Technology Transfer

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"Technology Transfer"

TECH TRANSFER TEAM

- Office of Corporate Relations
- University Research Park
- WARF (Wisconsin Alumni Research Foundation)

- Licensing of intellectual property
  - Transferring the results of University applied and direct research to solve real-world problems

Outline

- Introduction to Technology Transfer
- Manufacturing Considerations
  - Facilities
  - Equipment
  - Scale-up
  - (pre-) Validation
- Technology Transfer Guidance
  - *Who is responsible for technology transfer?*
  - *When does it occur during development?*

Definitions

- Technology Transfer
  - Drug Substance manufacturing process transfer
  - Analytical method transfer
  - Drug Product manufacturing process transfer
- Scale-up
  - Increase in batch size from development scale to pilot scale to full scale manufacturing
- Validation
  - Documented evidence that a system is designed to assure that the process consistently performs as it purports to do.

Technology Transfer

The ultimate test of scientific reproducibility:

The successful transfer of production responsibilities

from development scientists to production personnel

When does Tech Transfer occur?

Depending on organization, *frequently!*

- Preformulation
  - Pre-clinical Formulation
    - Phase 1/2a Formulation
      - Phase 2b/3 Formulation

Development

↓

Production Support

↓

Manufacturing/Validation/QC

What Technologies are Transferred?

- Development
  - Chemical Development
    - Active Pharmaceutical Ingredient (API)
  - Analytical Development & Clinical QA
    - Methods & Specifications
  - Product Development
    - Dosage Form Development
    - Manufacturing Process Development
- Manufacturing
  - Drug Substance Manufacturing Site
    - Active Pharmaceutical Ingredient (API)
  - QA / QC
    - Methods & Specifications
  - Drug Product Manufacturing Site
    - Manufacturing Process Validation

Successful Tech Transfer

- Process must be well defined
  - Identify areas of criticality, sensitivity and/or weakness
  - Analyze operational boundaries, risks
- Must be robust in R&D if expected in Production/QC
- Minimize process “improvements”
  - i.e. changes
- Members of Development and Production work jointly during initial run(s)/campaign

21 CFR Subpart F § 211.100(a)

...to assure...

- Identity
- Strength
- Quality
- Purity
- Functionality

...of drug product.

What are the challenges?

- **Technological**
  - Facilities
  - Equipment
  - Unit operations/processes
  - Overall process train
    - *no two are the same!*
- **Personnel**
  - Communication across organization
  - Remote sites
  - Historically, differences in mindset:
    - R&D = Creative, responsible for inventing change
    - Process Development = Problem solvers, troubleshooters
    - Production/QC = Detail-oriented, disciplined, observant
      - "Quality by Design" demands innovation throughout!

Linking Material Attributes…

- Excipient Functionality
  - *Proposed* USP General Chapter
    - <1059> Excipient Performance
      - Pharmacopeial Forum 33(4), 2007
  - PhEur General Chapter
    - Functionality Related Characteristics (FRCs) of Excipients (5.15)
      - Draft: Pharmeuropa 18(3), 2006
      - Adopted: Council of Europe, Supplement 6.1, Chapter 5.14, PhEur (2007)
- EMEA Committee for Medicinal Products for Human Use, *Guideline on Excipients in the Dossier for Application for Marketing of Medicinal Product*, November 2006
- ICH Q8, Guideline on Pharmaceutical Development, November 2005
  - Quality by Design **[QbD]**
- DHHS-FDA, *Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach*, September 2004

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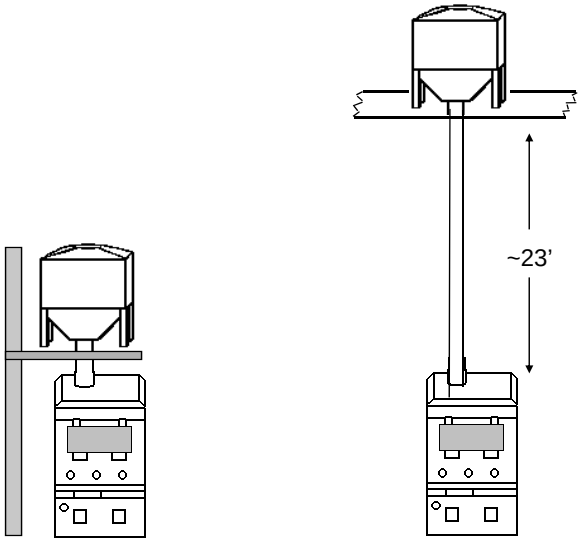
Manufacturing Site Considerations

- Facility Design
- Equipment
- Management
  - Training
  - Experience
- Documentation
- Interactive Relationship
  - Parent : Child
  - Siblings
  - Peers

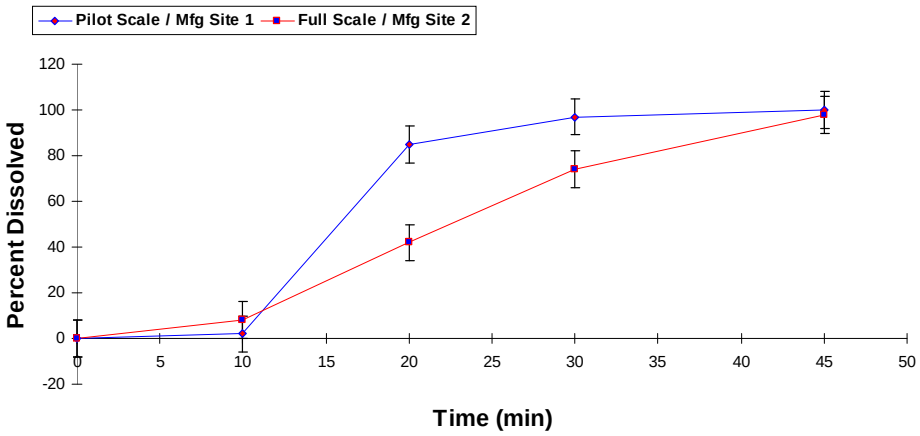
Facility Differences



Equipment Differences

- Blenders / Granulators
  - Rate of Shear
  - Geometry
  - Size
- Tablet Presses
  - Compression Mechanism - mechanical, pneumatic
  - Units of Force
  - Direct or Indirect Force Measurement
- Coating Pans
  - Size
  - Air handling system

Capsules



Elder, et. al. , Glaxo Research Institute, AAPS 1993 SERM

Domestic vs. International Manufacturing Considerations

- Regulatory Requirements
  - NDA
  - MAA
  - JNDA
  - NDS (Canada)
- < **ICH** >
  - CTD
- Excipient Specifications
  - USP/NF
  - BP
  - Ph.Eur.
  - JP
  - FCC
  - GRAS
  - WHO
  - FDA Inactive Ingredients Guide

Target Product Profile

- Target disease
- Target patient population
- Target indication(s)
  - Specific level of desired and minimal acceptable safety
  - Specific level of desired and minimal acceptable efficacy
  - Specific level of desired and minimal acceptable tolerability
- Target route of administration
- Target dose and dosing regimen and acceptable range of deviation
  - Course/duration of treatment
- Target drug product presentation and acceptable range of deviation
  - Packaging, Storage conditions, shelf life, etc.
- Target markets & market size
- Target cost and acceptable overage
- Target price and acceptable range

Market Image

- Product Identification
  - Single set of markings to satisfy worldwide regulatory requirements
- Colorants
  - Worldwide Acceptability
    - Titanium Dioxide (White)
    - Iron Oxide Red
    - Iron Oxide Yellow
    - FD&C Blue #2

Effective Process scale-up

- Approach lab process as “scaled-down version of commercial process”
- Understand the unit processes
  - Spray-drying: effect of nozzle, atomization P, flow rate on droplet size, spray pattern, velocity
- Identify critical process parameters
  - Sterile product: mode of sterilization, filtration, stirring rate, shear rate, batch size

What lends to process scalability?

- No change between *type* of equipment
- No significant change between surface-to-volume ratio
- Unit process is scaled up by repetition, not by increase in volume
  - Continuous vs batch mode
- Process less sensitive to time, temperature

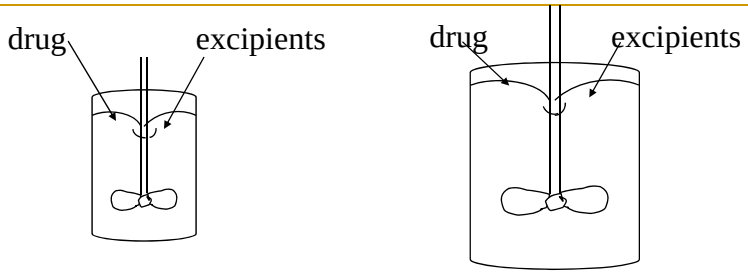
Additional Scale-up considerations

especially for Biologicals

- cGMP Scale-up equipment design
- Specs for process control, operator interface
- Contractors and the Request for Proposal process
- Integrating automation
- Installation, Commissioning, Development, FAT
- Equipment, Process, Cleaning Validation
- Maintenance

= long lead times!!!

Scaling up a suspension formulation



Batch size	**Biobatch 10 liters**	**Commercial batch 100 liters**
Mixing time	**15 mins**	**45 mins**

Are these processes equivalent?

Adapted from Colin R. Gardner, Presentation to Manufacturing Subcommittee of the FDA Advisory Committee for Pharmaceutical Science, Sept 17, 2003

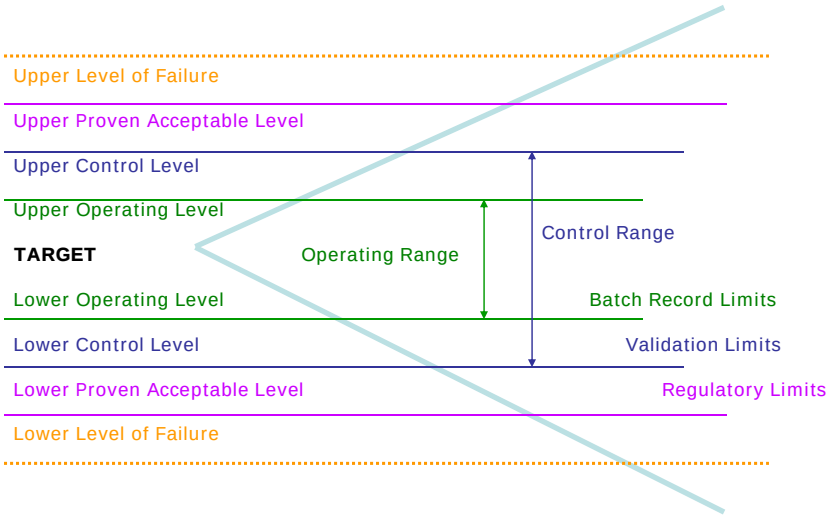
Components of Validation

- DQ
- IQ
- OQ
- PQ
- RQ
  - Change Control
- Pre-Validation

Qualification

- Design
- Installation
- Operational
- Process
- "Re-"
- QbD considerations

Process Ranges



Lessons Learned

- Build quality systems early, evolve strategically
- Provide effective training for a fast-growing workforce; hire, train ahead of curve where possible
- Understand the chemistry of the system
- Understand the fundamental phenomena of the process
- Take advantage of outside expertise

- Define commercial product early
- Do not assume everything will work the first time!
- Beware the law of unintended consequences
- Put change control procedures in place early
- Scale-UP communication
- Work with FDA, not against them
- Track the dynamically changing regulatory picture!

CQA…

- If you fail to pull a sample at any (non-) critical step of the process…
- That will be the sample that could have identified the cause of your problem.

Softgel Process Steps
- API
- Excipients
- Mixing
- Milling
- Filling
- Drying
- Sizing
- Printing
- Inspection
- Polishing
- Packaging
- Shipping / Distribution

Outline

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- Manufacturing Considerations
  - Facilities
  - Equipment
  - Scale-up
  - (pre-) Validation
- Technology Transfer Guidance

Technology Transfer Guideline

- Standardized Process
- Minimum Base of Documentation
  - Analytical Methods
  - Active Pharmaceutical Ingredients (APIs)
  - Dosage Forms

ISPE Good Practice Guide, Technology Transfer, 2003

Objectives

- To describe information that needs to be compiled...
  - to support manufacture
  - to provide for regulatory filings
- To provide effective approaches for ensuring information is available at the point of use.

Quality of Pharmaceutical Products

- Robust manufacturing processes
  - consistent and predictable operation
  - in accordance with cGMPs
  - facilitate ease of validation
- Extensive information set
  - defines all activities necessary to:
    - manufacture
    - control
    - measure
  - relevant and up-to-date

Definition of Success

- Receiving unit can routinely reproduce
  - product
  - process
  - method
    - against a predefined set of specifications
    - as agreed with the sending and/or development unit
- Regulated Environment
  - Documentation is CRITICAL

Experience & Knowledge Capture

- R&D to Manufacturing
  - formulation and rational
  - pivotal batch data
  - process evolution/history
- Business Factors
  - cost
  - capacity/volume
  - facilities and equipment
  - timelines
  - regulatory requirements
- Site to Site
  - manufacturing process and rational
  - annual product review documentation
  - batch comparison data
  - pivotal batch data
    - clinical, bio,stability, registration
  - batch list and pedigree
    - size, use, etc.

Dosage Form

- API
- Excipients
- Manufacturing Process
- Manufacturing Facility & Equipment
- Packaging/Device Components
- Packaging Operations
- Health, Safety & Environmental
- Qualification and Validation

General Excipient Information

- Functionality
- Manufacturer
- Specifications
- Special Considerations
  - heat, light, moisture, etc.
  - HS&E
- Regulatory Considerations
  - Compendial Status
  - Grade
  - Validation/Qualification of multiple suppliers
  - Drug Master File
  - Residual Solvents / Organic Volatile Impurities
  - BSE / TSE
  - Allowable range of use
    - SUPAC

Excipient Characterization

Characteristic	Oral Solid	Parenteral	Semisolid/ Topical	Liquid	Transdermal	Inhalation
Form/ Morphology	X					X
PS/ PSD	X				X	X
Bulk Density	X					X
Compaction	X					
Solubility	X				X	X
Water Content/ Hygroscopicity/ Moisture Content	X	X	X	X	X	X
pH/ Ionic Strength		X	X	X	X	
Specific Gravity/ Density		X	X	X	X	
Viscosity		X	X	X	X	
Osmolarity		X				
Microbiological Considerations		X	X	X	X	X
Melting Range			X			
Partition Coefficient					X	
Intrinsic Dissolution					X	
Adhesive Properties					X	

Experience & Knowledge Capture

- Critical processing parameters
- Specifications and rational
  - critical analytical data (release and stability)
- Qualitative and quantitative compositions
  - known differences in suppliers and performance
- Comparison of processing steps and equipment
- Comparison of analytical methods and instrumentation

More Details…

See Extra Slides

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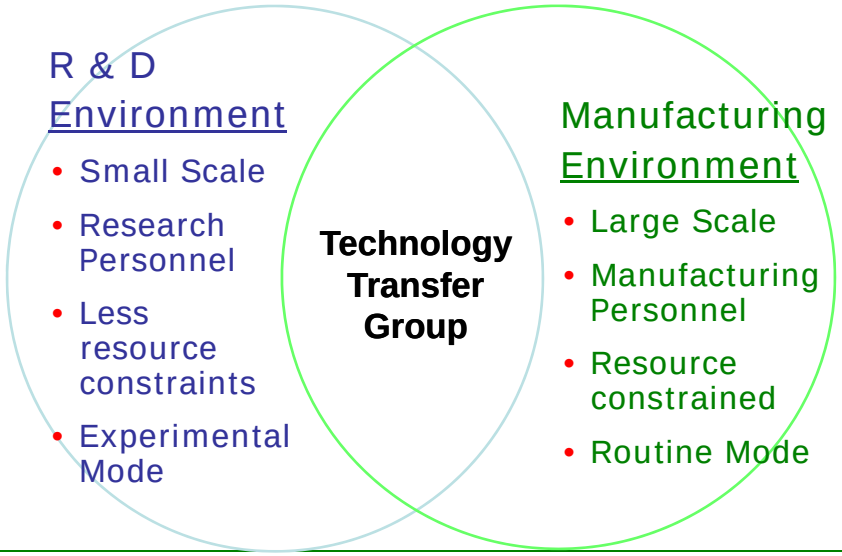
Technology Transfer Team

- Core Expertise
  - Product Development
    - Formulation Development
    - Process Development
    - Analytical
    - Device Development
    - Packaging Development
  - Manufacturing
    - Production
      - Manufacturing
      - Packaging
    - Technical Support
    - Engineering
    - Quality Assurance/Control
    - Validation
- Supporting Expertise
  - Regulatory
  - Health/Safety/ Environmental
- Line Management Support

Keys to Successful Product Transfer

- Establish trust between development, transfer and manufacturing groups
- Free information exchange
- Communication
- Open mind to diversity and alternate ideas/options
- Develop a standardized transfer policy
  - Define teams
  - Establish information requirements
  - Identify activities and responsibilities
- Identify manufacturing site(s) early in development

Technology Transfer Process



Scale Up and Technology Transfer

- Technology transfer and scale-up of pharmaceutical dosage forms must be well controlled and scientifically based
  - Transfer interactions, activities, and documentation must be well defined.
  - Pilot facilities must be constructed and equipped to adequately simulate full scale manufacturing operations.
  - Formulation and components must be well characterized early in development.
  - The manufacturing process must be well characterized and critical process variables must be identified, monitored and controlled during scale-up.
- The ultimate goal of all scale-up and transfer activities is to produce a product meeting all quality standards on a routine basis in production.
  - Adapted from: R.M.Franz, *Glaxo*, ~1992

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Chemical Development Role

- Develop synthetic route & scheme for efficiency, reliability, scalability
- Training of manufacturing staff
- Outline Batch Manufacturing Records
- Identify in-process variables
- Recommend in-process specifications
- Identify critical process variables for validation
- Assist with conducting and documenting validation
- Prepare technology transfer report
- Oversight of initial runs in production
- Assist with troubleshooting production problems
- Key chemistry/chemical engineering contact

Product Development Role

- Develop drug product manufacturing process for efficiency, reliability, scalability
- Training of manufacturing staff
- Outline Batch Manufacturing Records
- Identify in-process variables
- Recommend in-process specifications
- Identify critical process variables for validation
- Assist with conducting and documenting validation
- Prepare technology transfer report
- Oversight of initial runs in production
- Assist with troubleshooting production problems
- Key scientific contact for formulation/process

Analytical Technical Transfer Role

- Has led or contributed to developing analytical methods for efficiency, reliability, scalability
- Has managed or assisted initial methods transfer to QC
- Assists in preparing Analytical Test Procedures
- Trains QC staff
- Establishes RM and product specs
- Prepares Tech Transfer protocol and report
- Prepares and/or reviews Validation protocols
- Directs Methods Transfer Validation
- Troubleshoots QC problems
- Key scientific/QC chemist contact

Roadblocks

- R&D prima donna syndrome
- Manufacturing fire fighting
- Lack of organizational teamwork
- Band-aid fixes
- Lack of product focus
  - Analytical
  - Packaging
- Physical test methods not validated
  - Dissolution
- Acceptance criteria and responsibility not well defined - commercial vs. development batches

EXTRA SLIDES

Technology Transfer Guidance

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Regulatory Factors

- Pre-defined specification
- Adequate facilities and trained staff
- Establishment of protocols and Standard Operating Procedures (SOPs)
- Data

ISPE

Analytical Methods Transfer

Tests	API	Dosage Form						
		Solids	Parenterals	Inhalation	Semi-solids/ Ointments/ Creams	Liquids/ Suspensions	Transdermals	Ophthalmic
Assay	x	x	x	x	x	x	x	x
Content Uniformity		x	x	x	x	x	x	x
Impurities/ Degradants	x	x	x	x	x	x	x	x
Dissolution/ Release Rate/ Dose Delivery		x		x		x	x	
Identification	x	x	x	x	x	x	x	x
Cleaning Verification	x	x	x	x	x	x	x	x
Microbiological	x	x	x	x	x	x	x	x
Physical Criteria	x			x				

API
Active Pharmaceutical Ingredient

- Synthetic Route
- Form
- Process Materials
  - Starting Materials
  - Raw Materials
  - Reagents
  - Catalysts
- Facility & Equipment
- Health, Safety & Environmental
- Process
  - Critical Parameters
  - In-process Controls
  - Characterization
    - API & Intermediates
  - Cleaning
  - Reprocessing
- Packaging
- Qualification & Validation

BACPAC
Bulk Active post-Approval Changes

- I - Intermediates
- II - Drug Substance
  - (to be issued)
- Assessment of effects of change
  - Equivalence of impurity profiles
  - Equivalence of physical properties
- Types of change
  - Manufacturing site, scale, or equipment
  - Specifications
  - Manufacturing process
    - Multiple changes
- Regulatory Filings
  - Prior Approval Supplement
  - Changes Being Effected Supplement
  - Annual Report

API Information Requirements

- Manufacturer
- Flow Chart of Synthetic Pathway
- Form / Morphology
- Solubility
- Partition Coefficient
- Intrinsic Dissolution
- PS / PSD
- Bulk & Tap Density
- Water Content / Hygroscopicity
- Microbiological Considerations
- Specifications
- Stability
- Synthetic Impurities
- Degradants
- Potency Factor
- Special Considerations
  - heat, light, moisture, etc.
  - HS&E

Microbiological Considerations

<61>	Microbial Limit Tests
<71>	Sterility Tests
<85>	Bacterial Endotoxins Test
<151>	Pyrogen Test
<788>	Particulate Matter in Injections
<1111>	Microbiological Attributes of Nonsterile Pharmaceutical Products
<1211>	Sterilization and Sterility Assurance of Compendial Articles
<1227>	Validation of Microbial Recovery from Pharmaceutical Articles
<1231>	Water for Pharmaceutical Purposes

Excipient Justifications

- Preservative Level
  - <51> Antimicrobial Effectiveness Testing
  - <341> Antimicrobial Agents - Content
- Antioxidants
  - no compendial tests, but similar expectation
- Concentrations above guidelines
  - FCC limits
  - WHO limits
  - FDA Inactive Ingredients Guide
    - <1074> Excipient Biological Safety Evaluation Guidelines

SUPAC
Scale-up and post-Approval Changes

- IR
  - immediate release
- MR
  - modified release
- SS
  - non-sterile semisolids
- PACSAS
  - sterile aqueous solutions
- PAC-ATLS
  - analytical testing lab sites

- Regulatory Filings
  - Prior Approval Supplement
  - Changes Being Effected Supplement
  - Annual Report

SUPAC-IR

- Types of Change
  - Level I
    - unlikely to have any detectable impact…
  - Level II
    - could have significant impact…
  - Level III
    - likely to have significant impact…
      - on formulation quality and performance

Change	I	II	III
Components	AR	PAS	PAS+BE
	minor	non-crit	crit
	1 stab	3 accel	3 accel
Site	AR	CBE	CBE
	same	different	different
		(+) data	(-) data
		1 stab	3 accel
Batch Size	AR	CBE	
	<10x pilot	>10x pilot	
	1 stab	1-3 accel	
Equipment	AR	CBE	
	sim oper	different	
	1 stab	1-3 accel	
Process	AR	CBE	PAS
	>val<	<> val	different
		1 stab	1-3 accel

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Acceptance Criteria

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Quality Acceptance Criteria

- Manufacture of Validation Batches
  - Process and Controls Conform to Registration Dossier
  - Process Meets Acceptance Criteria
  - Product Meets Regulatory Specifications
- Commercial Product Equivalence
  - Pilot Scale
  - Clinical Batches
  - Bioequivalence Batch(es)
- cGMP Compliance
  - **Transfers often stop here**

Manufacturing Acceptance Criteria

- Manufacturing Cycle
  - Throughput
    - Time - Single Shift?
  - Cleaning
    - Water / Detergents / Solvents ?
    - Downtime ?
  - Equipment Effectiveness
    - Availability
    - Efficiency
    - Defect Rate
- Cost
- Manufacturing Process
  - Ranges for Processing Parameters
  - Process Yield
    - Minimize Material Waste
  - Process Capability Index
  - Six Sigma Excellence
- Batch Size Flexibility
- Packaging & Labeling
  - multiple configurations and languages

Influence Matrix

Process Step	Responses	Discharge Characteristics	Granulation Quality	Power Load	Moisture Content	Particle Size Distribution	Density	Flow Properties	Density	Uniformity	Fill Weight	Weight Variation	Content Uniformity	Dissolution
	Process Variables	G	G	G	D	S	S	B	B	B	F	F	P	P
G	Batch Size	S	S	S	?	?	?	N	?	?	?	?	?	N
G	Speed - main	W	M	S	N	W	W	N	N	N	N	N	N	N
G	Speed - chopper	M	W	W	N	W	W	N	W	N	N	N	W	W
G	Amount of Water	S	S	M	S	S	S	S	S	W	S	S	W	S
G	Water Addition Rate	W	S	W	N	W	W	W	W	M	W	N	N	N
G	Graulating Time	S	S	N	N	M	M	M	M	W	M	M	S	S
D	Initial Temperature	X	X	X	N	M	N	M	W	N	W	N	N	N
D	Drying Temperature	X	X	X	S	W	M	M	N	N	N	N	N	N
D	Air Flow Program	X	X	X	S	W	M	N	N	N	N	N	N	N
D	Drying Time	X	X	X	S	W	M	M	N	M	M	N	N	M
S	Screen Size	X	X	X	X	S	M	W	W	N	N	N	N	W
S	Feed Rate	X	X	X	X	M	W	N	N	N	N	N	N	N
B	Loading	X	X	X	X	X	X	N	N	W	N	N	W	N
B	Speed	X	X	X	X	X	X	N	N	W	N	N	N	N
B	Blending Time	X	X	X	X	X	X	N	N	S	N	N	S	N
F	Powder Level	X	X	X	X	X	X	X	X	X	S	S	N	N
F	Tamper Settings	X	X	X	X	X	X	X	X	X	S	S	N	W
F	Powder Dispersion Aid	X	X	X	X	X	X	X	X	X	M	M	N	N

Notes:	
S	Strong Effect
M	Moderate Effect
W	Weak Effect
N	No Effect
?	Unknown Effect
X	Not Applicable

Process Steps:	
G	Granulating
D	Drying
S	Sizing
B	Blending
F	Filling
P	Product

von Doehren et. al., Pharm Tech, 6(9):1982, 145

Confidence Intervals

$$95\%\ C.I. = mean +/- \frac{t_{0.05} \times Standard\ Deviation}{n^{1/2}}$$

$$95\%\ C.I._{ind} = mean +/- \frac{t_{0.05} \times Standard\ Deviation}{(n+1)^{1/2}}$$

- Population parameter with stated confidence
  - Data will be within stated limits 95% of the time
  - Useful for establishing batch record or validation limits

Tolerance Intervals

$$T.I._p = mean +/- (k_{p,\gamma} \times Standard\ Deviation)$$

- Confidence statement for a coverage of population
  - Interval containing p% of the population - 2 sided
  - p% will not exceed lower (upper) limit - 1 sided
- Wider than Confidence Intervals
  - Useful for predicting the distribution of data within a batch
  - Can be used to guide establishment of regulatory limits

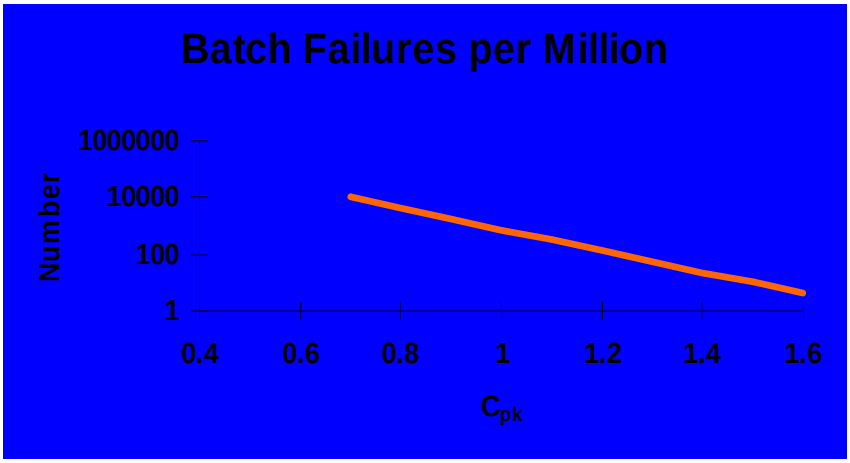
Process Capability Index

$$C_{pk} = min \left[\frac{\text{Mean - Lower Limit}}{\text{3 x Standard Deviation}} , \frac{\text{Upper Limit - Mean}}{\text{3 x Standard Deviation}} \right]$$

< 1.0	Process is Not Capable
1.0 - 1.33	Process is Marginal
1.34 - 3.0	Process is Good
> 3.0	Process is Excellent

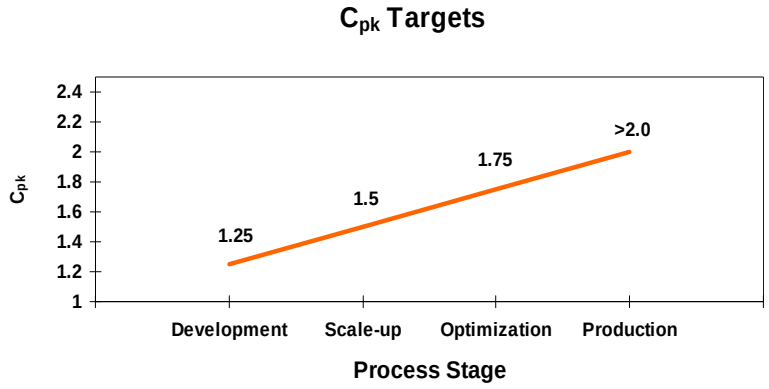
Miller & Miller, Statistical Methods for Quality with Applications to Engineering and Materials, Prentice-Hall, pp.214-218, 1995.

Process Capability and Process Failure



A.J.Duncan, Quality Control and Industrial Statistics, Irwin, p.456, 1986.

Process Capability for Technology Transfer



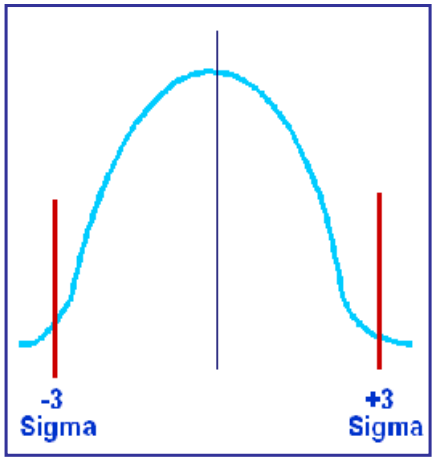
Cautions for Using C_{pk}

- Statistical control should be achieved before using C_{pk}
- Data must approximate a normal distribution
- Can underestimate effects if not enough data are available
- Non-representative sampling may result in high estimates of C_{pk}
- Treats both ends of the specification equally
- Only a good as the specifications on which it is based
- Not a summary parameter (can not be averaged)
- Can not separate sampling/testing error from process error
- Focus on reducing variability rather than C_{pk}
- Could result in wider specifications than necessary

Six Sigma

- Business philosophy
  - eliminate defects through fundamental process knowledge
- Business, statistical and engineering tools
  - reduce costs through self-funded improvement
  - reduce waste
  - better understand customer requirements
  - improve delivery and quality performance
  - provide critical process inputs to respond to changing customer requirements
  - develop robust processes and products
  - drive rapid improvement

Six Sigma Performance



- 99.9997%
- Why 99% is not good enough…
  - 30 spelling mistakes per page
  - 20,000 letters lost daily
  - 15 minutes of electrical failure per day
  - 2 crash landings daily at each major airport globally

Lean Manufacturing

- Tools to reduce waste and streamline operations
  - reduce waste
  - reduce inventory and floor space
  - create more robust production systems
  - develop appropriate material delivery systems
  - improve layouts for increased flexibility

Responsibilities Matrix

Project Task	Group Responsible for Task Completion									
	Form	TT	DV	AS	CQA	PE	QA	QAV	MF	QAS
Issue process/formulation comparison report	N	P				I			I	
Complete manufacturing master batch record	N	N,S				P,A	A	A	A	
Issue technical transfer document	**N,A**	**P,A**	**N**	**N**		**N,A**	**A**	**N,A**	**I,A**	
Generate validation master plan/protocols	I	N,A	N			N,A		P,A	A	A
FDA pre-approval inspection	N	N	N	N	N	N	P	N	N	N
Manufacture validation batches	I	N				N	S	N	P	S
Issue validation report	I	N,A				N,A	A	P,A	A	A

P = Primary Responsibility
N = Input Required
A = Approval
I = Informed
S = Support

Extra Slides

Validation

Quality Systems

- SPC
  - Histograms
  - Check Sheets
  - Pareto Charts
  - Cause and Effect Diagrams
    - Fishbone
    - Ishikawa
  - Defect Concentration Diagrams
  - Scatter Diagrams
  - Control Charts
- SQC
- Quality Circles
- TQM / TQC
- Quality One (Q1)
- ISO 9000...
- JIT
- Six Sigma
  - MAIC
  - DFSS
- Lean Manufacturing

FDA: "Process Validation"

"Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics."

From FDA's "GUIDELINE ON GENERAL PRINCIPLES OF PROCESS VALIDATION," May 1987

Process Validation

VIII. ELEMENTS OF PROCESS VALIDATION

A. Prospective Validation
   1. Equipment and Process
      a. Equipment : Installation Qualification
      b. Process: Performance Qualification
      c. Product: Performance Qualification
   2. System to Assure Timely Revalidation
   3. Documentation

B. Retrospective Process Validation

From FDA's "GUIDELINE ON GENERAL PRINCIPLES OF PROCESS VALIDATION," May 1987

Conducting Process Validation

- Three-batch validation at end of development, i.e. in commercial production site
- Focus on facilities, equipment, components, methods, process qualification
- PV execution thereby provides the necessary documentation to show product reproducibility, and a process under control

Note: *Failure* to execute PV successfully reflects incomplete understanding of the process