Regulatory Requirement in Pharmaceutical Industry

Jesse Wang
October 12th, 2011
Why Chemists Need to Know Regulatory?

- Pharmaceutical industry is a highly regulated industry
- Drug efficacy, safety and quality start at R&D
  - Until recently, FDA was not involved in the early R&D phases of a product. However, FDA is beginning to inquire about the results, documentation, and experiments that were performed during R&D because the ultimate safety and quality of a product depends on the foundation built during development.
- Understand the language
  - Regulatory Guidelines ensure that we speak the same language and have the same practice and standard across the industry and regulatory bodies
- Quality is everybody’s responsibility in the pharmaceutical industry
Outline

• Regulatory Bodies and Regulatory Guidelines
• Quality System in Pharmaceutical Industry
• Regulatory Submission
• QbD and Risk Management
Outline

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  • Quality System in Pharmaceutical Industry
  • Regulatory Submission
  • QbD and Risk Management
Regulatory Bodies and Regulations

- FDA
- EMEA
- Health Canada Therapeutic Products Directorate (TPD)
- Australian Government Department of Health and Ageing Therapeutic Goods Administration
- Good Manufacturing Practice
- PMDA Pharmaceuticals and Medical Devices Agency, Japan
- SFDA State Food and Drug Administration
- ICH harmonisation for better health
- Gilead
Regulatory Bodies’ Roles

• Establishing rules that ensure consumer protection
• Communicating the rules to industry and educating the public
• Monitoring industry compliance with the rules
• Performing scientific review and providing information and support to ensure that the rules are up-to-date
• Enforcing applicable laws and regulations
• Review and approval medical product applications and changes
  – Every country has its own regulatory authority to regulate pharmaceutical drugs and medical devices for human use.
Why Regulating Drugs?

- Drugs are not ordinary consumers’ products. the consumer cannot safely ascertain a drug product’s quality and safety on his or her own. The regulator plays a critical role.
- The use of ineffective, poor quality, harmful medicines can result in therapeutic failure, exacerbation of disease, resistance to medicines and sometimes death.
- In the pass 100+ years, many lives lost due to unsafe or ineffective drugs.
- Those lives promoted establishment and development of Drug Regulations and Regulatory Bodies.
- The history of FDA represents the history of drug regulation.
Pre-Regulation Era

- There were not any regulations at the beginning
  - No rules, laws, or regulations to set standards of hygiene, purity, or honesty in food or drug labeling
  - Many infants died from patent medicines containing opium and cocaine
  - There were not any requirements to test drug purity and efficacy.
USDA Bureau of Chemistry Era

- Started as one chemist Harvey Washington Wiley in U.S. Department of Agriculture in 1862, but no regulatory powers.
- 1906: Pure Food and Drug Act (also known as “Wiley Act”) signed into law. Regulatory powers began.
  - Forbade the manufacture, sale, or transportation of adulterated food products and poisonous patent medicines
  - Required that certain specified drugs, including alcohol, cocaine, heroin, morphine, be accurately labeled with contents and dosage
- Nation's first regulatory agency
- Acknowledged for first time circumstances where government must protect citizens against business rather than just protecting business
Establishment of the FDA

• In 1927, the Bureau of Chemistry's regulatory powers were reorganized under a new USDA body, the Food, Drug, and Insecticide organization.
• 1930: name shortened to FDA.
• Anyone could sell medicine, as long as it didn’t contain narcotics or a listed poison. There was no requirement to ensure the safety of new drugs.
• If drug found harmful or fatal, manufacturer not required to take it off market
• If FDA contested, manufacturer could change name and start over.

Then in 1937...
“…six human beings, all of them my patients, one of them my best friend, are dead because they took medicine that I prescribed for them…medicine which I had used for years…suddenly had become a deadly poison in its newest and most modern form, as recommended by a great and reputable pharmaceutical firm in Tennessee”

Letter from Dr. Archie Calhoun, October 22, 1937

http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/default.htm
Sulfanilamide

- The medicine that killed Dr. Calhoun's patients was Elixir Sulfanilamide
- Sulfanilamide, included in a class of drugs known as sulfonamides, or sulfa drugs, was praised in the 1930s as the first product to successfully treat bacterial infections.
- Dr. Gerhard Domagk, was awarded 1939 Nobel prize for his discovery of sulfa drugs.
- Sulfanilamide was originally manufactured as tablets or as an injectable drug. It saved many lives.

The Nobel Prize in Physiology or Medicine 1939
Gerhard Domagk
1937 Sulfanilamide Disaster

- June 1937: salesman for S.E. Massengill Co., in Tennessee, reported demand in the southern states for the drug in liquid form.
- Company’s chief chemist and pharmacist, Harold Cole Watkins, found sulfanilamide dissolved in diethylene glycol (DEG), an antifreeze.
- Although it was known at the time that DEG is poisonous to humans, but Harold Watkins was not aware of this.
- Not tested for toxicity (not required by law at the time)
- September: 633 shipments sent
- October 11: several deaths reported
- 107 people died, many children
- Harold Watkins fired, later committed suicide
1938: New FDA Authority

• Within six months of the Sulfanilamide Disaster, US Congress passed Food, Drug, and Cosmetic Act of 1938
  – Drugs had to be proven safe through testing before marketing
  – Companies required to submit “New Drug Application” (NDA)
  – NDA became effective after 60 days if FDA did not object

• 25 years later, it saved the US from an even greater drug tragedy--a thalidomide disaster--like that in Germany and England

• However, significant limitations still remained
  – Proof of efficacy not required
  – Animal testing not standardized
  – Human trials often poorly done
  – FDA did not review application until drug manufacturer finished its own tests
Thalidomide Tragedy

• Was introduced in Europe as a sedative drug in the late 1950s and typically used to cure morning sickness during pregnancy.
• In the late 1950s and early 1960s, more than 10,000 children in 46 countries were born with deformities such as phocomelia, as a consequence of thalidomide use.
• FDA Pharmacologist Frances Oldham Kelsey refused FDA approval to market thalidomide, saying further studies were needed.

(R)-isomer is effective against morning sickness, (S)-isomer causes the teratogenicity.
The enantiomers can interconvert in human body.
Thalidomide Tragedy

• Frances Oldham Kelsey received an award from President John F. Kennedy for blocking sale of thalidomide in the United States.

• In 1962, the US Congress passed laws requiring tests for safety during pregnancy before a drug can receive approval for sale in the U.S.
1962: Kefauver Harris Amendment

• Also known as “Drug Efficacy Amendment”
• The amendment was a response to the Thalidomide tragedy
• Drugs now required to be safe and effective
• Drug companies must prove premarket effectiveness ("proof-of-efficacy“)
• For the first time, FDA must formally approve NDA before product can be marketed.
• “Good Manufacturing Practices” (GMPs) for manufacturing, processing, packing, or holding finished pharmaceuticals were first published in 1963.
Approval Process

- Investigational New Drug (IND) application
- Phase I: is it safe?
- Phase II: does it work?
- Phase III: is it better than standard treatment or placebo?
- New Drug Application (NDA)

From now on, we entered modern drug regulatory era
Some Important Milestones After 60’s

- 1978. A major rewrite for the cGMPs for drugs and devices were published.
- 1979. GLPs (21(CFR 58) Final Rule
- 1988. Prescription Drug Marketing Act
- 1992. Generic Drug Enforcement Act
  - A result of the Congress generic drug scandal started in 1988
  - FDA focus changed from oversight to verification & enforcement – initiated pre-approval inspection (PAI)
- 1993. The Barr Decision
- 2001. ICH Q7A API Guidance published
World Health Organization (WHO)

WHO is the directing and coordinating technical agency for health within the United Nations system. WHO’s roles in drug regulation are:

– Issuing necessary norms and standards through its Expert Committees
– Supporting regulatory capacity building leading to implementation of drug regulation on national level and its harmonization on regional and global level.
– In selected areas of essential products, ensuring the quality, safety and efficacy of limited high public health value essential medicines and vaccines through "prequalification”.
– Facilitating exchange of regulatory information through International Conference of Drug Regulatory Authorities (ICDRA).
Three Major Regulatory Guidelines

- International Conference on Harmonization (ICH) Guidelines.
- European Medicines Agency (EMEA) Guidelines.

Pharmaceutical Industry Is a Highly Regulated Industry
ICH

• Need for the harmonization of requirements relating to the new innovative drugs.

• In 1990, the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) was established.

• A collaborative initiative between the EU, Japan and the US with observers from WHO, EFTA and Canada.

• ICH's mission is to achieve greater harmonization to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.
ICH Guidelines

• **Q** – Quality Guidelines
  – the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management

• **E** – Efficacy Guidelines
  – the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines

• **S** – Safety Guidelines
  – uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity.

• **M** – Multidisciplinary Guidelines
  – Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories.
Good Manufacturing Practice (GMP)

- **GMPs** are the part of quality assurance that ensures that products are consistently produced and controlled in such a way to meet the quality standards appropriate to their intended use, as required by the marketing authorization.

- **GMPs** are a set of regulations, codes, and guidelines for the manufacture of:
  - Drug substances and drug products
  - Medical devices
  - *In vivo* and *in vitro* diagnostic products
  - Foods

- They are adopted by pharmaceutical industry worldwide.

- The term "**cGMP**" is current Good Manufacturing Practices. By definition, "cGMP" indicates that the current GMP - which is "state of the art" - can change. "GMP" and "cGMP" are often used interchangeably and essentially they have the same meaning.
2000- GMP Guidance for APIs

- ICH Q7A: “Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients”
  - Established GMP standards for manufacturers of APIs.
  - Accepted world-wide.
Key Elements of GMP

Personnel
(Training, Hygiene)

Materials
(Supplies, Ingredients)

Premises
(Facilities and Equipment)

Documentation
10 Basic Rules of GMP

1. Get the facility design right from the start
2. Validate processes
3. Write good procedures and follow them
4. Identify who does what
5. Keep good records *(If you didn’t record it, you didn’t do it)*
6. Train and develop staff
7. Practice good hygiene
8. Maintain facilities and equipment
9. Build quality into the whole product lifecycle
10. Perform regular audits
Case Study: Synthesis of Sildenafil

Peter J. Dunn, et al, OPRD, 2000, 4, 17-22

Controls increase as process proceeds to final preparation and isolation steps!
Drug Development Process: CMC
Regulatory Roadmap

**Discovery**

**Pre-clinical**

**Phase 1**

**Phase 2**

**Phase 3**

**Commercialization**

**Product Life-cycle Management**

**Analytical**

- Stability Q1A-E
- Validation Q2
- Impurities Q3A-C
- Pharmacopeia Q4
- Specifications Q6

**API (DS)**

- GMPs for API Q7A

**Pharmaceutical**

- Pharmaceutical Development Q8
- Quality Risk Management Q9
- Pharmaceutical Quality System Q10

**EU Guideline**

Good Manufacturing Practice: Medicinal Products for Human and Veterinary Use: Annex 13 Investigational Medicinal Products (2010)

**FDA Guidance for Industry**

- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products (1995)
- cGMP for Phase 1 Investigational Drug (2008)

**ICH**

**API**

- Dev/Manuf. of Drug Substance Q11
ICH Impurities Guidelines

• Guidelines
  – Q3B(R): Impurities in New Drug Products
  – Q3C: Impurities: Residual Solvents
  – Q3D: Impurities: Guideline for Metal Impurities (concept paper)

• Organic Impurities:
  – Starting materials, by-products, intermediates, degradation products, reagents, ligands and catalysts

• Residual solvents / Organic Volatile Impurities (OVIs)

• Inorganic Impurities:
  – Reagents, ligands and catalysts, metals, inorganic salts, other materials (e.g. filter aids, charcoal)

• Scope:
  – Identification, Qualification, Reporting, and Specification
## Organic Impurity Limit in Drug Substance

According to ICH Q3A(R), the maximum daily dose qualification threshold to be considered is as follows:

<table>
<thead>
<tr>
<th>Maximum daily dose</th>
<th>Reporting Threshold(^1,,2,,3)</th>
<th>Identification Threshold(^3)</th>
<th>Qualification Threshold(^3)</th>
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</thead>
<tbody>
<tr>
<td>(\leq 2,\text{g/day})</td>
<td>0.05%</td>
<td>0.10% or 1.0 mg per day intake (whichever is lower)</td>
<td>0.15% or 1.0 mg per day intake (whichever is lower)</td>
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<tr>
<td>(&gt;2,\text{g/day})</td>
<td>0.03%</td>
<td>0.05%</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

1. The amount of drug substance administered per day
2. Higher reporting thresholds should be scientifically justified
3. **Lower threshold can be appropriate if the impurity is unusually toxic**
Risk-Based Classification of Solvents

Three classes of solvents:

**Class 1** – Unacceptable toxicities; **should be avoided**, unless their use can be strongly justified in a risk-based assessment.

Examples: benzene, Carbon tetrachloride, 1,2-Dichloroethane, 1,1-Dichloroethene and 1,1,1-Trichloroethane.

**Class 2** – Less severe toxicities; **should be limited**.

**Class 3** – Less toxic; **should be used where practical**.
Tests for Drug Substance

- **Universal Tests**
  - Description
  - Identification
  - Assay
  - Impurities

- **Specific Tests**
  - Physicochemical
  - Polymorphism
  - Genotoxic impurities
  - Solubility
  - Hygroscopicity
  - Water content
  - Enantiomeric purity
  - Inorganic impurities
  - Counter-ion assay
  - Residual solvents
  - Particle size
  - Surface area
  - Microbial limits/endotoxins
Validation

• It is a requirement of GMP (ICH Q7A, section 12)
• It is defined as the documented act of demonstrating that a procedure, process, and activity will consistently lead to the expected results.
• Qualification of critical equipment and ancillary systems should be completed before validation
  – 4Qs: Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ)
• Three Validations:
  – Process Validation
  – Cleaning Validation
  – Analytical Method Validation
Process Validation: 3 Stages

Stage 1
Process Design
Build process knowledge and understanding
Establish a strategy for process control

Stage 2
Process Qualification
The products consistently meet the specifications,
The process parameters meet the acceptance criteria,
The fluctuations are measured objectively

Stage 3
Continued Process Verification
Monitoring and improving control and reducing product and process variation during commercial manufacture

Design of a facility and qualification of utilities and equipment
Process Performance Qualification (PPQ)

Confirmation
Changes

Distribute
Regulatory Inspections

• Regulatory authority conducts regulatory inspections
• Aim of Regulatory Inspections
  – to evaluate a firm’s commercial manufacturing capability, adequacy of production and control procedures, suitability of equipment and facilities, and effectiveness of the quality system in assuring the overall state of control. Notably, pre-approval inspections include the added evaluation of authenticity of submitted data and link to dossier.
• Types of Regulatory Inspections
  – System based (including general statements)
    • Routine GMP inspection
  – Product oriented
    • Pre Approval Inspections (PAI)
    • Post approval (often combined with system inspections).
    • For Cause Inspections e.g. handling suspected quality defects or, in the EU and Japan, the assessment for licensing manufacturing sites.
"Smile, you're on Compliance Camera!"
FDA 483’s and Warning Letters

Form FDA 483, “Inspectional Observations,” is a form used by the FDA to document and communicate concerns discovered during these inspections.

- A recipient of a 483 should respond to the FDA, addressing each item, indicating agreement and either providing a timeline for correction or requesting clarification of what the FDA requires within 15 days.

Warning Letter is issued for violations of regulatory significance, i.e., those that may actually lead to an enforcement action if the documented violations are not promptly and adequately corrected.
## FDA Enforcement Summary 2010

<table>
<thead>
<tr>
<th>Enforcement</th>
<th>Total</th>
<th>Drugs</th>
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<tr>
<td>Seizures</td>
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<td>3</td>
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<tr>
<td>Injunctions</td>
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<td>1</td>
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<tr>
<td>Warning Letters</td>
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<td>171</td>
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<td>Recall Events</td>
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<tr>
<td>Recalled products</td>
<td>9,361</td>
<td>868</td>
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<tr>
<td>Debarments</td>
<td>13</td>
<td>6</td>
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</table>

http://www.fda.gov/ICECI/EnforcementActions/ucm247813.htm
Section 1 Summary

• Pharmaceutical Regulatory Bodies
• History of FDA and Pharmaceutical Regulations
• GMP and cGMP
• Regulatory Guidelines
  – ICH Guidelines
  – FDA Guidance for industry
  – EMEA Guidelines
• Validations
• Regulatory Inspections
Outline

• Regulatory Bodies and Regulatory Guidelines
• Quality System in Pharmaceutical Industry
• Regulatory Submission
• QbD and Risk Management
Quality Systems

• A Quality System is an approach to doing business that stresses building in quality through techniques such as risk management, design controls, continuous improvement, auditing, and management review.

• Pharmaceutical Quality System (PQS): Management system to direct and control a pharmaceutical company with regard to quality (ICHQ10).
Systems covered

• Quality System
• Facilities and Equipment System
• Materials System
• Manufacturing System
• Packaging and Labeling System
• Laboratory Control System
• Information System.
Some Common Terminologies

• QA: Quality Assurance
• QC: Quality Control
• RA: Regulatory Affair
• SOP: Standard Operating Procedure
• Change Control: A systematic approach to managing all changes made to a product or system
• Deviations: Departure from a defined range
• CAPA: Corrective Action and Preventive Action
• MBR and PBR: Master Batch Record and Production Batch Record
• CPP: Critical Process Parameter
• CQA: Critical Quality Attribute
• PAR: Proven Acceptable Range
• APR: Annual Product Review
Pharmaceutical Quality Unit

- **R&D**
- **HR**
- **Management**
  - **Production**
  - **Material Management**
- **QC**
  - **Laboratory Systems (QC and Stability)**
    - Sample Management
    - Reference Standards
    - SOPs and Test Methods
    - Method validation and Transfer
    - Instrument Qualification/Calibration and Maintenance
    - Data Analysis, Records, and Document Control
    - Change Control
    - Contract Laboratory Management
- **QA**
  - **Site Quality Systems:**
    - SOPs and Document Control
    - Master and Production Batch Records (MBR, PBR)
    - Batch Record Review and Product Release
    - Failure Investigations and CAPA
    - Training
    - Site Change Control
    - Validation (Facilities, Equipment, and Computer)
    - Supplier Management and Control
    - Complaints
    - Annual Product Review
    - Management Notification
- **Compliance**
  - **Policies and Standards Audit (Internal and External)**
  - Regulatory Commitments and Documents
  - Recall
Quality Assurance

• Quality assurance is the heart of Quality Unit
• Must ensure that quality policies are followed.
• Must be independent of financial pressures.
• Must have final authority in product acceptance, rejection and release to public.
• Integral to production, not an add-on.
• Responsible for day-to-day operations and for longer term goal settings.
• Quantitative discipline with specified parameters.
The quality of this batch is very poor

We had to ship the order urgently

The starting material you purchased last month has poor quality

We had to cut costs by going to the cheapest bidder

The drug we shipped last month killed 100 patients and FDA is asking us to recall the product

How could this happen? Where the hell were you?

This is what happened when QA doesn’t have the authority!
Citations from FDA 483 Observations and Warning Letters

• “Quality assurance is not overseeing overall product quality. QA does not have independence and authority over the release and rejection of manufactured lots that do not conform to quality standards.” (483)

• "Failure to establish the appropriate responsibility, authority, and interrelation of all personnel who manage, perform, and assess work affecting quality, and provide the independence and authority necessary to perform these tasks, as required by 21 CFR 820.20(b)(1)." (Warning Letter)
Diagram of the ICH Q10 Pharmaceutical Quality System Model

- Pharmaceutical Development
- Technology Transfer
- Commercial Manufacturing
- Product Discontinuation

Investigational products

GMP

Management Responsibilities

- Process Performance & Product Quality Monitoring System
- Corrective Action / Preventive Action (CA/PA) System
- Change Management System
- Management Review

PQS elements

Enablers

- Knowledge Management
- Quality Risk Management
Section 2 Summary

- What is Pharmaceutical Quality System (PRS)
- Quality Unit
  - QA
    - QA must have final authority in product acceptance, rejection and release to public
  - QC
  - Compliance (RA)
- ICH Q10: Pharmaceutical Quality System Model
Outline

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**Drug Development and Regulatory Review in the US**

<table>
<thead>
<tr>
<th>Development/Registration</th>
<th>Pre-Clinical Research</th>
<th>Clinical Studies</th>
<th>NDA/BLA</th>
<th>Post-Marketing</th>
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<td>Drug Discovery</td>
<td>Pre-Clinical Research</td>
<td>Clinical Studies</td>
<td>NDA/BLA</td>
<td>Post-Marketing</td>
</tr>
<tr>
<td>Synthesis &amp; Purification</td>
<td>Months to years</td>
<td>Phase 1</td>
<td>Phase 2</td>
<td>Phase 3</td>
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<tr>
<td>Animal Testing</td>
<td>Phase 2</td>
<td>Phase 3</td>
<td>Phase 4</td>
<td>Post-approval changes</td>
</tr>
<tr>
<td></td>
<td>Avg: 3-8 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IND</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>NDA/BLA</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Approval</td>
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</tr>
</tbody>
</table>

- **Drug Development and Regulatory Review**
  - **Pre-Clinical Research**
  - **Clinical Studies**
    - Phase 1
    - Phase 2
    - Phase 3
  - **NDA/BLA**
    - 6 months to years
  - **Post-Marketing**
    - Adverse reaction Report (post marketing surveillance)
    - Phase 4
    - Post-approval changes

- **FDA Review**
  - 30 days for original IND and major amendment (to the same IND)
  - 6 months for Priority NDA; 10 months for standard NDA (but may be much longer)
  - 4-18 months for prior approval, 60 days review period for Changes being-effected supplement
IND Filing

• Food Drug & Cosmetic Act 505(i) exempts a drug intended solely for investigational use by qualified experts from filling an NDA or ANDA. Application for this exemption is called Investigational New drug Application (IND)
• The goal is to provide pre-clinical data of sufficient quality to justify the testing of the drug in humans
• FDA has 30 days to review an IND application
• Must be filed annually until the completion of clinical testing
• Numerous guidances to industry, including:
  – “Content and Format of INDs for Phase 1 studies of drugs, including well-characterized, therapeutic, biotechnology-driven products” (1995)
  – “INDs for phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information” (2003)
  – “cGMP for phase 1 Investigational Drugs” (2008)
NDA Filing

• New Drug Application (NDA) is an application required by law for approval before a new drug can be introduced into interstate commerce in the US.
• Upon desirable results from Phase 3, New Drug Application (NDA) will be submitted
• The FDA has 60 days to decide whether to file it so that it can be reviewed
• NDA contains data supporting the efficacy and safety of the drug
• The FDA review of NDA
  – Priority NDA: 6 months
  – Standard NDA: 10 months (but may takes years)
• Drugs are subject to ongoing review, making sure no adverse side effects appear from the drug.
• After FDA’s approval, the drug can be marketed and distributed

http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm
ICH M4:
The Common Technical Document


The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

Format of Quality Section of ICH Common Technical Document (CTD)

• Module 2: Quality Overall Summary
• Module 3: Quality Section of CTD
  – 3.1.3 Table of Contents
  – 3.2 Body of Data
    • 3.2.S Drug Substance
      – 3.2.S.1 General Information
      – 3.2.S.2 Manufacture
      – 3.2.S.3 Characterization
      – 3.2.S.4 Control of Drug Substance
      – 3.2.S.5 Reference Standards or Materials
      – 3.2.S.6 Container Closure System
      – 3.2.S.& Stability

Drug Approval Criteria

"Rilovonin? I don't like the sound of it - let's reject it."
Drug Approval Criteria

#1. Drug is safe.

#2. Drug is efficacious.
NDA Approval

Emtricitabine

Rilpivirine

Tenofovir disoproxil fumarate

Gilead Sciences, Inc
Attention: Shalini Gidwani, M.Sc. RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Gidwani,

Please refer to your New Drug Application (NDA) dated and received February 10, 2011 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for COMPLERA™ (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) 200 mg/25 mg/300 mg fixed dose combination tablets.
Post-Approval Changes

- FDA requires drug manufacturers to report postapproval changes to process and product to ensure drug quality throughout the product lifecycle:
  - Components and composition, manufacturing sites, manufacturing process, specifications, container closure system, labeling, miscellaneous changes and multiple related changes.

- Reporting categories
  - **Major change**: substantial potential to have an adverse effect on the identity, quality, purity or potency. Require *Prior Approval Supplement (PAS)*
  - **Moderate change**: moderate potential.
    - *Supplement –Changes Being Effected in 30 Days (CBE-30)*
    - *Supplement-Changes Being Effected (CBE), 60 days review*
  - **Minor change**: minimal potential. Describe it in the next *Annual Report (AR)*.

- Postapproval changes must be report to each market authority but different market may have different requirement/protocols.

*FDA Guidance for Industry: Changes to an Approved NDA or ANDA (2004)*
Post-Marketing Surveillance Trial

- Phase 4 Trial
- Involves the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold
- May be required by regulatory authorities or may be undertaken by the sponsoring company
- The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase 1-3 clinical trials.
- Harmful effects discovered by Phase 4 trials may result in a drug recall, or restricted to certain uses: recent examples involve cerivastatin (Baycol and Lipobay, Bayer, 2001) and rofecoxib (Vioxx, Merck, 2004).
FDA Withdrawal of Drugs

- 20 drugs withdrawn since inception of FDA in 1936

**Omniflox** – antibiotic that causes hemolytic anemia

**Rezulin** – diabetes drug that causes acute liver failure

**Vioxx** – anti-inflammatory drug that increases risk of heart attack

**Baycol** – cholesterol-lowering drug that causes severe muscle injury, kidney failure, and death

**Seldane** – antihistamine that causes heart arrhythmias and death

**Lotronex** - drug for IBS that caused ischemic colitis

The FDA approval does not mean a product is harmless
Canadian Drug Approval System

- All drugs sold in Canada – both those manufactured here and those imported from other countries – must be authorized for sale by Health Canada.
- Clinical Trial Application (CTA)
  - Special Access program (SAP)
- Clinical Trials
  - Phases I, II and III
- New Drug Submission (NDS)
  - The Therapeutic Products Directorate (TPD) in Health Canada reviews and authorizes new drugs.
  - About 4000 drug submissions each year but only 80 are for new drugs
- Notice of Compliance (NOC)
- Post NOC changes
- Post-Market Surveillance
  - Health Canada’s Marketed Health Products Directorate (MHPD) monitors drug adverse events and investigates complaints and problem reports.
Section 3 Summary

- Drug Approval Process
  - IND Submission and Approval
  - NDA submission and Approval
- Post-Approval Changes
- Post-Marketing Surveillance
- Canadian Drug Approval System
Outline

• Regulatory Bodies and Regulatory Guidelines
• Quality System in Pharmaceutical Industry
• Regulatory Submission
• QbD and Risk Management
New Quality Roadmap

• Started with FDA Initiatives: “Pharmaceutical cGMP for the 21st Century: A Risk Based Approach”, the report issued in 2004
  – To enhance and modernize the regulation of pharmaceutical manufacturing and product quality — to bring a 21st century focus to this critical FDA responsibility.

• 4 ICH Guidelines
  – Q9 Quality Risk Management (2005)
  – Q11 Development and Manufacturing of Drug Substances (Chemical Entities and Biotechnological /Biological Entities) (2011)
Objectives of the FDA Initiatives

• To encourage the early adoption of new technological advances by the pharmaceutical industry

• To facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance

• To encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas

• To ensure that regulatory review and inspection policies are based on state-of-the-art pharmaceutical science

• To enhance the consistency and coordination of FDA's drug quality regulatory programs, in part, by integrating enhanced quality systems approaches into the Agency's business processes and regulatory policies concerning review and inspection activities.

http://www.fda.gov/cder/gmp/index.htm
Characteristics of the Desired State

- Manufacturers have extensive knowledge about critical product and process parameters and quality attributes.
- Manufacturers control process through quality systems over life cycle and strive for continuous improvement.
- FDA Role: Initial verification, subsequent audit.

Janet Woodcock, M.D.
Deputy Commissioner/Chief Medical Officer, FDA
Pharmaceutical Quality Initiatives Workshop
March 2, 2007
### An Opportunity for Change

#### Traditional Approach
- Empirical
- Data driven
- Retrospective
- “Test to document quality” (QbA)
- Acceptance criteria based on limited batch data
- Variability not understood and avoided
- Reluctant to change due to regulatory hurdles (perceived or real)

#### Desired State
- Systematic
- Knowledge driven
- Prospective
- **Quality by Design (QbD)**
- Science and Risk based
- Acceptance criteria based on patient needs
- Variability explored and understood (Design Space)
- Innovation and continuous improvement in product development
- Life cycle management for process and system control
QbA vs QbD

• **QbA: Quality by Analysis**
  – Producing a quality product through analysis
  – Current state: Majority of DS and DP
  – Quality risk. Not economical
  – Does not incorporate the best manufacturing technology.

• **QbD: Quality by Design**
  – Systematic approach to development
  – Begins with predefined objectives. Higher level of assurance of product quality for patient
  – Emphasizes product and process understanding and process control
  – Based on sound science and quality risk management
  – Streamline post approval manufacturing changes and regulatory processes
  – Provide opportunity for continuous improvement, facilitate innovation
  – Increase efficiency of manufacturing process
Quality by Design

• Quality is not an add-on: it begins with R&D
• Quality by Design
  – Define target product quality profile
  – Design and develop process to meet target product quality profile
  – Identify critical raw material attributes, process parameters, and sources of variability
  – Control raw materials and process to produce consistent quality over time
• PAT, DOE, and risk assessment are tools to facilitate the implementation of QbD
Example QbD Approach (Q8)

- 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
Design Space

• Definition
  – The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality

• Regulatory flexibility
  – Working within the design space is not considered a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process
Process Analytical Technology (PAT)

- A mechanism to design, analyze, and control pharmaceutical manufacturing processes through the measurement of Critical Process Parameters (CPP) which affect Critical Quality Attributes (CQA) with the goal of ensuring final product quality.

- The long term goals of PAT are to:
  - reduce production cycling time
  - prevent rejection of batches
  - enable real time release
  - increase automation
  - improve energy and material use
  - facilitate continuous processing

*FDA*, *Guidance for industry: PAT — A framework for innovative pharmaceutical development, manufacturing and quality assurance; September 2004*
Design of Experiment (DoE)

• DOE is a systematic approach to investigation of a system or process. A series of structured tests are designed in which planned changes are made to the input variables of a process or system. The effects of these changes on a pre-defined output are then assessed.

• DOE is important as a formal way of maximizing information gained while resources required. It has more to offer than 'one change at a time' experimental methods, because it allows a judgment on the significance to the output of input variables acting alone, as well input variables acting in combination with one another.
DOE Example

Design-Expert® Software

Assay
- Design points above predicted value
- Design points below predicted value

X1 = A: NaBH4
X2 = B: Temperature

Actual Factor
C: Concentration = 5.00

RCOOR1 $\xrightarrow{\text{NaBH}_4}$ RCH$_2$OH

Solvent
Risk and Risk Management

• **Risk** is an uncertain event or condition that, if it occurs, has a negative impact on
  – Project objectives – **product quality** and product availability
  – Project timelines, cost, resources

• **Risk Management**: process of identifying, analyzing and responding to project risks, thereby reducing their impact on the project.
  – Goal: maximize positive outcomes and minimize negative ones.
  – Philosophy: deal with known risks proactively before they occur

• There is no **ONE** way to manage risk. There are various methodologies available.
Why Perform Risk Management in the Pharmaceutical Industry?

• To be proactive
  – Enhancing quality, minimizing delays and costs

• To employ best practices
  – Reduces subjectively, documents rationale for decision and cost-benefit trade offs and harmonizes communication

• To allow prioritization (ranking of risks)
  – Understand the business and what matters most
  – Allocate resources accordingly

• To better fulfill our mission and meet patients’ needs
  – Develop and deliver quality medicines to people that need them quickly and consistently

• It is a regulatory expectation
  – Quality Risk Management (ICH Q8, Q9, Q10 and Q11)
Quality Risk Management Process (Q9)

- Initiate Quality Risk Management Process
  - Risk Assessment
    - Risk Identification
    - Risk Analysis
    - Risk Evaluation
  - Risk Control
    - Risk Reduction
    - Risk Acceptance
  - Output / Result of the Quality Risk Management Process
- Process Development
- Control Strategy Development
- Continual Improvement

- Risk Communication
- FMEA
Section 4 Summary

- New Quality Road Map
  - FDA new quality initiatives
  - Q8, Q9, Q10 and Q11
- Quality by Design (QbD)
  - Design space
  - Process Analytical Technologies (PAT)
  - Design of Experiment (DOE)
- Risk Management
Questions?
Back Up Slides
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION 

DATE OF INSPECTION: 01/25/2010 - 02/12/2010*  

PREMISES: GILEAD Science Center  
19701 Fairchild  
Irvine, CA 92612  
(949) 608-2900  Fax: (949) 608-4417  

INDUSTRY INFORMATION: www.fda.gov/oc/industry 

TO:  General Manager  

FACILITIES AND EQUIPMENT SYSTEM 

OBSERVATION 1  
Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations related to aseptic processing of drug products.  
Specifically, the firm’s initial qualification of Aseptic Processing Areas (APAs) 1077/1077B and 1079 performed 6/2/08 through 8/19/08 following replacement of HEPA filters in 1077/1077B and room modifications to 1078 and 1079 in support of the installation of the RAB (RAB) filling line is deficient. Filling room 1079 did not meet the performance qualification acceptance criteria of Operational ISO 5 Classification for Non-viable Particles. The qualification of 1079 was approved on 9/17/08 as Operational ISO 6 classification. Partially stoppered vials of AmBisome 50 mg/vial (liposomal formulation of amphotericin B) are conveyed through 1079 to the lyophilizer accumulation table in 1077. Eighty-one (81) lots of AmBisome were filled in 1079 and released from 8/21/08 through 4/3/09 until modifications and requalification of the room was performed 3/17/09 through 3/24/09 re-classifying 1079 as Operational ISO 5; twenty of those lots were distributed in the US market.  

OBSERVATION 2  
Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.  
Specifically, the firm’s environmental monitoring practices used to assess the environmental quality within the aseptic filling areas are not adequate:  

a. The firm’s procedure SDSOP-0776, Environmental Monitoring of Product Fill, Revision 26 states that for pre-fill monitoring of APA 1077/1077B and 1079 multiple random samples per room for airborne microbial testing by RCS and non-viable particles (NVP) are to be monitored. There is no documentation at the time of sampling where within the room the samples have been taken so that any alert or action levels documented can be adequately assessed. 

b. There is no data to support that the filling equipment locations selected for post-fill monitoring of surface microbial contamination (RODAC) are appropriate in assessing the filling equipment surfaces. There is no monitoring of filling needles that directly contact product and enter vials or of the needle manifold surface that 

SEE REVERSE OF THIS PAGE  
Carla J. Lundi, Investigator  
02/12/2010 

GILEAD
FDA Issued Warning Letters and an Import Alert to Ranbaxy Laboratories Citing Serious Manufacturing Deficiencies

The FDA on September 16, 2008, issued two Warning Letters to Ranbaxy Laboratories Ltd., of the Republic of India, and an IAP for generic drugs produced by Ranbaxy's Dewas and Paonta Sahib plants in India. FDA inspected the pharmaceutical manufacturing facilities on January 28 through February 12 and March 3 through 7, 2008, respectively.

The Warning Letters identified the Agency's concerns about deviations from CGMP regulations. Because of the extent and nature of the violations, the FDA issued an Import Alert, under which U.S. officials may detain at the U.S. border any API (the primary therapeutic components of a finished drug product), and both sterile and non-sterile finished drug products manufactured at these Ranbaxy facilities offered for import into the United States (U.S.).

The problems FDA investigators identified at these two Ranbaxy plants relate to deficiencies in the company's drug manufacturing process. The actions were proactive measures that the FDA undertook in order to assure that all drugs that reach the American public are manufactured according to CGMP requirements. The action did not involve removing products from the market because the FDA had no evidence to date that Ranbaxy had shipped defective products. The FDA continues to monitor the situation.

The current announcement did not impact products from Ranbaxy's other plants. FDA had inspected those facilities and, to date, the facilities had met CGMP requirements for drug manufacturing.

Earlier, the FDA informed Ranbaxy that until the firm resolved the deficiencies at each of these two facilities and the plants came into compliance with CGMP requirements, FDA would recommend denial of approval of any NDAs and Abbreviated New Drug Applications (ANDA) that list the Paonta Sahib or Dewas plants respectively as the manufacturer of APIs or finished drug products. Ranbaxy is one of the largest foreign suppliers of generic drugs to the U.S.

The FDA Import Alert covers more than 30 different generic drug products produced in multiple dosage forms and dosage amounts (i.e., 25 mg, 50 mg, and 100 mg) at these two locations. The FDA evaluated whether these actions would create any potential drug shortages in the U.S., and determined that with one exception, other suppliers could meet market demand. Because Ranbaxy was the sole supplier to the U.S. of one drug product, Ganciclovir oral capsules (an antiviral drug), to avoid creating a shortage of the drug, the FDA did not detain shipments of this product, and planned to arrange for additional oversight and controls until the company resolved the manufacturing issues.

CDER said with this action FDA was sending a clear signal that drug products intended for use by American consumers must meet FDA standards of safety and quality. The FDA notified other agencies and health care professionals so that appropriate action could be taken to advise patients as needed.

Following the two inspections, the Agency evaluated the findings, Ranbaxy's responses, and the firm's overall inspectional history. The evaluation was complex due to the scientific and technical issues at both sites and the identified deficiencies. Ultimately, FDA concluded that the firm's responses were not adequate and that Warning Letters were the appropriate regulatory response.

This represents the second time in less than three years FDA issued a Warning Letter to Ranbaxy. In 2006, FDA cited Ranbaxy for violations of U.S. CGMP regulations at the Paonta Sahib facility.

To read the full text of the FDA Warning Letters:
http://www.fda.gov/foi/warning_letters/s6922c.htm
http://www.fda.gov/foi/warning_letters/s6923c.htm

Pharmacopeias

- Two most important pharmacopeias: The United States Pharmacopeia (USP) and European Pharmacopoeia (EP)

- First USP was published in 1820

- Pharmacopeia establishes written (documentary) and physical (reference) standards for the quality, purity, identity, and strength of medicines, food ingredients, and dietary supplements manufactured, distributed and consumed worldwide. USP’s drug standards are enforceable in the United States by the FDA, and are used by regulatory agencies and manufacturers worldwide.

- Not all drugs are listed
Who Are Regulatory Bodies?

• Regulatory authority or Regulatory Agency
• Every country has its own regulatory authority to regulate pharmaceutical drugs and medical devices for human use. Prior to being given market authorization, a manufacturer must present substantive scientific evidence of a product's safety, efficacy and quality to the regulatory authority.
• FDA is a regulatory body in the US
Main Regulatory Bodies

• US Food and Drug Administration (FDA)
• European Agency for Evaluation of medicinal Products (EMEA) & Individual Countries Regulatory Agencies in Europe
• Japanese Pharmaceuticals and Medical Device Agency (PMDA)
• Health Canada's Therapeutic Products Directorate (TPD)
• Australia Therapeutic Goods Administration (TGA)
• International Conference on Harmonization (ICH)
• World Health Organization (WHO)
Different Change Management (Flexibility) Approaches Over the Life Cycle

Level of effort and formality

Change Management
Local Technical R&D Function

Pre-Clinical Phase

Clinical Phase

Clinical Trial Application
Registration Batches
First Regulatory Submission

Market Phase

Consider notification or approval according to regional regulations

Local and Corporate Change Management Process

Time
The CQAs Process Assessment for API

Drug Product \rightarrow API Critical Quality Attributes \rightarrow Potential Process Critical Parameters

\rightarrow Critical Steps \rightarrow Critical process Parameters (CPPs)

\rightarrow Additional Control Points
Role of Quality Risk Management Over the Product Life Cycle

Product Development
- Product/Prior knowledge
  - Risk Management
  - Excipient & Drug Substance Design Space

Process Development
- Manufacturing process/Prior knowledge
  - Risk Management
  - Manuf. process Design Space

Conclusions & Tech. Transfer
- Product and Process Dev. Knowledge
  - Risk Management
  - Product quality/control strategy

Commercial Manufacturing
- Process history
  - For life cycle management
  - Continual improvement

QRM: Risk Assessment – Risk Control – Risk Communication – Risk Review

Process understanding

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IND Review Objectives

- In early phase of IND
  - Safety predominates
  - Study protocol can be modified based on experience without prior notification of FDA
  - Amount of CMC and toxicity information depends on nature and extent of clinical study
- FDA’s primary objectives in reviewing an IND are
  - To assure the safety and rights of subjects in all phases of investigation
  - To focus on assessing the safety in Phase I
  - To help assure that quality of clinical protocols and related information is adequate to permit assessment of safety and effectiveness of the drug in Phases 2 and 3
Process Validation: General Principles and Practices

The new FDA Guidance describes process validation as an activity that coincides with the *entire product lifecycle*, with three “Stages”:

- **Stage 1: Process Design**
  - Building and capturing process knowledge and understanding
  - Establishing a strategy for process control

- **Stage 2: Process Qualification**
  - Design of a facility and qualification of utilities and equipment
  - Process performance qualification (PPQ) produces scientifically measurable proof
    - that products consistently meet the specifications,
    - that the process parameters meet the acceptance criteria and
    - that the fluctuations are measured objectively

- **Stage 3: Continued Process Verification**
  - Monitoring and improving control and reducing product and process variation during commercial manufacture

Example of Risk Assessment Tools in Product & Process Development

• Tools for parameter screening
  – Examples: Ishikawa diagrams, What-if analysis, HAZOP analysis

• Tools for risk ranking
  – Examples: FMEA/FMECA, Pareto analysis, Relative ranking

• Experimental tools for process understanding
  – Examples: Statistically designed experiments (DOE), mechanistic models

• Risk control tools
  – Training procedures, equipment procedures, process controls, in-process testing, end-product testing, specifications, etc.
Post-Marketing Surveillance Trial

- Phase 4 Trial
- Involves the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold
- May be required by regulatory authorities or may be undertaken by the sponsoring company
- The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase 1-3 clinical trials.
- Harmful effects discovered by Phase 4 trials may result in a drug recall, or restricted to certain uses: recent examples involve cerivastatin (Baycol and Lipobay, Bayer, 2001) and rofecoxib (Vioxx, Merck, 2004).
The Vioxx Recall

• In May 1999, FDA approved Merck’s COX-2 inhibitor Vioxx for treating patients with arthritis and other conditions causing chronic or acute pain. It soon gained widespread acceptance among physicians.
  – Merck invested $500 million in consumer and professional advertising
  – 20 million American users
  – Merck profit: $50 million/month
• On September 30, 2004, Merck announced an immediate withdrawal of Vioxx following a clinical study indicating it more than doubled the risk of heart attack and stroke
• An FDA study published post-recall estimated that Vioxx caused as many as 140,000 heart-related injuries & 56,000 deaths in five years
• By March 2005, Merck was facing 1357 injury claims against its defective drug
FDA Withdrawal of Drugs

- 20 drugs withdrawn since inception of FDA in 1936
  - Omniflox – antibiotic that causes hemolytic anemia
  - Rezulin – diabetes drug that causes acute liver failure
  - Fen-Phen and Redux – weight loss drugs that cause heart valve injury
  - PPA (Phenylpropanolamine) – OTC decongestant and weight loss drug that caused hemorrhagic stroke in women
  - Rovan – antibiotic that cause acute liver failure
  - Lotronex – drug for IBS that caused ischemic colitis
  - Baycol – cholesterol-lowering drug that caused severe muscle injury, kidney failure, and death
  - Seldane – antihistamine that caused heart arrhythmias and death
  - Propulsid – drug for nighttime heartburn that caused heart arrhythmias and death

The FDA approval does not mean a product is harmless
IND Content

• INDs generally are required to contain sufficient information in the following three categories to permit an assessment as to whether the investigational drug is safe for testing in humans for the intended use
  – Clinical protocols and list of investigators
  – Pharmacological and toxicological studies in animal or in vitro
  – Chemistry, manufacturing, and controls (CMC)
NDA Content

• Goals of the NDA are to provide enough information to permit FDA reviewers to reach the following key decisions:
  – Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks
  – Whether the drug’s proposed labeling (package insert) is appropriate, and what it should contain
  – Whether the methods used in manufacturing the drug and the controls used to maintain the drug’s quality are adequate to preserve the drug’s identity, strength, quality, and purity.
FMEA Inputs and Outputs

Inputs

- Process Map
- Knowledge
- Experience
- Procedures
- Pre-determined rating scales

Outputs

- Action Plan
- Action Rational
- Actions history
- Re-assessed risk

FMEA
Failure Model Effects Analysis (FMEA)

- FMEA Steps
  1. Identify the steps and ways in which a process can fail (Failure mode)
  2. Identify the potential effect of the failure on the customer/product
  3. Identify the potential causes of the failure
  4. Estimate the risk of the failure mode = RPN

**Severity of the effect (or impact)**

- 10
- 9
- 8
- 7
- 6
- 5
- 4
- 3
- 2
- 1

**Probability of occurrence**

- 10
- 9
- 8
- 7
- 6
- 5
- 4
- 3
- 2
- 1

**Detectability of failure**

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10

- **S x P**
- **Criticality**
- **S x P x D**

* Higher detection ability (e.g. 1) lowers risk score

**“RPN” or “Risk priority number”**

Bad       Good

* "GILEAD"
Failure Model Effects Analysis (FMEA)

- FMEA Steps
  1. Identify the steps and ways in which a process can fail (Failure mode)
  2. Identify the potential effect of the failure on the customer/product
  3. Identify the potential causes of the failure
  4. Estimate the risk of the failure mode = RPN
  5. Identify and prioritize future actions to control the risk
     - Deal with RPN > 100 with highest ranked risk first
     - Assigned actions to responsible parties and specify timing for implementation
  6. Later, at specified time (s), revise risk estimation after actions are implemented
## FMEA Table Example

<table>
<thead>
<tr>
<th>Part/Process</th>
<th>Failure Mode</th>
<th>Failure Effects</th>
<th>Severity</th>
<th>Causes</th>
<th>Controls Occurrence</th>
<th>Detection</th>
<th>RPN</th>
<th>Actions</th>
<th>Responsibility &amp; Target Completion Date</th>
<th>Actions taken</th>
<th>SEV</th>
<th>OCC</th>
<th>DET</th>
<th>RPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>(What is the function of each step)</td>
<td>(Describe what could go wrong)</td>
<td>(How does the failure affect the function of the step)</td>
<td>(What is the root cause or reason for the failure)</td>
<td>(What controls are currently in place to catch or prevent this failure)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Risk Management Example

- Project objective: Go to New York for New Year Party

1. Book Flight and Hotel
2. Drive to Airport
3. Board Airplane
4. Fly
5. Take Taxi to Hotel
6. Attend the Party
## Risk Analysis Example

<table>
<thead>
<tr>
<th>Risk</th>
<th>Cause</th>
<th>Effect</th>
<th>Probability Scale 1-10</th>
<th>Impact Scale 1-10</th>
<th>Detection 1-10</th>
<th>RPN (risk score)</th>
<th>Risk Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>I arrive late to New York</td>
<td>Flight delay</td>
<td>I miss the party</td>
<td>7</td>
<td>10</td>
<td>10</td>
<td>700</td>
<td></td>
</tr>
<tr>
<td></td>
<td>My car breaks on the way to airport and I miss flight</td>
<td></td>
<td>3</td>
<td></td>
<td>3</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>I miss the party</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All flights that week canceled due to bad weather</td>
<td></td>
<td>1</td>
<td>10</td>
<td>7</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Couldn’t find hotel</td>
<td>All hotels are full</td>
<td>No place to stay</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>125</td>
<td></td>
</tr>
</tbody>
</table>
Risk Criticality = probability x impact

<table>
<thead>
<tr>
<th>Impact/Severity of effect</th>
<th>Probability of occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Very Low</td>
<td>1</td>
</tr>
</tbody>
</table>

- A – Avoidance
- B – Mitigation
- C – Transference
- D - Acceptance
## Risk Analysis and Response Example

<table>
<thead>
<tr>
<th>Risk</th>
<th>Cause</th>
<th>Effect</th>
<th>Probability Scale 1-10</th>
<th>Impact Scale 1-10</th>
<th>Detection 1-10</th>
<th>RPN (risk score)</th>
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<td>I arrive late to New York</td>
<td>Flight delay</td>
<td>I miss the party</td>
<td>7</td>
<td>10</td>
<td>3</td>
<td>700</td>
<td><strong>Avoid</strong>: Book flight departing 3 days earlier</td>
</tr>
<tr>
<td></td>
<td>My car breaks on the way to airport and I miss flight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Avoid</strong>: Don’t drive, take shuttle or taxi</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Reduce</strong>: car inspection and maintenance a week earlier</td>
</tr>
<tr>
<td></td>
<td>All flights that week canceled due to bad weather</td>
<td></td>
<td>1</td>
<td>7</td>
<td>7</td>
<td>70</td>
<td><strong>Avoid</strong>: cancel</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Transference</strong>: buy travel insurance to mitigate financial impact</td>
</tr>
<tr>
<td>Couldn’t find hotel</td>
<td>All hotels are full</td>
<td>No place to stay</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>125</td>
<td><strong>Avoid</strong>: Book hotel ASAP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Transference</strong>: Stay with friends</td>
</tr>
</tbody>
</table>