



## 2011 IPAC-RS

*Bringing Value To The Patient In A Changing World*  
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# A Regulatory (GMP) Perspective on Supply Chain Quality and Security

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## Outline

- Disease Overview and Statistics
- MedWatch Snapshot for OINDPs
- Complexity of OINDPs
  - ◆ Drug – Device Combination Products
- Supply Chain Quality and Management
  - ◆ Drug Components
  - ◆ Container-Closure System Components
  - ◆ Regulatory Expectations and Tools



## 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

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## Disease Overview: Asthma Statistics

- ~ **300 million** people **worldwide** suffer from asthma, with 250,000 annual **deaths** attributed to the disease.
- ~ **34.1 million** Americans diagnosed with asthma during their lifetime
  - ◆ **17.5 million** (7.7%) **Adults** (non- institutionalized) currently having asthma
  - ◆ **7.1 million** (9.6%) **Children** (non-institutionalized) currently having asthma
  - ◆ **9 million** U.S. children under 18 have been diagnosed with asthma at some point in their lifetime.
  - ◆ An average of **1 out of every 10** school-aged child has asthma.
  - ◆ **3rd-ranking cause** of hospitalization among **children under 15**.
  - ◆ Accounts for approximately 500,000 hospitalizations each year.
  - ◆ Deaths per 100,000 population: 1.1
    - ◆ Number of deaths: 3,447
- Asthma prevalence rate in US (2011) : **8.4%** as per the [Center for Disease Control](#)
- Annual expenditures for health and lost productivity estimated at
  - ◆ over \$20 billion, as per the NHLBI (National Heart, Lung and Blood Institute)

<http://www.cdc.gov/nchs/fastats/asthma.htm>

<http://www.aaaai.org/media/statistics/asthma-statistics.asp>

<http://www.who.int/mediacentre/factsheets/fs307/en/index.html>

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## Disease Overview: Chronic Obstructive Pulmonary Disease (COPD)

### Morbidity (2009)

- 9.9 million non-institutionalized adults diagnosed with **chronic bronchitis** in the past year
- 4.9 million non-institutionalized adults diagnosed with **emphysema**
- 2.2% non-institutionalized adults diagnosed with **emphysema**

### Health Care Use (2004): Nursing home care

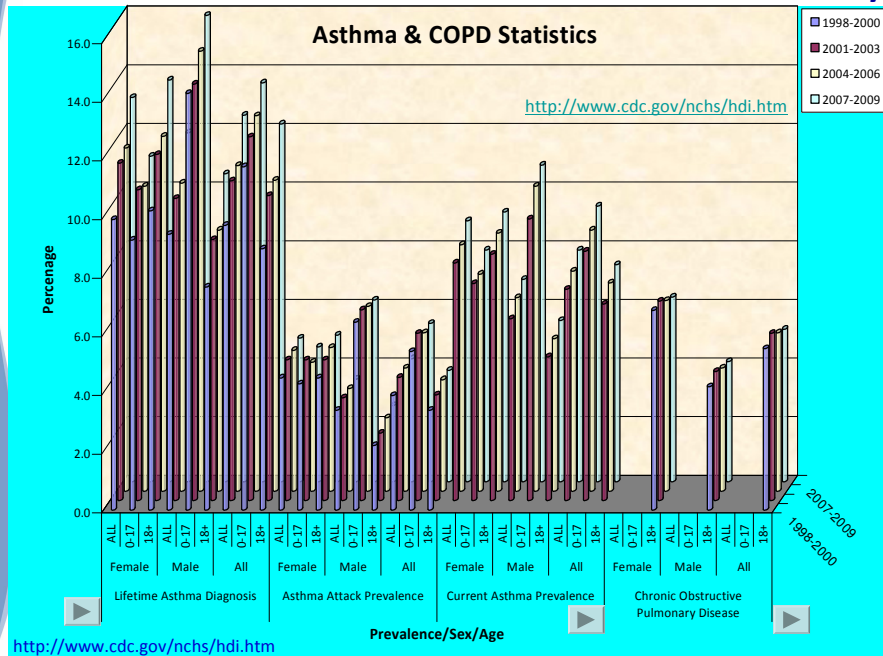
- Number of residents with **COPD: 190,000** (13%)

### Mortality (2007)

- Deaths due **bronchitis** to (chronic and unspecified) : **667**
  - ◆ **Bronchitis** (chronic and unspecified) deaths per 100,000 population: **0.2**
- Deaths due to **emphysema** : **12,790**
  - ◆ **Emphysema** deaths per 100,000 population: **4.2**
- Deaths from other chronic lower respiratory diseases (w/o asthma): **111,020**
  - ◆ Deaths per 100,000 population: **36.8**

<http://www.cdc.gov/nchs/fastats/copd.htm>

## Disease Statistics Summary





## **MEDWATCH**

### **The FDA Safety Information and Adverse Events Reporting Program Snapshot for OINDPs**

- Drug Quality Reporting System (DQRS)
- Year Range: 01/2005 – 03/24/2011
- Query Criteria: Inhalation, Aerosol, Powder
- Product Defect Categories/Groupings
  - ◆ Device related (D)
  - ◆ Product/Process related (P)
  - ◆ Therapeutic Efficacy/Equivalence (T)

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### **Product Defect Categories: MDI**

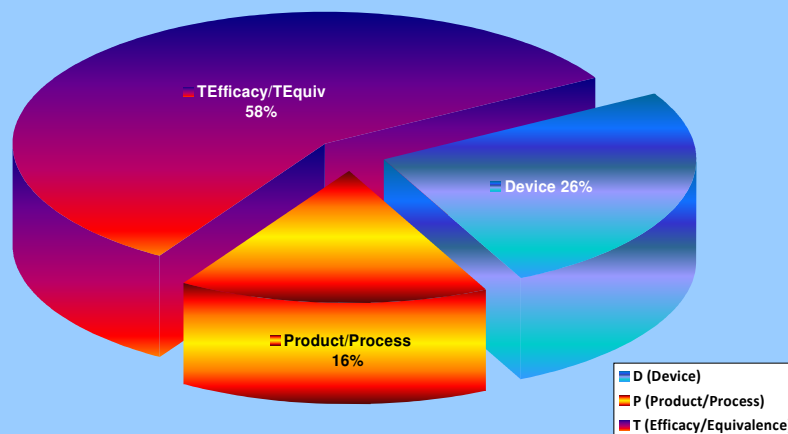
<b>Product/Process Related (P)</b>		<b>Efficacy/Equiv Related (T)</b>
<ul style="list-style-type: none"> <li>▪ Admin Dev Contamintd</li> <li>▪ Unexpected Appearance</li> <li>▪ Clumping</li> <li>▪ Dosage Units Missing</li> <li>▪ Dried Out</li> <li>▪ Drug Shortage</li> <li>▪ Empty Units</li> <li>▪ Foreign Material</li> <li>▪ Odor/Taste Abnormal</li> <li>▪ Qty Missing/Wrong</li> <li>▪ Volume Variation</li> </ul>	<ul style="list-style-type: none"> <li>▪ Volume Amount Missing</li> <li>▪ Label Incorrect Carton</li> <li>▪ Label Confusing/Misleading</li> <li>▪ Label Misleading</li> <li>▪ Potency Lost Over Time</li> <li>▪ Product Specs</li> <li>▪ Packaging Change</li> <li>▪ Shipped Improperly</li> <li>▪ Tamper Seal Defect</li> </ul>	<ul style="list-style-type: none"> <li>▪ ADR Recognized</li> <li>▪ Available To Public</li> <li>▪ Death</li> <li>▪ Formulation Questioned</li> <li>▪ Generic Substitution Questioned</li> <li>▪ Hospitalization Resulted</li> <li>▪ Lack of Patient Acceptance</li> <li>▪ Mix-up Look-Alike</li> <li>▪ Patient Reaction</li> <li>▪ Potency Questioned</li> <li>▪ Therapeutic Effect Lacking</li> </ul>
<b>Device Related (D)</b>	<ul style="list-style-type: none"> <li>▪ Admin Device Malfunction</li> <li>▪ Aerosol Non-Function</li> <li>▪ Container Defect</li> <li>▪ Design Defect</li> </ul>	<ul style="list-style-type: none"> <li>▪ Dispense Device Malfunction</li> <li>▪ Flow Characteristic Poor</li> <li>▪ Mechanical Malfunction</li> <li>▪ Pump Malfunction</li> <li>▪ Spray Excessive</li> </ul>

## Product Defect Categories: DPI

Product/Process Related (P)	Device Related (D)	Efficacy/Equivalence Related (T)
<ul style="list-style-type: none"> <li>▪ Dosage Units Missing</li> <li>▪ Empty Units</li> <li>▪ Expiration Date Questioned</li> <li>▪ Formulation Questioned</li> <li>▪ Capsule Fill Varies</li> <li>▪ Clumping</li> <li>▪ Product Standards Suspected</li> <li>▪ Product Specifications Products</li> <li>▪ Quantity Missing</li> <li>▪ Volume Amount Missing/Questioned</li> </ul>	<ul style="list-style-type: none"> <li>▪ Admin Device Malfunction</li> <li>▪ Aerosol Non-Function</li> <li>▪ Design Defect</li> <li>▪ Dispense Device Malfunction</li> <li>▪ Capsule Separation</li> <li>▪ Closure Removal Difficult</li> <li>▪ Cracked Dosage Form</li> </ul>	<ul style="list-style-type: none"> <li>▪ Generic Substitution Questioned</li> <li>▪ Growth Visible</li> <li>▪ Label Confusing/Misleading</li> <li>▪ Lack Of Patient Acceptance</li> <li>▪ Patient Reaction</li> <li>▪ Potency Questioned</li> </ul>

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**Inhalation Aerosol (MDI) Product Defects**  
Year Range: 01/2005 - 03/2011  
Source: Adverse Events Reporting System  
EVENTS (N) = 1245

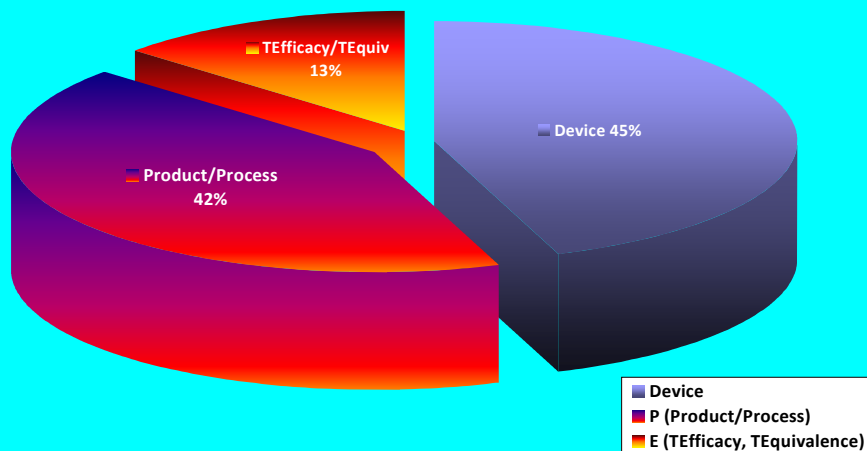


### Inhalation Aerosol Powder (DPI) Product Defects

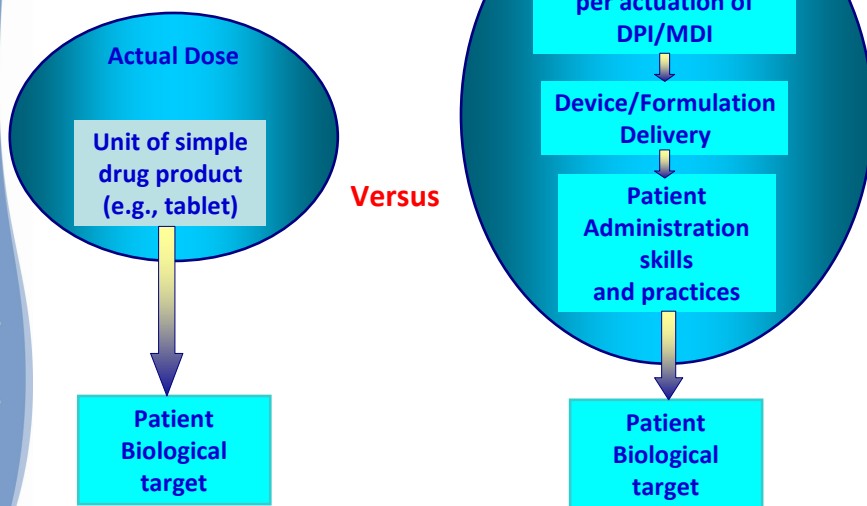
Year Range: 01/2005 - 03/2011

Source: Adverse Events Reporting System

EVENTS (N) = 90

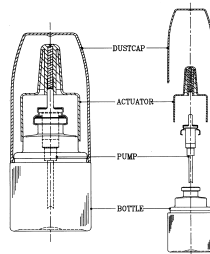
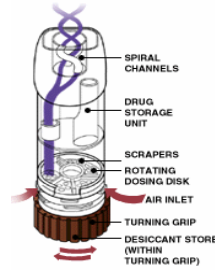
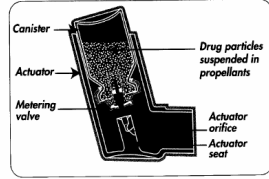


### Complexity of Dosing OINDPs



### OINDP Components: MDI and DPI Nasal DPs

#### Metered Dose Inhaler

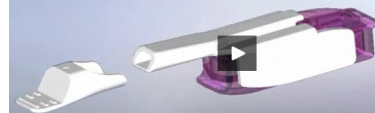
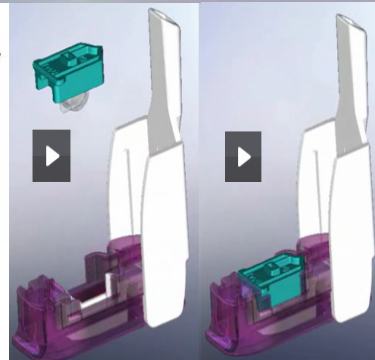
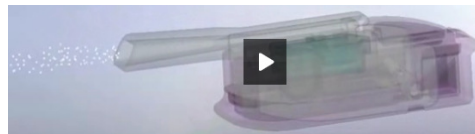
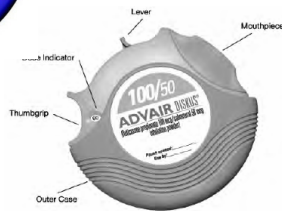


Sources of Images: IPAC-RS SQC WG and suppliers' public catalogues

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### OINDP Components: DPI

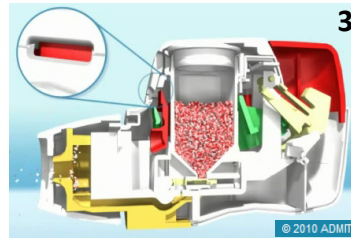
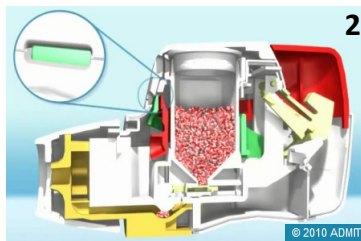
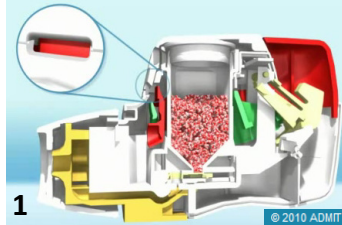


Sources of Images: suppliers' public catalogues, Internet, compny's websites...

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## Device-Metered DPIs



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## Supply Chain Management

- Supply Chains
  - ◆ Drug Components
    - ◆ Active Pharmaceutical Ingredient (API)
    - ◆ Excipients
    - ◆ Process aids
  - ◆ **Container-Closure System (CCS) Components**
    - ◆ Primary CCS components
    - ◆ Secondary CCS components
  - ◆ Contract Manufacturing
  - ◆ Globalization
- Regulatory Expectations and Tools
  - ◆ CGMP Requirements
  - ◆ Management Responsibility

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## Globalized Drug Manufacturing

- Outsourcing, Contracting, Importing
  - ◆ API, Excipients, Raw materials, starting materials
- Supply Chain
  - ◆ Contract manufactures
  - ◆ Traders/Brokers
  - ◆ Distributors
    - ◆ Repackaging
    - ◆ Relabeling
  - ◆ Transportation Companies
  - ◆ Storage facilities



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## Supply Chain Drug Components and Container-Closures

N - 3	N - 2	N - 1	N
Ingredients Mfr/Supplier	Raw Material Mfr/Supplier	Drug/CCS Component Mfr /Supplier	Pharma Company
<ul style="list-style-type: none"> <li>• Fine Chemicals</li> <li>• Reagents</li> <li>• Solvents</li> <li>• Process aids</li> <li>• Monomers</li> <li>• Additives</li> <li>• Antistatic Agents</li> <li>• Slip aids</li> </ul>	<ul style="list-style-type: none"> <li>• Starting Materials</li> <li>• Resin polymers</li> <li>• Metal alloy</li> <li>• Elastomers</li> <li>• Gaskets</li> <li>• Foil laminates</li> </ul>	<ul style="list-style-type: none"> <li>• API manufacturers</li> <li>• Excipient Mfrs</li> <li>• In-Process materials Mfrs</li> <li>• Valve Manufacturer</li> <li>• Canister Fabricators</li> <li>• Moulders (INJ, BFS)</li> <li>• Device Manufacturers</li> <li>• Converters</li> <li>• Assemblers</li> <li>• 2° Pkg Components Mfrs</li> </ul>	<ul style="list-style-type: none"> <li>• API</li> <li>• Excipients</li> <li>• Device parts</li> <li>• Canister</li> <li>• Valve</li> <li>• Actuators</li> <li>• Spacers</li> <li>• 2° Pkg Components</li> </ul>

Adapted from IPAC-RS presentations/publications

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## Contractor and Contract Giver are Liable for Adulterated Product

- The Federal FD&C Act (the Act) states that a drug is considered to be **adulterated** if the drug is not manufactured in conformance with **CGMP** [21 U.S.C. 351(a)(2)(B) ]
  - ◆ Applies to **finished drug products, drug components** and all sites under contract to manufacture or supply drugs and drug components
- Manufacturer and private label distributor can both be held **liable**
  - ◆ Introducing or causing the introduction of adulterated drugs into interstate commerce is prohibited. [21 U.S.C. 301]

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## Regulatory Requirements Pertaining to Contract Manufacturing Relationships

- Primary manufacturer is **responsible**
  - ◆ **21 CFR 200.10(b)**
    - ◆ The Food and Drug Administration ..... regards **extramural facilities** as an extension of the manufacturer's own facility.
  - ◆ **21 CFR 211.22(a)**
    - ◆ Quality Control Unit (QCU) is **ultimately responsible** for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company

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## Regulatory Requirements Incoming Components

- **21CFR Sec. 211.84** Testing and approval or rejection of components, drug product containers, and closures.
- (a) **Each lot** of components, drug product containers, and closures **shall be withheld from use** until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.
- (b) **Representative samples** of each shipment of each lot shall be collected for testing or examination.
  - ◆ The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as **statistical criteria** for
    - ◆ component variability,
    - ◆ confidence levels, and
    - ◆ degree of precision desired,
    - ◆ the past quality history of the supplier, and
    - ◆ the quantity needed for analysis and reserve where required by 211.170.

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## Regulatory Requirements Incoming Drug Components

- **21CFR Sec. 211.84 (d)** Samples shall be examined and tested as follows:
- (3) **Containers and closures** shall be tested for **conformity** with all appropriate written specifications.
  - ◆ **In lieu** of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, **provided that**
    - ◆ at least a visual identification is conducted on such containers/closures by the manufacturer
    - ◆ the manufacturer **establishes** the **reliability** of the supplier's test results through appropriate **validation** of the supplier's test results at **appropriate intervals**.

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## Regulatory Requirements Incoming Components

### § 21CFR 211.94 Drug product containers and closures.

- (a) **shall not be reactive, additive, or absorptive** so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.
- (b) **shall provide adequate protection** against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.
- (c) **shall be clean** and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.
- (d) **Standards or specifications, methods of testing,** and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.

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## ICH Q9 - Quality Risk Management Guidance Regarding Outsourcing

- Members of the supply chain are **partners**
  - ◆ Play a role in determining success.
- **Q9** recommends a comprehensive evaluation of suppliers and contract manufacturers
  - ◆ including auditing and implementing supplier quality agreements
- A manufacturer's quality system will drive the management of outsourced processes and entities (risk and quality management)

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## ICH Q10 - Pharmaceutical Quality Systems Guidance Regarding Outsourcing

- Control and review of all outsourcing activities is an element of a manufacturer's pharmaceutical quality system.
- Manufacturer is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials.
- A manufacturer should have adequate procedures for auditing and qualifying facilities prior to outsourcing and throughout the process and for contract management and supervision.

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## CGMP - Providing High Quality Products Goes Beyond Good Product Design

- Personnel Qualifications and Training
  - ◆ Train, observe, and if necessary retrain
- Design of Facilities and Equipment
  - ◆ Suitability for intended purpose
- Documenting and Review of Records
  - ◆ Investigation of variance
- Continual Quality Monitoring
- Continual Improvement
- Validation
  - ◆ Continual verification
  - ◆ adequacy of control strategy

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## ICH Q9 - Application of Quality Risk Management to Making Sourcing Decisions

- How does one quantify the true cost of ownership in a sourcing relationship?
  - ◆ What are the worst case scenarios?
  - ◆ Will there be some learning curve that dictates a need to be present at contractor?
- How well do the supplier's quality systems assure product quality?
  - ◆ Systems often look good on paper
  - ◆ Trust and confidence are built gradually

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## Management of Members of Supply Chain

- The degree of rigor and formality of quality risk management should reflect available knowledge...(see ICH Q9 section on *Risk Management Methodology*)
  - ◆ Proper selection of a 'partner' is based on gathering enough knowledge to properly assess risk
- What are the risks to quality and how should they be addressed?
  - ◆ Risk mitigation strategy
  - ◆ Control strategy
  - ◆ Monitoring strategy

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## Supplier Management Qualification of Suppliers

- **Qualification** is part of a **lifecycle** approach to supplier management
  - ◆ Unlikely that any one approach can possibly cover all qualification scenarios
- **Lifecycle** includes
  - ◆ Prospective supplier selection
  - ◆ Qualification activities
  - ◆ Supplier approval
  - ◆ Maintenance of qualified status of supplier
  - ◆ Periodic audits

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## What is the Role of the Management?

- Makes change happen
- Manages risk
- Determines resource allocation
- Develops high level plans
- Provides visionary leadership
- Reaps rewards for success
- Owns responsibility for failure

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## Good Communication is Essential For Mutual Benefit

- Applies to management of contractors and suppliers
- Activities involving good communication
  - ◆ Investigations of nonconformance and complaints from market
  - ◆ **Change management**
  - ◆ Supplies of excipients and packaging and ancillary materials coming into contact with or in the vicinity of your product or starting materials are not to be overlooked
- Communication ground rules should be established in a formal quality agreement

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## Knowledge, Prevention, Detection

- Qualify entire supply chain
  - ◆ Audits (qualified 3<sup>rd</sup> parties are OK)
  - ◆ Certification and accreditation (accredited 3<sup>rd</sup> party)
  - ◆ Starting materials are part of supply chains
- Secure the entire supply chain
  - ◆ Tamper evident seals
  - ◆ Supply chain stewardship
- Know the distribution routes
- Know the origin of starting materials

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## Validation and Continuous Process Verification

- **Quality should be built in**
  - ◆ Design, validation and evidence of state of control
- Verification (testing) is an element of process validation
  - ◆ Validation is about establishing the process is and will remain in state of control
  - ◆ Establishing the process is in control is about testing and measurement (combination of both)
    - ◆ Verifying that process is in control is part of every batch release decision (CGMP)
- **Defects are result of process and material variation**
- PAT is a route toward getting at the defect rate
  - ◆ although measurements without action in response are not truly in the spirit of PAT
- At- or on-line finished product testing can establish defect rate

## Quality Assurance Under CMC & GMP



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Protecting and Promoting Public Health

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## Quality Assurance Under CMC & CGMP

**Improve it**

**Quality Under CGMP**

**Say What You Do**

**Do What You Say**

**Prove it**

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

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## Public Health 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

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## References

- **Draft Guidance for Industry, Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, and Controls Documentation**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070573.pdf>
- **Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070575.pdf>
- **Draft Guidance for Industry and FDA Current Good Manufacturing Practice for Combination Products**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070268.pdf>
- **Guidance for Industry: PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, September 2004**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070305.pdf>
- **Guidance for Industry: Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations, September 2006**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070337.pdf>
- **Guidance for Industry: Q9 Quality Risk Management, June 2006**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073511.pdf>
- **Guidance for Industry: Q8(R2) Pharmaceutical Development Revision 2, November 2009**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073507.pdf>
- **Guidance for Industry: Q10 Pharmaceutical Quality System, April 2009**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073517.pdf>
- **Guidance for Industry: Process Validation: General Principles and Practices, January 2011**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>

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## Acknowledgements

- IPAC-RS Organizing Committee
- Steve Wolfgang, DMPQ, OC, CDER

**Thanks**  
**Questions**  
**???**

"That's  
 all  
 folks!"



**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>



