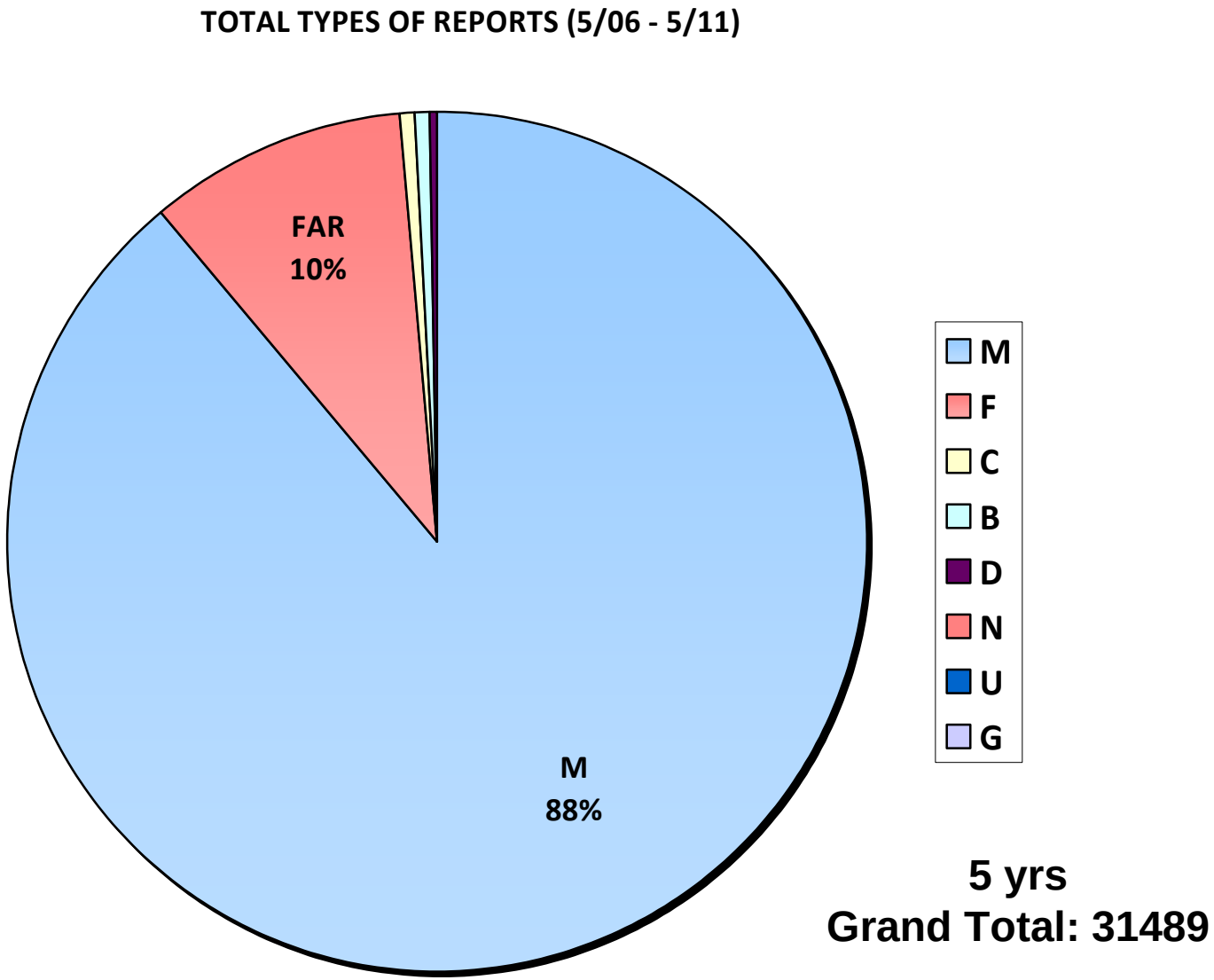
- Discoloration
- Precipitation
- cloudy
- Clumping
- Odor/Taste abnormal
- Foreign particulates
- Chipped, cracked DF

- Microbial contamination
- Visible growth

- Container/closure defects
- Syringe malfunction or Damaged
- Dispense/Admin device malfunction
- Aerosol non-function
- Pump malfunction
- Excessive Spray
- Adhesion lacking

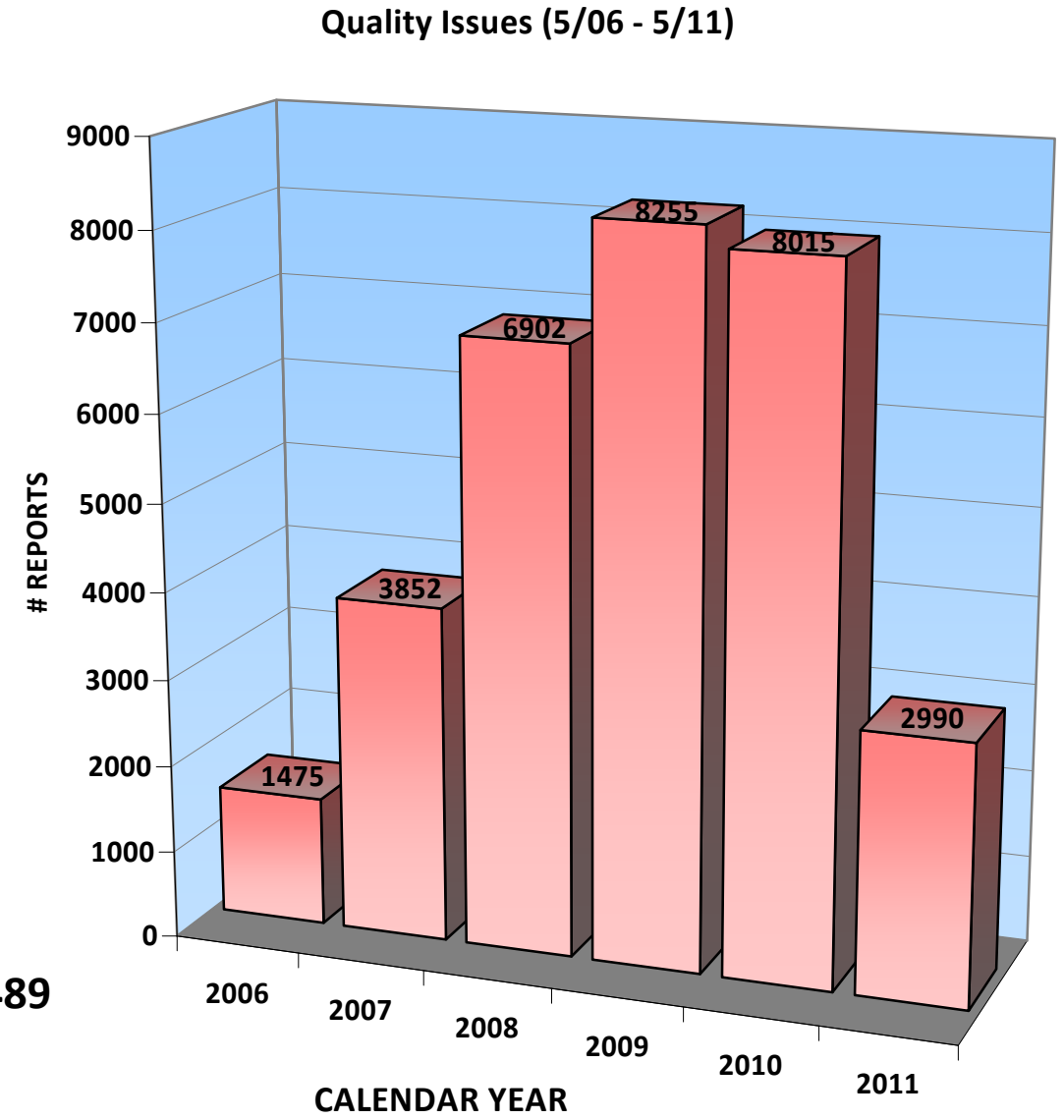
- Patient reaction
- Death

Quality Issues by Report Types



5 yrs
Grand Total: 31489

Quality Issues & Trend by Year



5 yrs

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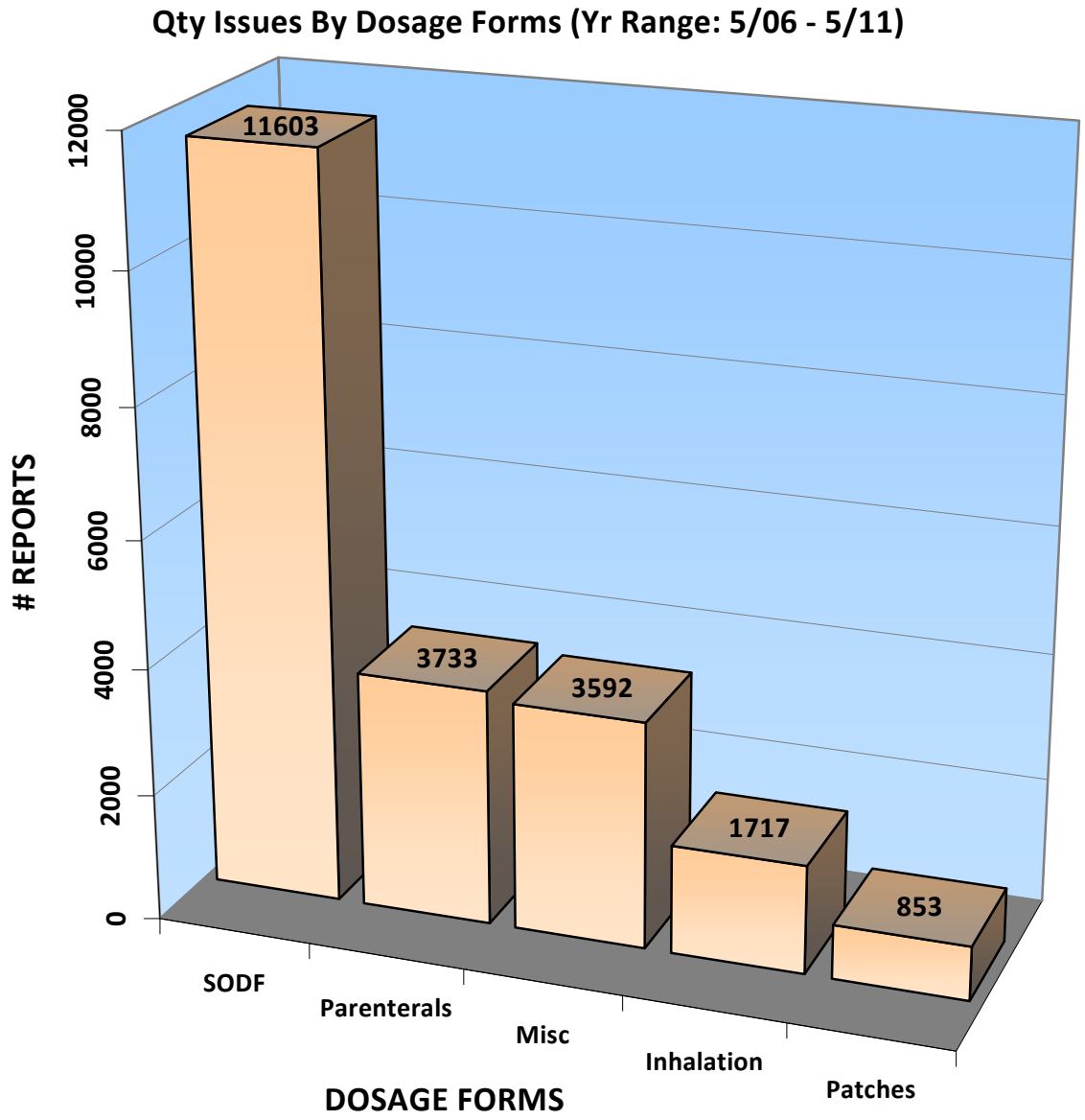
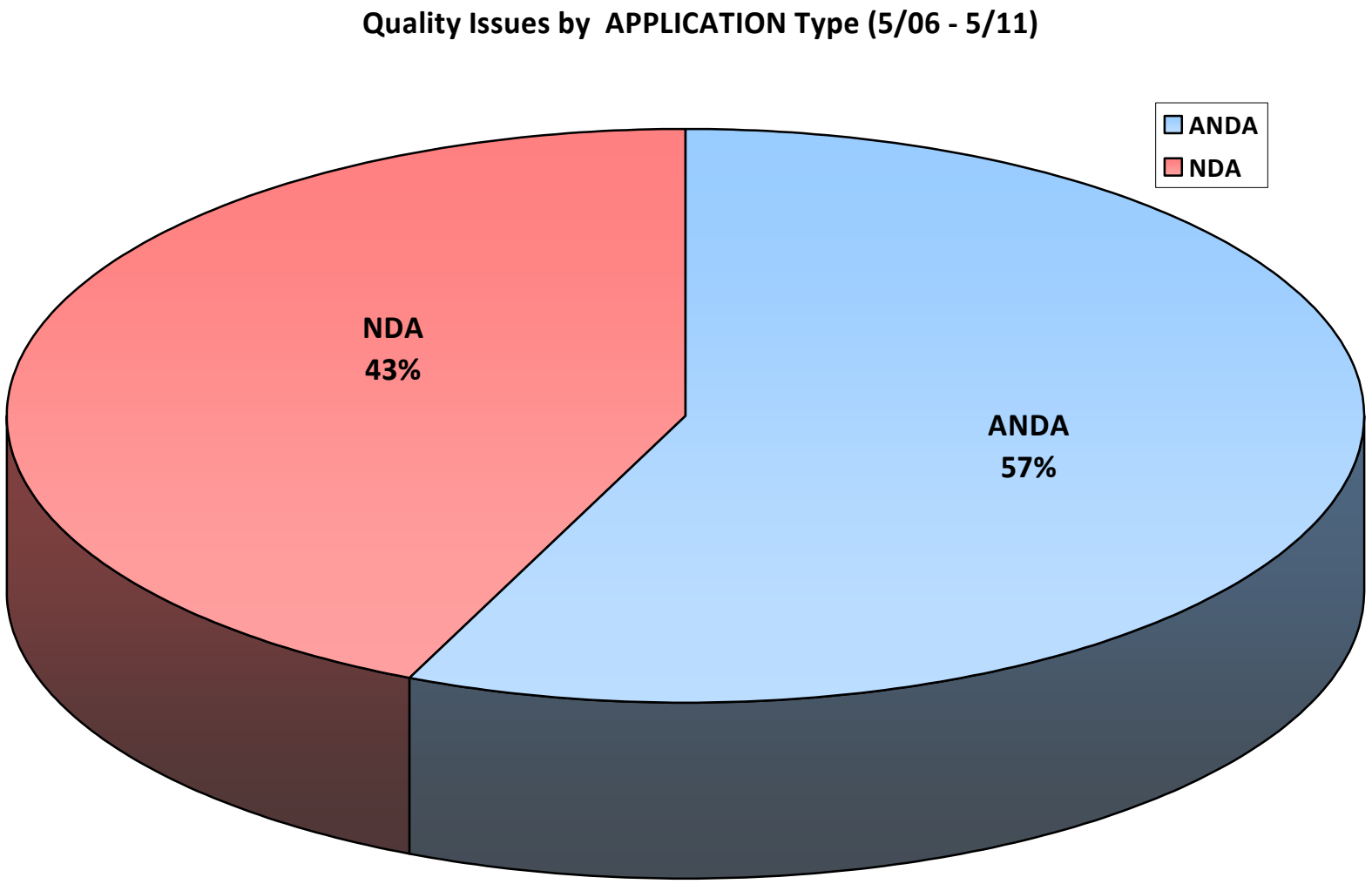
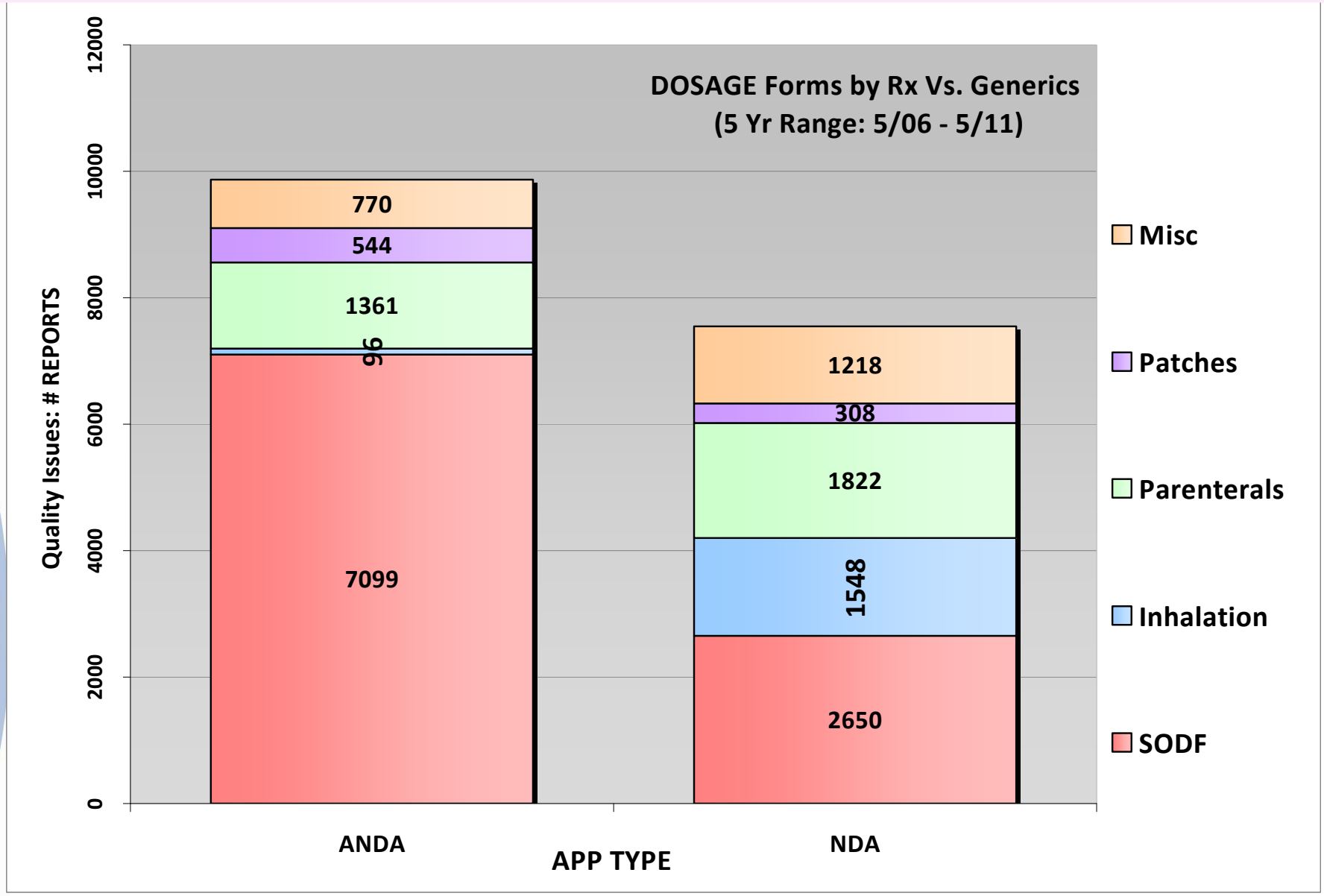
Quality Issues by Dosage Forms



Quality Issues by Application Type

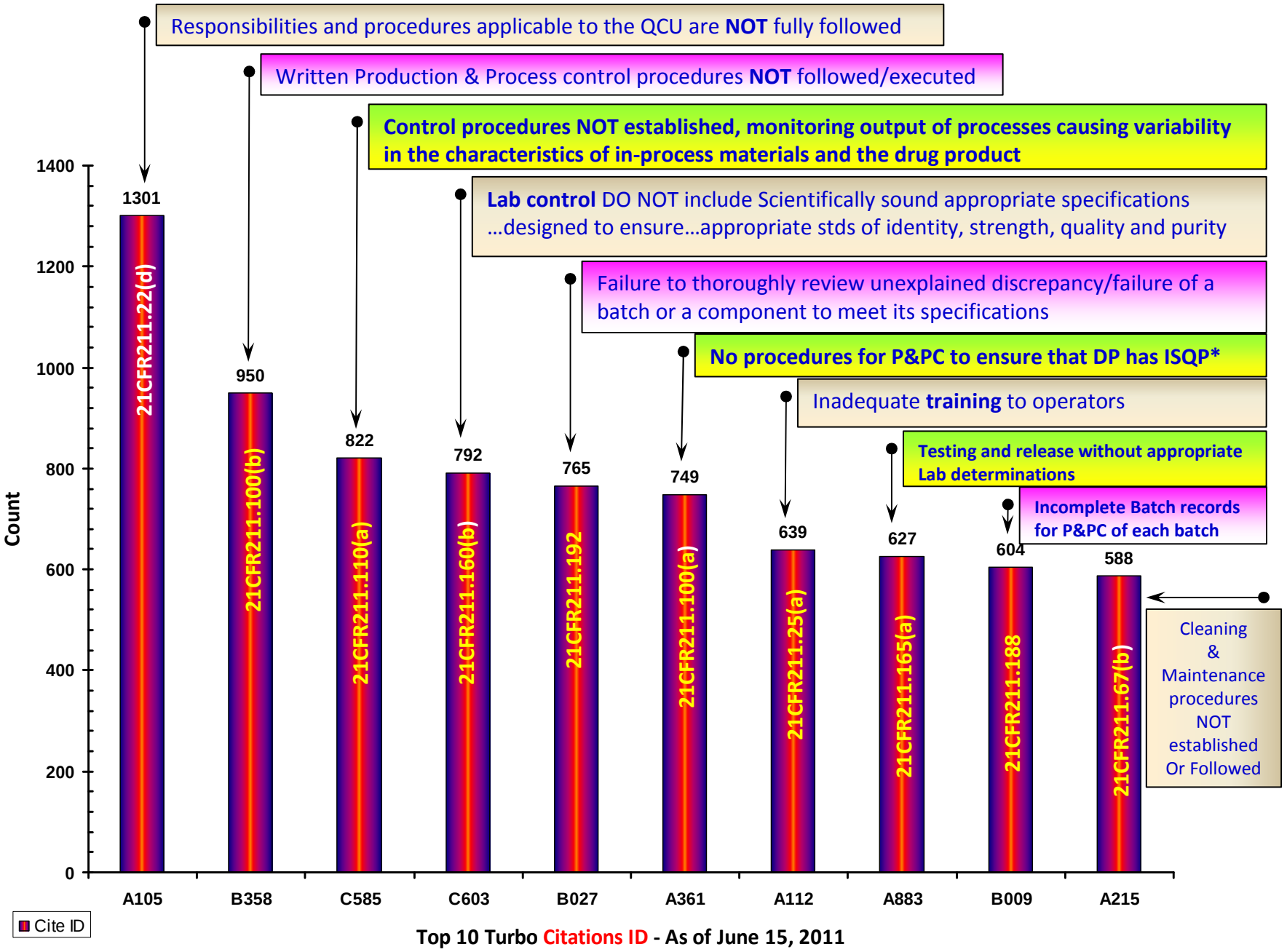


Quality Issues by Dosage Forms and Application Type



Human Drug Recall Reasons

- ***Top most common reasons for recalls***
  - **CGMP Deviations**
  - Impurities/Degradation Products
  - Failed USP dissolution test requirements
  - Presence of Foreign Substance(s)
  - Marketed without an approved NDA/ANDA
  - Defective Container
  - Labeling: Illegible, Incorrect or Missing Package Insert
  - **Super potent** (Single Ingredient Drug)
  - Miscalibrated and/or Defective Delivery System
  - **Sub potent** (Multiple Ingredient Drug)
  - **Super potent** (Multiple Ingredient Drug)



Top 10 Turbo Citations ID - As of June 15, 2011

***ISQP** = Identity, Strength, Quality, Purity

https://oeapps.ora.fda.gov/turboEIR/reports/reportcanned.cfm?selcanned=40

A snapshot…

Current state of Pharmaceutical Manufacturing

Operations in Pharmaceuticals Compare Poorly to Other Industries

*The pharmaceutical industry **lags** similar industries in key measures of operations performance, most notably in overall **equipment effectiveness, labor value-add time and direct/indirect labor ratio**, McKinsey's Ted Fuhr told the recent CDER on CMC conference in Bethesda, Md. Many of the shortcomings reflect poor quality practices and represent cost savings opportunities for the quality by design paradigm. Estimates are from McKinsey Operations Practice.*

Measure	Pharma	Auto	Aero-space	Computer	Consumer Packaged Goods
Overall equipment effectiveness	10% to 60%	70% to 85%	50% to 70%	80% to 90%	70% to 90%
Annual productivity improvement	1% to 3%	5% to 15%	5% to 10%	1% to 3%	5% to 15%
First-pass yield - zero defects	60%	90% to 99%	70% to 90%	90% to 99%	90% to 99%
Production lead times in days	120 to 180	1 to 7	7 to 120	5 to 10	3 to 7
Finished goods inventory in days	60 to 90	3 to 30	3 to 30	5 to 50	10 to 40
Labor value-add time	20%	60% to 70%	60% to 70%	60% to 70%	60% to 90%
Direct/indirect labor ratio	1:1	10:1	10:1	10:1	10:1

- The Gold Sheet, January 2009

Product Quality & Process σ

	Sigma	ppm Defects	Yield	Cost of Quality
Pharma	2σ	308,537	69.2%	25-35%
	3σ	66,807	93.3%	20-25%
	4σ	6,210	99.4%	12-18%
Semicon	5σ	233	99.98%	4-8%
	6σ	3.4	99.99966%	1-3%

- Doug Dean and Frances Bruttin, PwC Consulting, FDA Science Board Meeting, Nov 16, 2001

Putting in to perspective:

Getting right 99 percent of the time is =

- 20,000 lost articles of mail every hour
- 5,000 botched surgical procedures every week
- 4 accidents per day at major airports...

How Do we Move forward?

- **Need** a fundamental shift in our thinking how to
  - Design, manufacture, control and ensure Quality/parameters of Quality
  - Quantify parameters of Quality
  - Measure process performance
- **Minimize/mitigate** the risks to poor quality
  - Establish a Culture of Quality across the organization
  - Strive for an Operational Excellence (OpEx)
- **Leverage** OpEx knowledge from other industry sectors and adopt what works for your own mfg operations
- **Aim** for 6 sigma process performance and **strive** to outperform 6 sigma process under continual improvement when possible

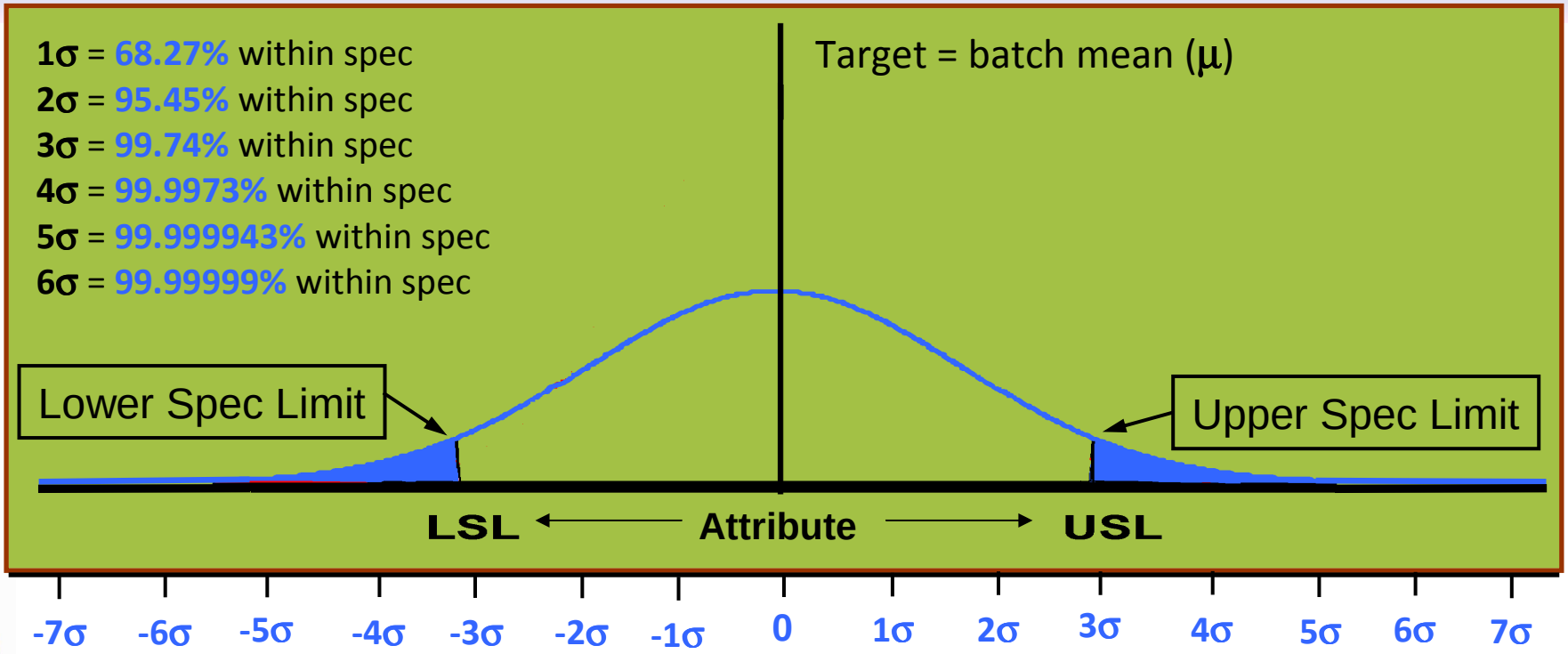
Some definitions of Quality

- Meets (USP) compendial standards for marketed drugs
- The suitability of either a drug substance or drug product for its **intended use**. This term includes such attributes as the *identity*, *strength*, and *purity* - (ICH Q6A)
- The degree to which the inherent properties of the product, system or process, fulfill requirements – (ICH Q9)
- Lack of adverse effect of the change on the *identity, strength, quality, purity, or potency* of the product as they may relate to the *safety* or *effectiveness* of the product - (inferred from CFR)
- Is not contaminated, mislabeled etc. and manufactured in compliance with cGMPs - (inferred from CFR)
- The state of having an acceptably low risk of failing to achieve the desired clinical attributes.
  - *J. Woodcock, M.D. (Amer. Pharm. Rev., November–December 2004)*

Quantitative Description of Quality – an Example

- **Confidence Statement** quantifying the "**true**" risk by use of applicable statistical tools, for example:
  - Representative Sample size, mean, and sample standard deviation
  - Confidence Level
    - Confidence Interval
    - Tolerance Interval
    - Prediction Interval
  - Process Capability (C_{pk})/Process Performance (P_{pk}) Indices
    - Lower Confidence Bound
  - Producer's risk (Alfa)
    - Process efficiency implication
    - Protection from waste (throwing away good product)
  - Consumer's Risk (Beta)
    - Safety and Efficacy implications
    - Protection from accepting poor quality product

Batch Quality & Variation (Std Dev)



- **In theory, (μ ± 3σ) = 99.74%** of units **within** the spec limits (LSL-USL)
- **0.26%** of the product (shaded area) **outside** the spec limits
- With few exceptions, by and large the **μ ± 3σ** has been the "**accepted**" quality standard for most of the mfg operations

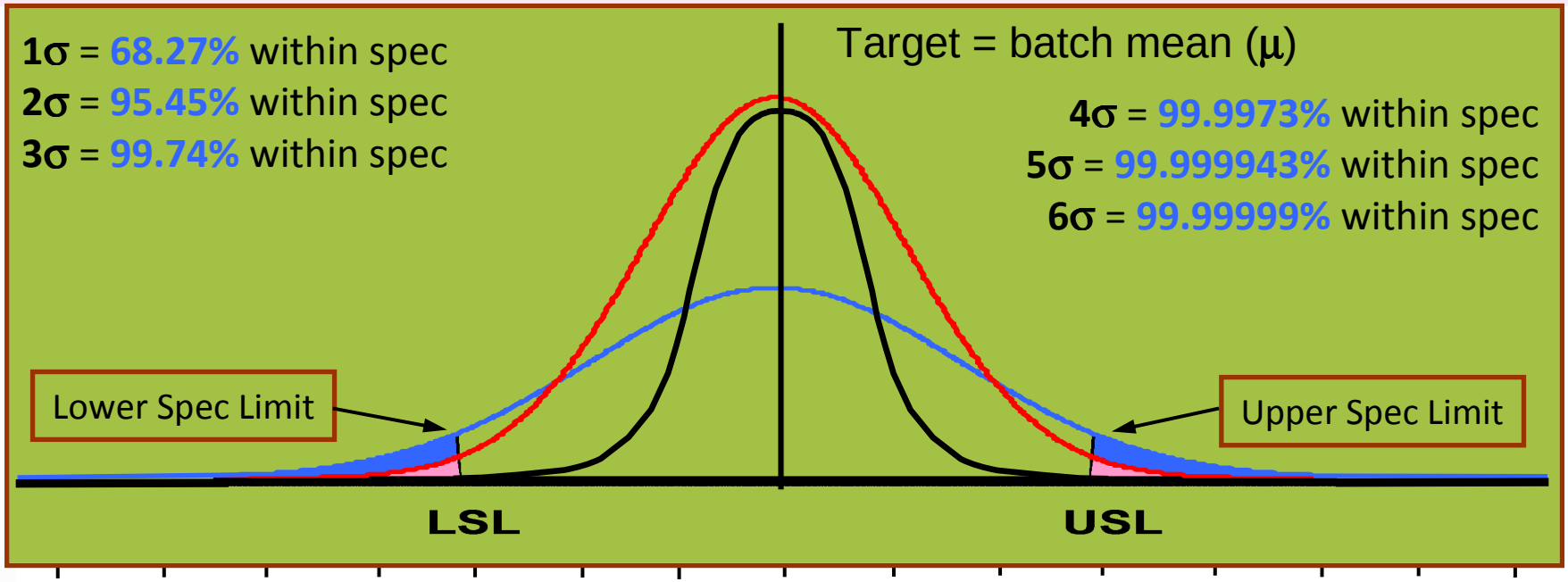
Numbers of tablets out-of-spec

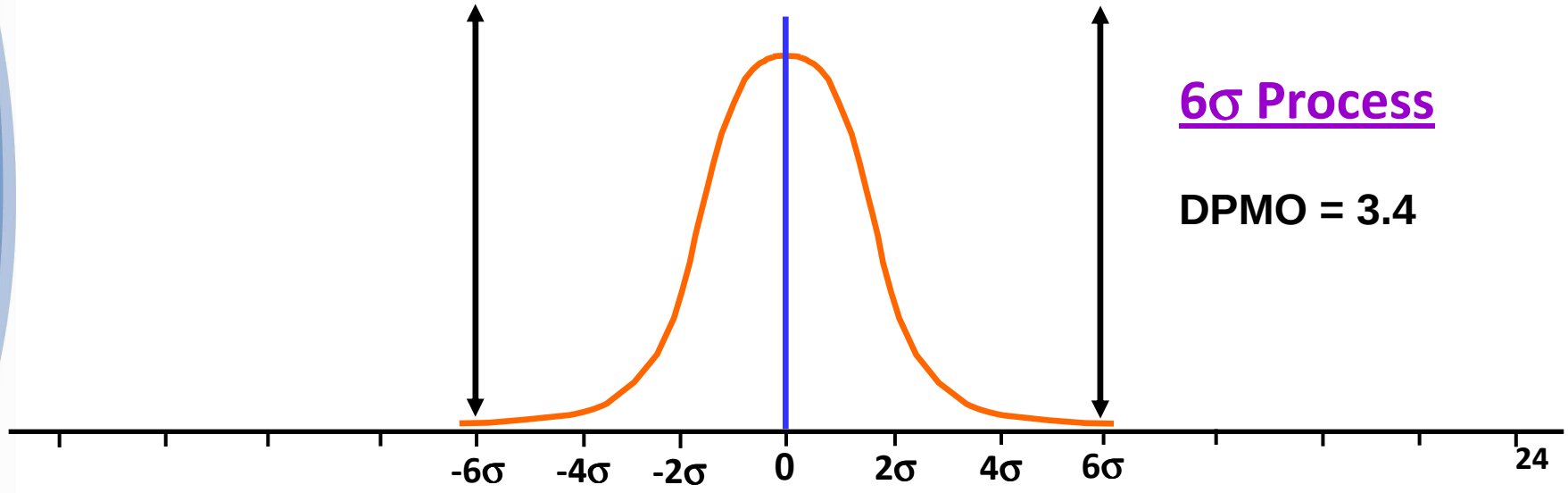
Spec range = 75-125%
batch size = 1,000,000 tablets

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

Dr. Janet Woodcock, April 9, 2002

Batch Quality & variation





6σ Process

DPMO = 3.4

What Does that Mean?
Process Capability/Performance

Process Sigma Level	Total Sigma Spread	Defects per Million Observations (DPMO)	Success rate (RTY)
0σ	-	933,000	7%
1σ	2σ	691,000	31%
2σ	4σ	309,000	69.10%
3σ	6σ	66,800	93.32%
4σ	8σ	6,210	99.38%
5σ	10σ	233	99.98%
6σ	12σ	3.4	100.00%

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Pharmaceutical CGMPs for 21st Century
A Risk-based Approach

- Initiative began in 2002
- Purpose of the initiative was to enhance and modernize the regulation of pharmaceutical manufacturing and product quality
- **Guiding principles**:
  - Risk-based orientation
  - Science-based policies and standards
    - Facilitates innovation
  - Integrated quality management systems orientation
    - Adoption of Quality Systems model for Agency's operations
    - CMC and CGMP Inspection programs
  - International cooperation (and collaboration)
    - ICH
    - Pharmaceutical Inspection Cooperation Scheme (PIC/S)
  - Strong public health protection

http://www.fda.gov/Cder/gmp/gmp2004/GMP_finalreport2004.htm

Pharmaceutical CGMPs for 21st Century

Objectives:

- Encourage the early adoption of **new technological** advances
- Facilitate adoption of **modern quality management** techniques to pharmaceutical production and quality assurance
- Encourage implementation of **risk-based approaches** both by industry and Agency
- Ensure that regulatory ***review***, ***compliance***, **and** ***inspection*** policies are driven by state-of-the-art pharmaceutical science
- Enhance the consistency and coordination of FDA's drug quality regulatory programs by
  - Integration of quality systems model into the Agency's business processes and regulatory policies concerning review and inspection activities

Pharmaceutical CGMPs for 21st Century

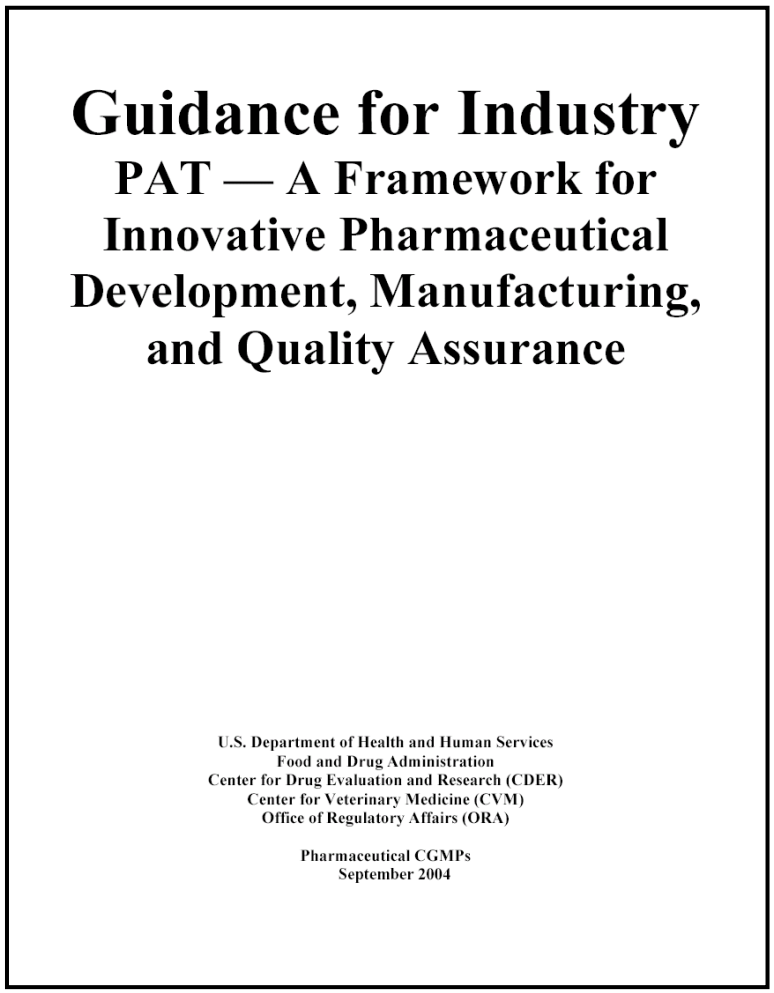
Some Key Accomplishments:

- Guidance documents Issued
  - **PAT** – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, Sept 2004
  - Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP, Jan 2006
  - Quality Systems Approach to Pharmaceutical CGMP Regulations, Sept 2006
  - CGMPs for Phase I Investigational Drugs, July 2008
  - ICH Q8, Q9, Q10
  - **Process validation**, Jan 2011
- Ongoing Quality Management Systems implementation
- Ongoing Implementation of PAT and Quality by design initiatives
- Ongoing Pharmaceutical Inspectorate Program
- **Voluntary Consensus Standards participation** (per OMB Circular A-119)
- Scientific Collaboration Activities (e.g., CRADA projects)

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm

PAT Framework Guidance

- Draft Guidance in Sept 2003
- Final guidance in Sept 2004
- An Enabling Framework approach
  - For innovation in development, manufacturing and quality assurance
- Not a "**how to**" guidance, but emphasis on
  - **Team approach** to review and inspection with joint training, certification, expert consultant and research support
  - **Systems approach** to provide flexibility to manufacturing and regulation
  - **To address** areas of regulatory uncertainty and fear
- Expanded to Biotech products



http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070305.pdf

PAT Regulatory Framework Tenet

Quality

cannot be **tested**

into products

It should be **built-in**

or

should be **by design - QbD**

PAT Framework: QbD Requirements

QbD requires comprehensive understanding of:

- The intended therapeutic objectives; patient population; route of administration; and pharmacological, toxicological, and pharmacokinetic characteristics of a drug
- The chemical, physical, and biopharmaceutical characteristics of a drug
- Design of a product and selection of product components and packaging based on drug attributes listed above

What is PAT ?

- **Process analytical technology (PAT)** is:
  - A system for *designing*, *analyzing* and *controlling* manufacturing
  - through ***timely*** measurements (i.e., during processing) of *critical quality* and *performance* attributes of raw and in-process materials and processes
  - with the goal of **ensuring** final product quality

- **ICH, ASTM, and PAT**

- The term, ***analytical*** in Process Analytical Technology is viewed broadly to include ***chemical, physical, microbiological, mathematical***, and ***risk analysis*** in an **integrated** manner.

PAT Framework…

- **scientific**, and **risk-managed** framework
  - founded on **process understanding**
  - support **innovation** and **efficiency** in pharmaceutical development, manufacturing, and quality assurance
  - facilitate **risk-managed** **regulatory decisions**
    - both by the Industry and the Agency

- The framework has **two** components:
  - a set of **scientific principles and tools** supporting innovation
  - a **strategy** for **implementation** that will accommodate innovation

PAT Framework: Principles &Tools

- **PAT Tools supporting innovation**
  a. Multivariate tools for design, data acquisition and analysis
  b. Process analyzers
  c. Process control tools
  d. Continuous improvement and knowledge management tools

- **Scientific Principles**
  1. Risk-Based Approach
  2. Integrated Systems Approach
  3. Real Time Release

- An appropriate **combination** of *some*, or *all*, of these tools can be applied to…
  - **single**-unit operation,
  - **more than one** Unit Operation or
  - an **entire** manufacturing process and its quality assurance

PAT Framework: PAT Tools

- Multivariate tools for design, data acquisition and analysis include
  - multivariate mathematical approaches, e.g.,
    - statistical design of experiments (sDoE)
    - response surface methodologies (RSM)
    - process simulation
    - pattern recognition tools
    - statistical evaluation of model predictions
  - knowledge management systems
  - design of manufacturing processes using principles of engineering, material science, and quality assurance

PAT Framework: PAT Tools

- **Process analyzers**:
  - Can provide nondestructive measurements
  - contain information related to biological, physical, and chemical attributes of the materials being processed
  - **At-line**: Measurement where the sample is removed, isolated from, and analyzed in close proximity to the process stream.
  - **On-line**: Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream.
  - **In-line**: Measurement where the sample is not removed from the process stream and can be invasive or noninvasive

PAT Approach

- Product quality and performance
  - Ensured through **design** of effective and efficient (well understood) manufacturing processes
- Product and process **specifications**
  - Based on a *mechanistic* understanding
  - How formulation and process factors affect product performance
  - Process knowledge becomes the basis for specifications
- Continuous ***real time*** control of manufacturing, quality assurance and opportunity for *real time release* under the oversight of *Quality Unit*
  - Output validates the performance of the process
  - Each batch is an opportunity for optimization

PAT Approach..

- Goal is to move away from uncertainty-based (current) state to a risk-managed (desired) state to
  - Support relevant regulatory policies and procedures
  - Establish relevant and effective Standards

- For Any Process…
  - Minimize (or Reduce) Uncertainty
  - Quantify Risk (to product quality)
  - Manage Variability (feed forward and feed back control)
  - Capture, retain and utilize knowledge

PAT Regulatory Framework

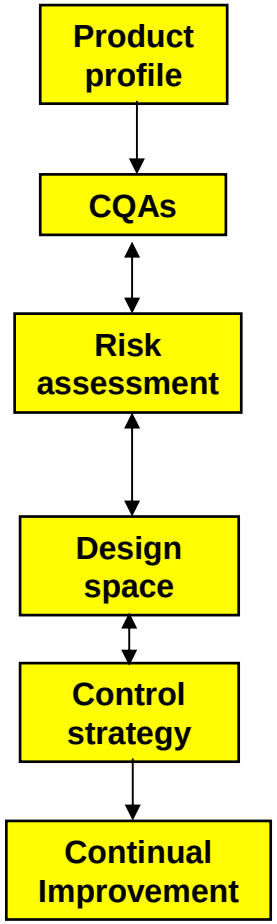
Summing-up

- The **cornerstone** of Agency's overarching drug quality initiative: *Pharmaceutical CGMPs for the 21st Century - A Risked Based Approach* to
  - Support *innovation* and *efficiency* in pharmaceutical development, manufacture and quality assurance
  - Provide a regulatory framework for implementation
  - Alleviate industry's perceived concern of regulatory hurdles for timely approval
- The **central thesis** of this regulatory framework guidance is that
  - A holistic approach to identifying sources of **variability** (in raw materials, in-process materials and process factors)
  - Managing such **variability** through **process understanding** and **risk-mitigating control strategies** can improve productivity and product quality throughout the product life-cycle.
  - Quality cannot be tested into products; it should be built-in (i.e., by design)
- In that sense, the PAT guidance truly is an **enabler** of the
  - ICH Pharmaceutical Quality Vision
  - Most visionary core regulatory document, supportive of and complementary to
    - both ICH quality guidelines (Q8, Q9 and Q10)
    - Agency's Process Validation guidance

What is Quality by Design?

- **QbD** as per ICH Q8(R):
  - A systematic approach to drug **development**
  - Begins with predefined objectives
    - Product design – therapeutic profile
    - Process design
  - Emphasizes **product** and **process understanding** and **process control**
  - Employs sound science and quality risk management principles

Example of QbD Approach (Q8R)



- Target the product profile
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

- Christine Moore, Acting Deputy Director, ONDQA, IFPAC-2009

PAT and QbD - demystified

"....if you truly understand FDA's new paradigm, you'd understand that **PAT** is really the **underpinning** of the entire concept of **Quality by Design**, that is **understanding process**."

- Helen Winkle, Director, OPS, CDER, FDA

- PAT facilitates the implementation of QbD
- QbD and PAT = Tremendous benefits to industry, FDA and the public!

- Helen winkle, Director, OPS, IFPAC-2010, February 2, 2010

How Does PAT Fit with QbD?

- PAT and QbD are two sides of a coin and share similar goals
  - Process understanding
  - Process monitor and control
  - Risk-based decisions
- PAT generates *Process Understanding* and provides a practical mechanism for implementing a control strategy
  - a **crucial** component for the foundations of QbD
- PAT offers perhaps the best mechanism and a regulatory framework for **implementing** *continuous improvement* through product lifecycle
- QbD implementation without PAT is like navigating a cruise ship blindfolded without any controls through icebergs….
  - Any success in sailing through and survive will purely be a gamble and by chance!
  - If you do not monitor and measure – you can not control the process

PAT, QbD and Process Validation

- Goal of process validation (**PV**) is to demonstrate with sufficiently rigorous scientific evidence that the designed commercial process
  - works as intended
  - remains under state of control
  - is capable of reliably delivering quality product
- Product and process knowledge obtained through adoption of
  - systematic approaches such as QbD and PAT principles during development can establish the foundation of commercial process design

Process Validation –
A Lifecycle Approach

- Overall validation is not "completed" but **ongoing**
- Necessitates comprehensive process design to understand **sources of variability** and achieve process understanding
- Incorporates risk management
- Recognizes that more knowledge will be gained post commercialization

- Requires **statistically representative samples**
- It is, has been, and will remain a legally enforceable GMP requirement

Guidance for Industry: Process Validation: General Principles and Practices, January 2011
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf

Process validation - A lifecycle approach

- ***Stage 1, Process Design:***
  - Lab, pilot, small scale and commercial scale studies to **establish** process; process/product development
- ***Stage 2, Process Performance Qualification (PPQ)*:**
  - Facility, utilities and equipment
  - Performance Qualification (confirm commercial process design)
- ***Stage 3, Continued Process Verification (CPV):***
  - Monitor, collect information, assess during commercialization
  - Maintenance, continuous verification, process improvement
- Requires **Statistical Quality Control** criteria for
  - Appropriate acceptance or rejection levels

Guidance for Industry: Process Validation: General Principles and Practices, January 2011
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf

Process validation-A lifecycle approach

Stage 1: Process Design

- The **goal** of this stage is to **design** a process
  - suitable for routine commercial manufacturing that can consistently deliver a product that meets its critical quality attributes
  - important to understand the degree to which models represent the commercial process
- Control of the process through operational limits and in-process monitoring is essential
  - where the product attribute is not readily measurable due to limitations of sampling or detectability (e.g., viral clearance or microbial contamination), or
  - when intermediates and products cannot be highly characterized and well-defined quality attributes cannot be identified.
- Use of more advanced strategies, such as Process Analytical Technology (PAT)*, is encouraged

*PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, USFDA, Sep 2004

Process validation-A lifecycle approach

Stage 2: Process Qualification

- Two elements:
  - **Design** of the *facility* and **qualification** of the *equipment* and *utilities*, and
  - **Process Performance Qualification** (PPQ) confirming the commercial process design
- manufacturer is expected to have accumulated enough data and knowledge about the commercial production process
  - must follow CGMP-compliant procedures and successful completion necessary to support post-approval commercial distribution
- Products manufactured during this stage, if acceptable, can be released

Process validation - A lifecycle approach

Stage 3: Continued Process Verification

- The **goal** of the third validation stage is to **continually assure** that the process remains in a **state of control** (the validated state) during commercial manufacture
- Recommends **continued** monitoring and/or sampling
  - at the level established during the process qualification stage until sufficient data is available to **generate significant variability estimates**
  - Once the variability is known, sampling and/or monitoring should be adjusted to a **statistically appropriate and representative level**
- Process **variability** should be periodically assessed and sampling and/or monitoring adjusted accordingly
- Requires Statistical Quality Control criteria for
  - Appropriate acceptance or rejection levels

Relevant CGMP Sections within PV Guidance

Emphasizing importance and application of Statistics:

- 210.3 (b) (20)
  - relates to , “Acceptance Criteria”
- 211.84 (b)
  - relates to “Selection of Representative samples”
- 211.110 (a)
  - relates to “…sampling, tests, and controls to validate performance of the process causing variability….”
- 211.110 (b)
  - relates to “…derivation of in-process and final specifications based on previous acceptable process average and process variability estimates determined by….suitable statistical procedures….”
- 211.165 (d)
  - relates to “statistical quality control criteria to include appropriate acceptance and/or rejection levels”

From the PV Guidance:

- "We recommend that a statistician or person with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures used in measuring and evaluating process stability and process capability.[18]"
- "We recommend that the manufacturer use **quantitative, statistical methods** whenever appropriate and feasible.
- Scrutiny of intra-batch as well as inter-batch **variation** is part of a comprehensive continued process verification program under § 211.180(e)."
- **Footnote (18)** refers to ASTM Standards that may be useful
  - **ASTM E2281-03**: "Standard Practice for Process and Measurement Capability Indices,"
  - **ASTM E2500-07**: "Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment," and
  - **ASTM E2709-09**: "Standard Practice for Demonstrating Capability to Comply with a (Lot) Acceptance Procedure."

Continuous Process Verifications
Why Use Consensus Standards?

- Consensus Standards:
  - ANSI, ASTM, ISO
  - Peer recognized and go through a critical review process by experts
- OMB Circular A-119
  - "…this Circular **directs** agencies to use **voluntary consensus standards** in lieu of government-unique standards except where inconsistent with law or otherwise impractical."
    - http://www.whitehouse.gov/omb/circulars/a119/a119.html
- Some Applications of ASTM Standards:
  - Selection of and justification for chosen Sampling plans
  - justify a position that the process is in statistical control
  - Explain Capability analysis from a specific manufacturing process
  - Determine whether established regulatory limits or targets have been met
    - Test methods, Sampling procedures, Protocols

http://standards.gov/standards_gov/index.cfm

Consensus Standards and FDA's authority

- "This policy does not preempt or restrict agencies' authorities and responsibilities to make regulatory decisions authorized by statute."

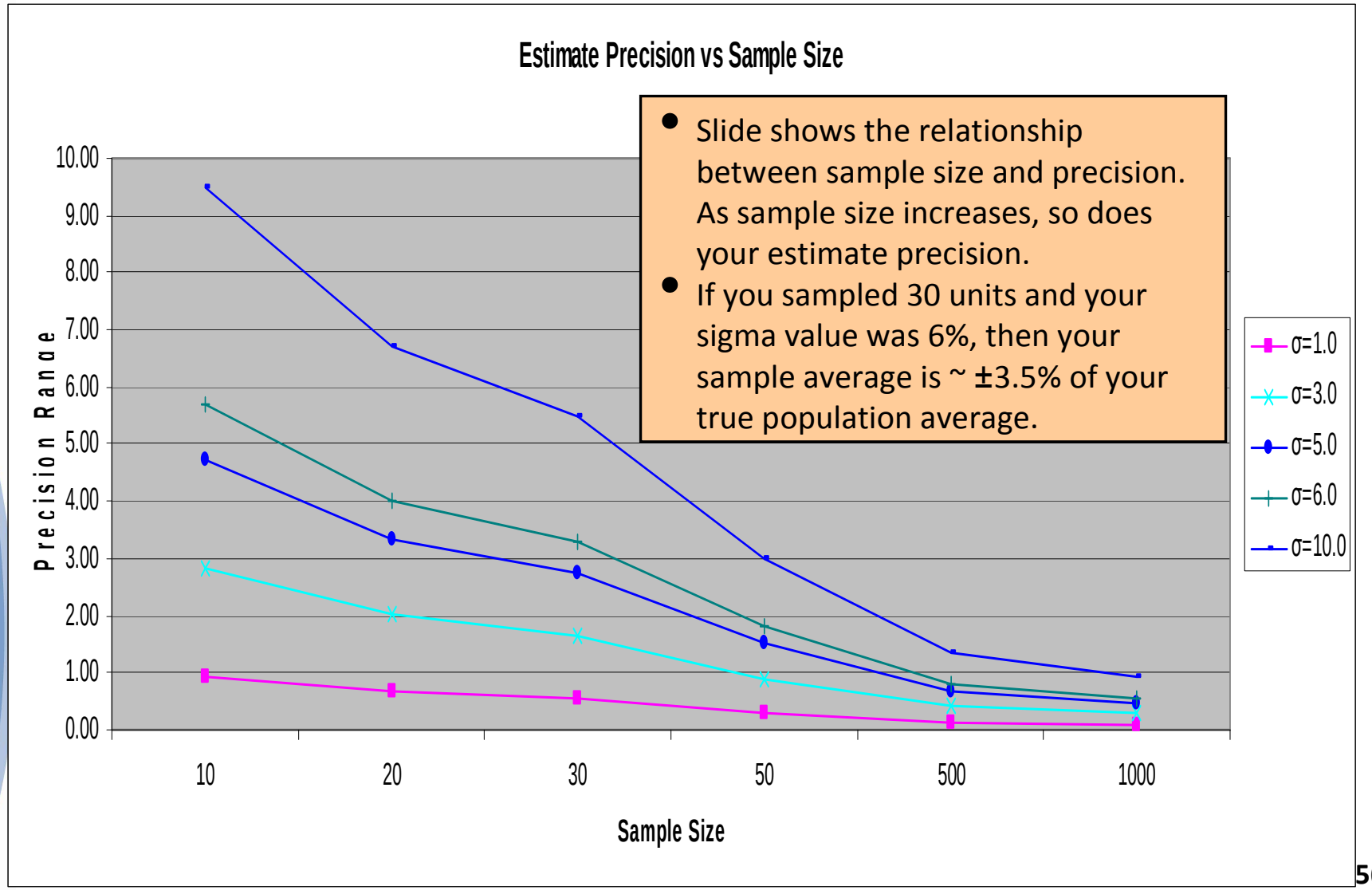
- These include
  - "Determining the level of acceptable risk"
  - "Setting the level of protection"
  - "Balancing risk, cost and availability of technology in establishing regulatory standards."

Some Useful ASTM Standards for Sampling / Statistics

E105 - 10:	Probability Sampling Of Materials
E122 - 09:	Calculating Sample Size to Estimate, With Specified Precision, the Average for a Characteristic of a Lot or Process
E141 - 10:	Acceptance of Evidence Based on the Results of Probability Sampling
E178 - 08:	Dealing With Outlying Observations
E2709 - 10:	Demonstrating Confidence in Complying with Acceptance Procedures
E2587 - 10:	Statistical Process Control
E2334 – 09:	Confidence in Attribute Sampling
E2281 – 10:	Process Capability

ASTM E122

Standard Practice for Calculating Sample Size to Estimate, With Specified Precision, the Average for a Characteristic of a Lot or Process

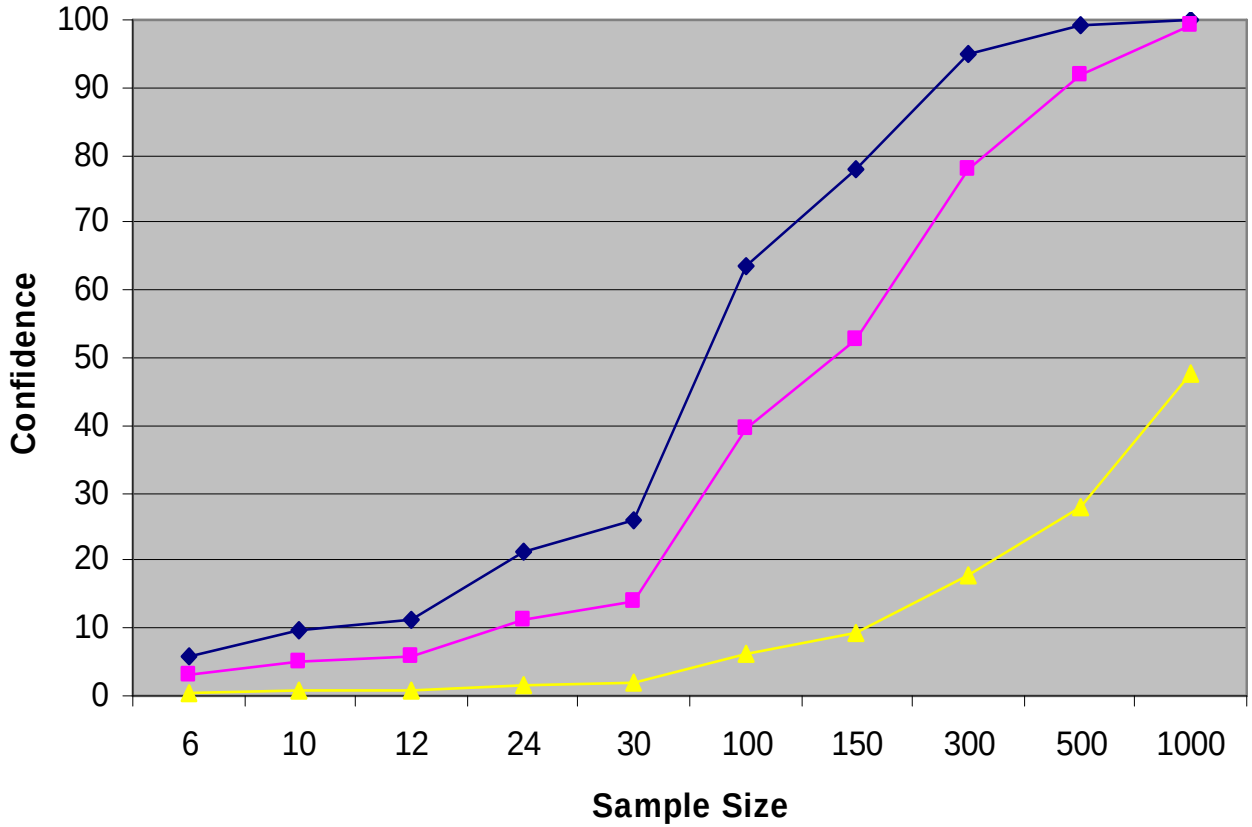


- Slide shows the relationship between sample size and precision. As sample size increases, so does your estimate precision.
- If you sampled 30 units and your sigma value was 6%, then your sample average is ~ ±3.5% of your true population average.

ASTM E2334

Setting an Upper Confidence Bound For a Fraction or Number of Non-Conforming items, or a Rate of Occurrence for Non-conformities, Using Attribute Data, When There is a Zero Response in the Sample

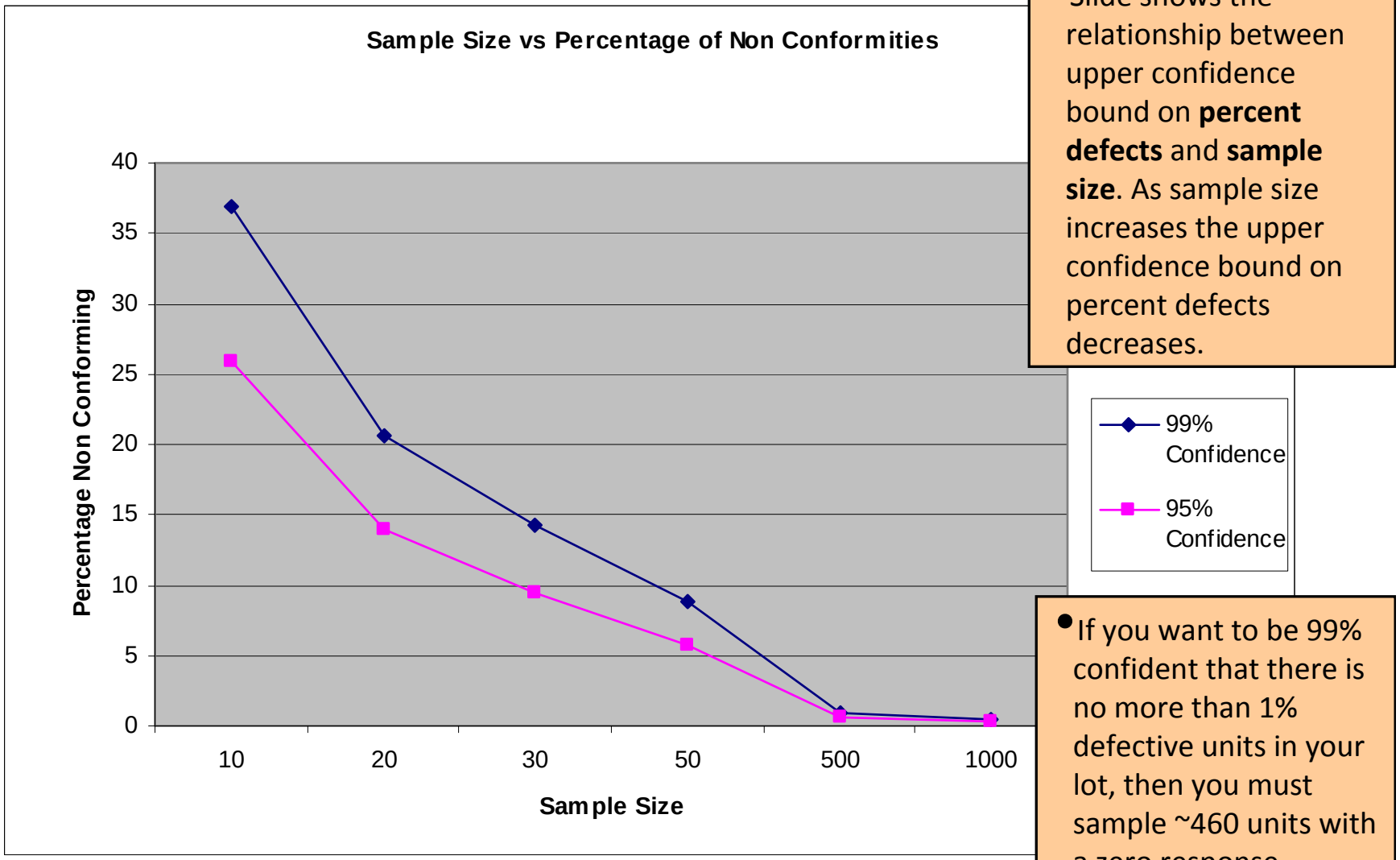
- Slide shows the relationship between **Confidence** and **Sample Size**. As sample size increases, so does your confidence.



- If you desire a percent defective of no more than 0.5% and sample 30 units and no failing units were observed, then you are only ~15% confident that your lot has no more than 0.5% defects

ASTM E2334

Setting an Upper Confidence Bound For a Fraction or Number of Non-Conforming items, or a Rate of Occurrence for Non-conformities, Using Attribute Data, When There is a Zero Response in the Sample



- Slide shows the relationship between upper confidence bound on **percent defects** and **sample size**. As sample size increases the upper confidence bound on percent defects decreases.

- If you want to be 99% confident that there is no more than 1% defective units in your lot, then you must sample ~460 units with a zero response

ASTM E2709

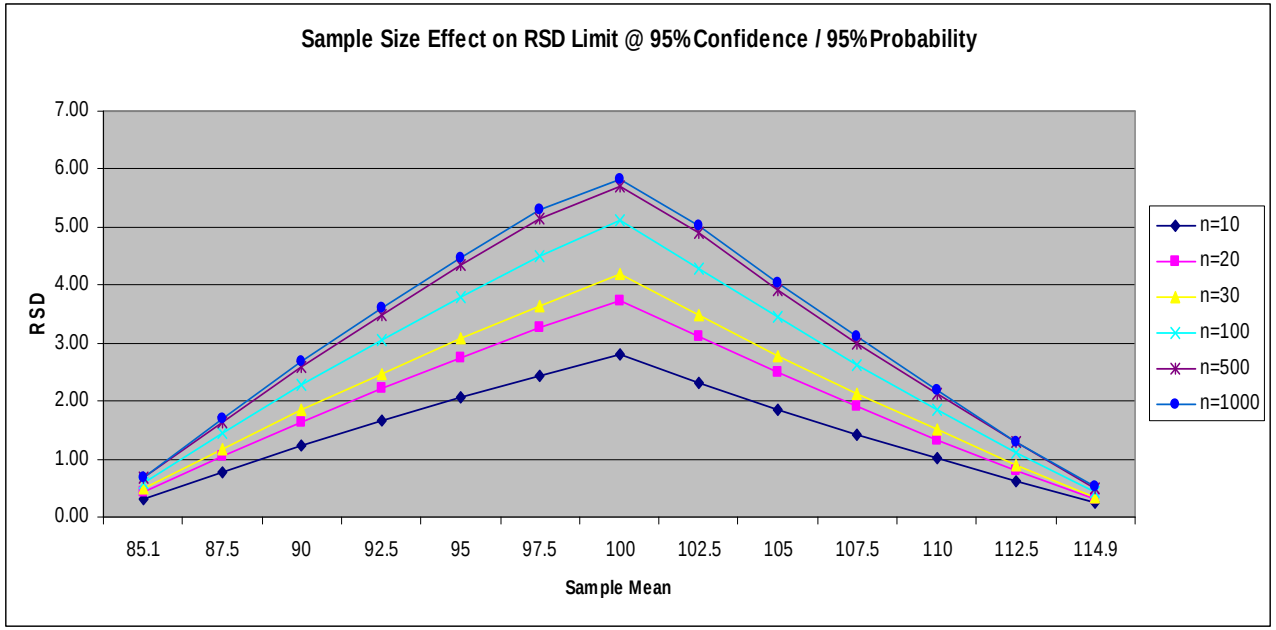
Standard Practice for Demonstrating Capability to Comply with Acceptance Procedure

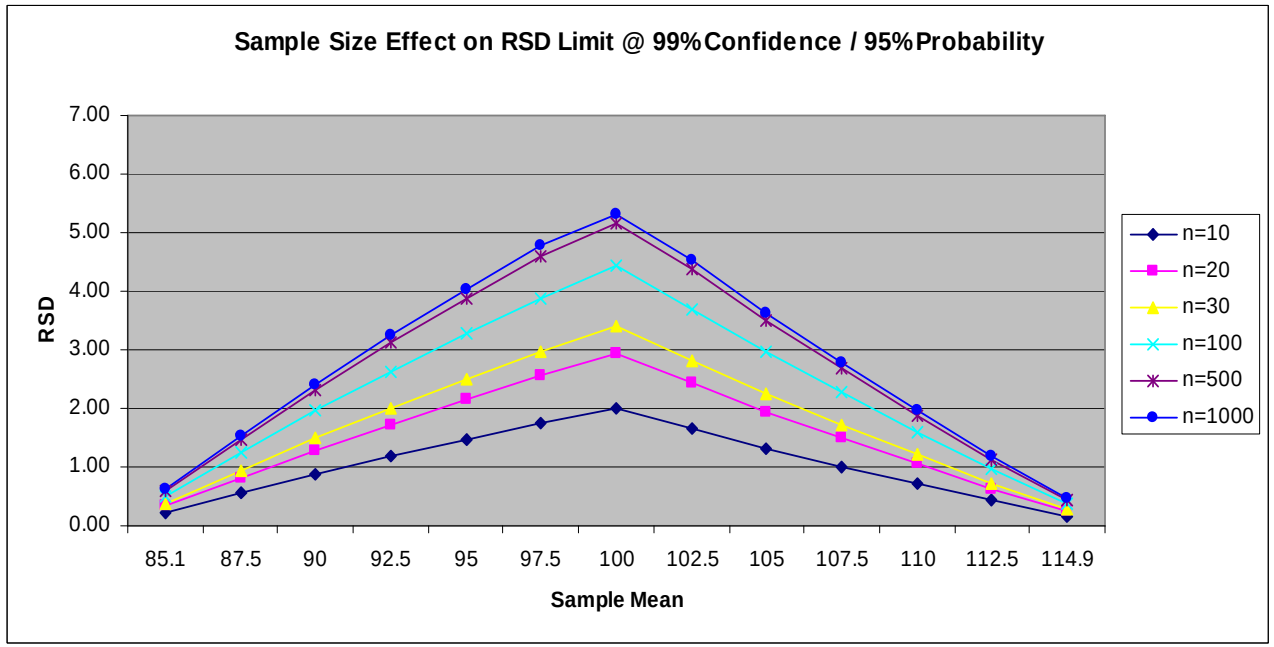
One tool to analyze Uniformity of Dosage Units

- Slide shows the relationship between **sample size** and **tolerance for variability**. As sample size increases, so does the tolerance for variability

For example:

- If you sampled 30 units and had a sample mean of 95%, then
- the maximum RSD value for those 30 units would be ~3.0% to be 95% confident that there is at least a 95% probability a future sample from the lot would pass the USP UDU test.





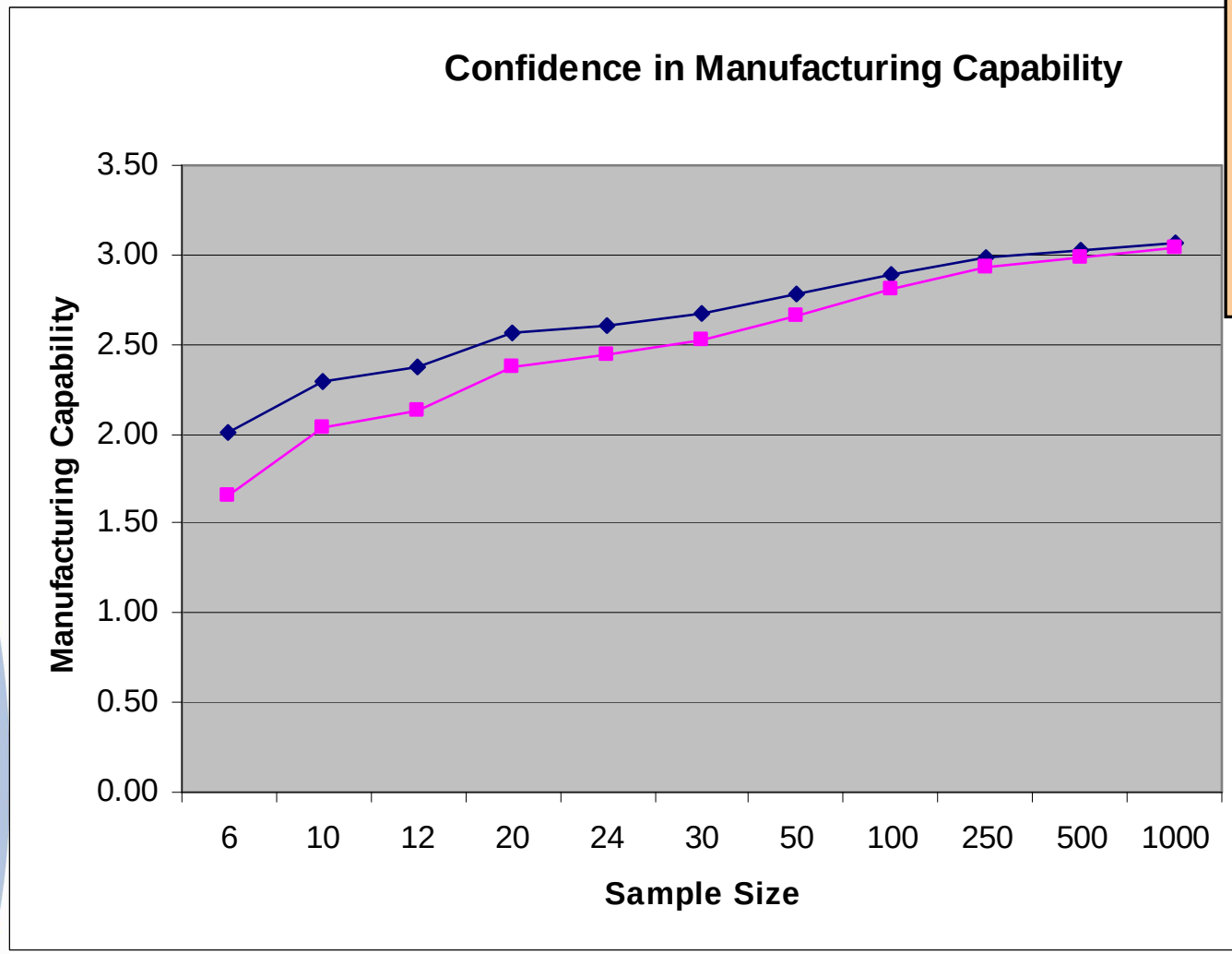
E2709: Example of Utility

- Product: X
- Q value: 70%
- Background: Firm was having recall issues due to dissolution failures on stability. Recalls branch requested dissolution data.

Unit 1	Unit 2	Unit 3	Unit 4	Unit 5	Unit 6	Unit 7	Unit 8	Unit 9	Unit 10	Unit 11	Unit 12	Mean	SD	RSD	USP - PASS or FAIL	ASTM E2709 Probability @ 95% confidence
96%	72%	82%	74%	102 %	70%	97%	63%	71%	78%	74%	60%	**78%**	**14%**	**17%**	**Pass**	**0.14%**
77%	73%	90%	95%	92%	59%	73%	94%	60%	72%	62%	85%	**78%**	**13%**	**17%**	**Pass**	**0.14%**

ASTM E2281

Standard Practice for Process and Measurement Capability Indices

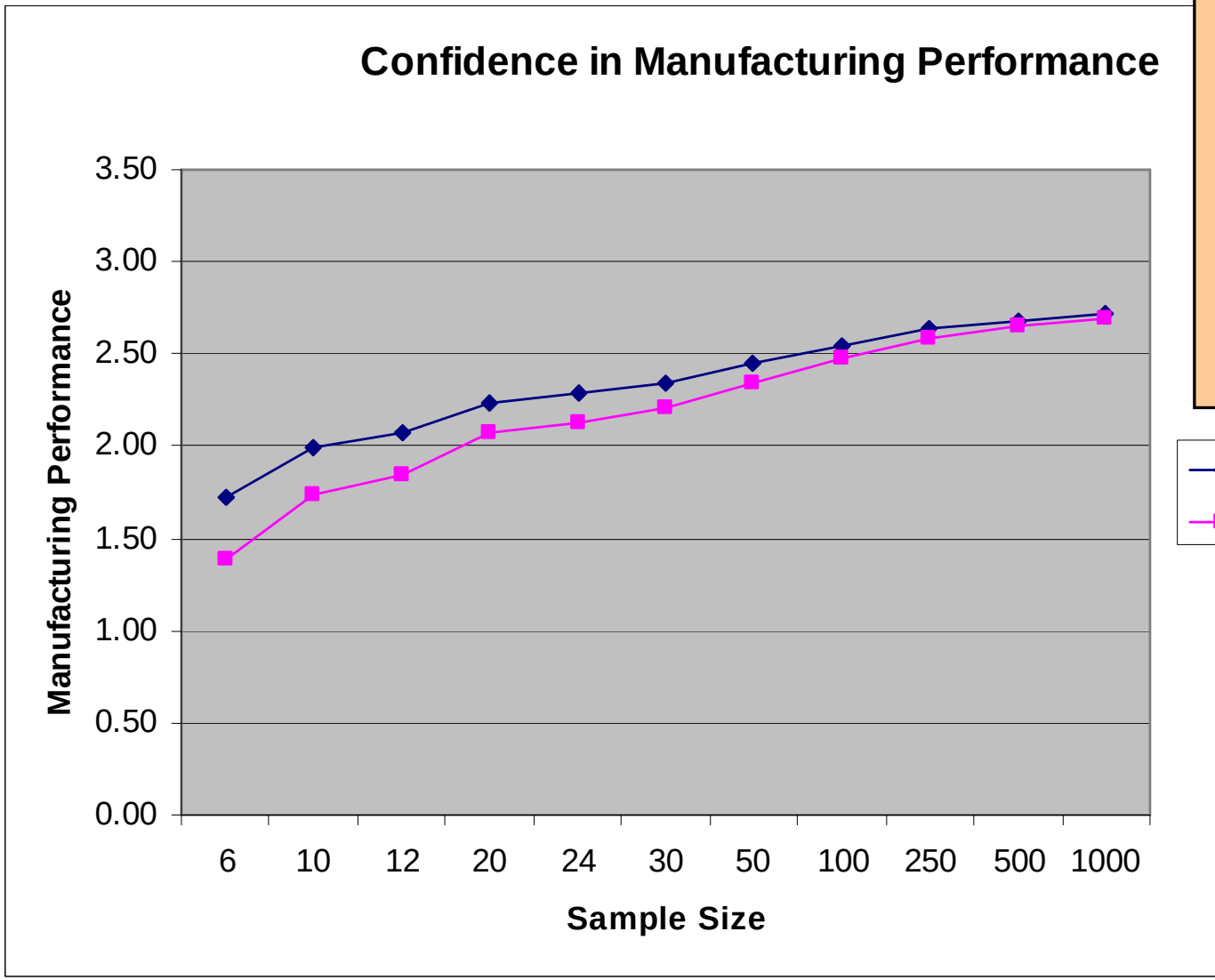


- Slide shows the relationship between a reported Process Capability Index (Cpk (3.14)) and sample size. As sample size increases, so does the reported Cpk.

- If you sampled 30 units and estimated a Cpk of 3.14, then the value reported should be ~2.5 (that is I am 99% confident that the Cpk for my process is at least 2.5).

ASTM E2281

Standard Practice for Process and Measurement Capability Indices



- Slide shows the relationship between a reported Process Performance Index (Ppk (2.79)) and sample size
- As sample size increases, so does the reported Ppk.

- If you sampled 30 units and estimated a Ppk of 2.79, then the value reported should be ~2.2 (that is I am 99% confident that the Ppk for my process is at least 2.2).

Summing up…

- We discussed today utility of some ASTM standards
  - Some Statistical tools to consider with respect to defining product quality and process performance.
  - Use of statistics to quantify relationship between confidence associated with attribute, variable and or parameter of interest with respect to the sample size collected.
    - To make inferences on untested units.
    - Can be applied to In-coming, In-process, or Finished samples.
    - Can be used for real time manufacturing and or annual/periodic product reviews.
- Other Statistical Tools
  - Sampling plans
    - Do they describe Consumers Risk?
    - How are true defect rates calculated to use a particular sampling plan?
  - Confidence, Prediction, and Tolerance Intervals

Summing up…

In a nutshell:

- Statistics is a tool to elicit information to confirm that a specific manufacturing process is producing quality product.
- The specific statistical tools and analysis depends on what variables, attributes, parameters are being used to monitor process performance and product quality.
- The preceding examples are just one set of statistical methods available to monitor and demonstrate process performance and product quality.

PAT, QbD and PV

If **QbD** is the **vision** for 21st Century Pharmaceuticals….

PAT Framework

(Process understanding, monitoring and control)

And

Process Validation & Continuous Process verification

(State of Control)

can be considered as

an enabling, **flexible regulatory**

Roadmap

to achieve this vision

from development

through **Product Life Cycle**

Closing Remarks

- Successful implementation of **QbD** and **PAT** under **FDA's CGMP program** relies on industry's adoption of innovative approaches to
  - **development** that are based on sound (material) science, engineering, and quality risk management principles
  - **manufacturing process** through
    - process understanding and timely process monitoring
    - implementing risk-commensurate process control strategy
      - to prevent/mitigate risk to product quality and performance
  - **quality assurance** through
    - Validated processes (under state of control)
    - Continuous Process/Quality Verification
    - Real Time Release

Closing Remarks..

- Agency's guidance documents (PAT, PV, QS) and ICH quality guidelines [Q8(R2), Q9, Q10] **collectively** provide sufficiently flexible **regulatory framework** and tools to adopt QbD and PAT in Pharmaceutical manufacturing
- Existing CGMP regulations being **minimal** requirement are sufficiently flexible to support and encourage QbD/PAT implementation in manufacturing
- Agency's CGMP program is committed to facilitating innovation in pharmaceutical manufacturing
- An effective **Pharmaceutical Quality System** is the **KEY** component
  - to ensure product quality and performance and
  - for an efficient Pharmaceutical Sector in a global economy

Quality Assurance Under CMC & GMP

Quality Assurance Under CMC & CGMP

In theory, there is no difference between theory and practice. **But**, in practice, there is.

Acknowledgements

- U of Heidelberg Organizing Committee
- Karthik Iyer and Alex Viehmann

Thanks

Questions ???

CGMP Contact information…

CGMP Subject Contacts: http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm096102.htm

Questions and Answers:

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124740.htm