

# Regulation of Pharmaceutical Ingredients

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# History of Excipients

- Sources
  - Commodities from chemical and food suppliers
  - Natural origin
- 1965 USP (United States Pharmacopeia) monographs for:
  - PVP
  - Microcrystalline Cellulose
- Establishment of NF (National Formulary)
  - Relationship to USP
- New Excipients
  - New dosage form manufacturing processes
  - New dosage delivery forms

# Excipients Defined

- Other than API
- Evaluated for safety
- Added to:
  - aid processing
  - Protect, support or enhance stability, bioavailability, or patient acceptability
  - Product identification, or
  - Enhance any other attribute of the overall safety and effectiveness of the drug product during storage or use.

# Excipients

- ~773 FDA “allowed”
- ~385 USP/NF
  - ~100 currently identified for addition
- Functionality
  - **Adding that “spoonful of sugar”-and more**
    - ❖ *Modern Drug Discover*, May 2002, 5(5), pp 34-38.

# Excipient Functionality

## ▶ Binder

- Povidone
- Calcium Phosphate

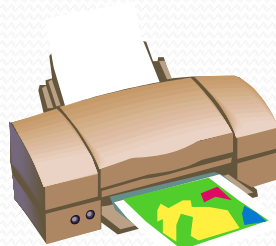
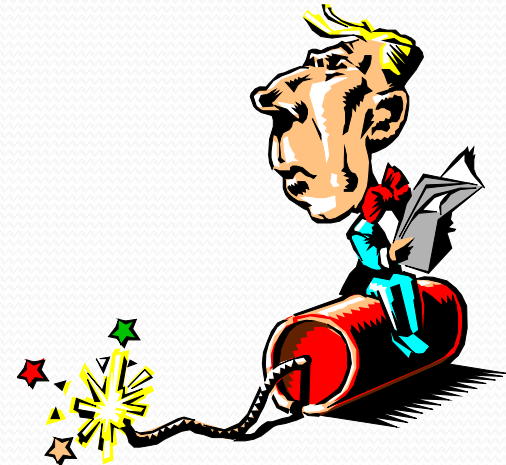
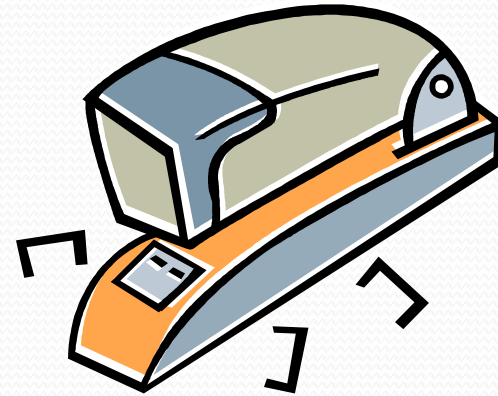
## ▶ Compression Aid

- Dextrose
- Microcrystalline Cellulose

## ▶ Disintegrant

- Crospovidone
- Starch

## ▶ Color/Flavor



# Excipient Functionality

## ▶ Filler

- Calcium Phosphate
- Lactose

## ▶ Sweetener

- Sucrose

## ▶ Lubricant

- Magnesium Stearate

## ▶ Preservative

- Parabens
- BHT



# Excipient Functionality

## ▶ Glidant

- Colloidal Silica
- Talc

## ▶ Suspending/dispersing

- Titanium Dioxide
- Propylene Glycol
- Glycerin
- Ethanol

## ▶ Coating/Film former

- Shellac
- Methyl Cellulose

## ▶ Printing Ink



# Statutory Requirements

- Food, Drug, and Cosmetic Act
  - Components of drugs and drug products are drugs [section 21(g)]
  - Drugs (components and drug products) must be manufactured in conformance with current good manufacturing practice [section 501(a)(2)(B)]
  - A drug whose name appears in an official compendium, must meet the standards set forth in the official compendium [section 501(b)]

# FDA BPC Inspection Guide

“Although the GMP regulations under 21 CFR, Parts 210 and 211, apply only to finished dosage for drugs, Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act requires that all drugs be manufactured, processed, packed, and held in accordance with current good manufacturing practice (cGMP). No distinction is made between BPCs and finished pharmaceuticals, and failure of either to comply with cGMP constitutes a failure to comply with the requirements of the Act.”

# Current GMP Regulations

## Pharmaceuticals

- 21 CFR Parts 210 and 211
  - Requirements for manufacturers of finished pharmaceuticals (i.e., in-process materials and drug products)
  - They are not requirements for manufacturers of drug components (but may be used as guidance for manufacturers of excipients, APIs)

# Current GMP Regulations

## Dietary Supplements

- 21 CFR Part 111

- Sec. 111.70 What specifications must you establish?

- ❖ For each component, you must establish :

- An identity specification;
- Component specifications to ensure the purity, strength and composition of dietary supplements manufactured using the components; and
- Limits on contamination that may adulterate or may lead to adulteration of the finished dietary supplement.

- Sec. 111.73 What is your responsibility for determining whether established specifications are met?

- You must determine whether the specifications you establish under Sec. 111.70 are met.

# Current GMP Regulations

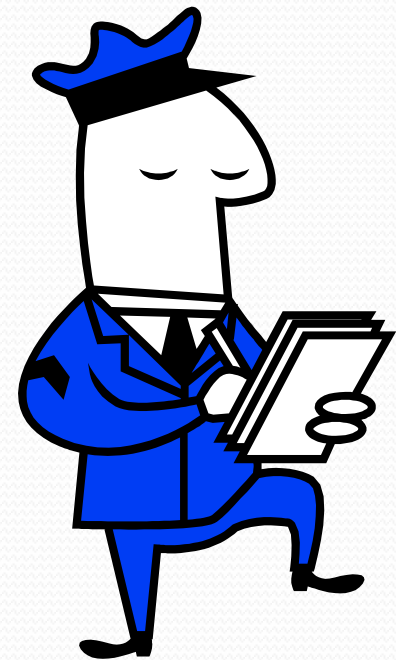
## Dietary Supplements

- 21 CFR Part 111
  - Sec. 111.75 What must you do to determine whether specifications are met?
    - ❖ Before you use a component, you must:
      - Conduct at least one appropriate test or examination to verify the identity of any component; and
      - Rely on a certificate of analysis from the supplier of the component that you receive, provided that:
        - You first qualify the supplier by establishing the reliability of the supplier's certificate of analysis through confirmation of the results of the supplier's tests or examinations;
        - You maintain documentation of how you qualified the supplier;
        - You periodically re-confirm the supplier's certificate of analysis; and

# FDA Regulation

## Dosage Form

- **21 CFR 211**
- Guidance Documents
  - Drug Applications (NDA, ANDA)
  - Post-Approval Changes
  - Inspection Guidelines
  - ICH Guidelines
- Books
- Trade journals articles
- Pre-approval Inspection (PAI)
- Routine Audit every 2 years



# FDA Regulation

## Active Pharmaceutical Ingredient (API)

- 21 CFR 211
- FDA Guidance Documents
  - BACPAC
- ICH Guidance Documents
  - ICH Q7
  - ICH Q3A, B, and C: Impurities
- USP General Chapters
- Books
- Trade journal articles
- PAI when NDA or ANDA filed
- Audit periodically



# FDA Regulation

## Excipient

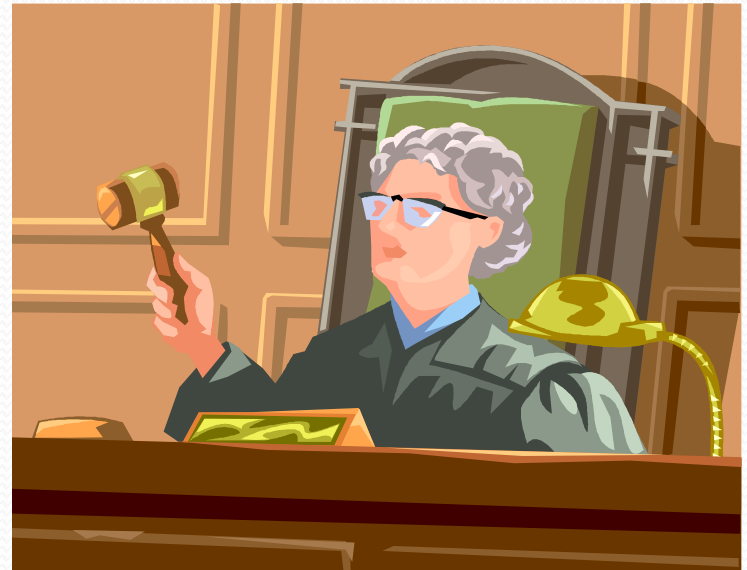
- 21 CFR 211
- FDA Guidance Documents-DMF
- USP General Chapters
- IPEC Guidelines
- Books
  - Excipient Dev for Pharm, Biotech and Drug Delivery Systems
- Trade journal articles
- Non-routine Audit
  - New excipient or functionality
  - For cause
  - Oops (by mistake)



# FDA Regulations

## Consequences of Not Complying

- FDA 483
- Warning Letter
  - <http://www.fda.gov/foi/warning.htm>
- Regulatory Actions
  - Consent Decree
  - Seizure
  - Recall
  - Cease and desist
  - **Criminal penalties**



# Excipient “Incidents”

- **USA** 1937 105 deaths
- **South Africa** 1969 7 deaths
- **India** 1986 14 deaths
- **Bangladesh** 1990 – 1992 236 deaths
- **Nigeria** 1990 47 deaths
- **Argentina** 1992 23 deaths
- **Haiti** 1995-1996 88 deaths
- **China** 2006 6 deaths
- **Panama** 2007 >>100 deaths

# IPEA



- Incorporated in 2001
  - Subsidiary of IPEC-Americas
- Mission: Facilitate Site Assessment for Qualification of Excipient Suppliers
- Objective: Reduce Costs for Both Makers and Users
- Approach: Sharing of Excipient Audit Reports
- Standard: Excipient GMP Guideline
- Report: Document How Site Meets GMP Expectations

# Our Mission

Facilitate assessment of excipient manufacturers to appropriate GMP standards. To achieve this, IPEA provides audits of pharmaceutical and nutraceutical excipient manufacturing facilities to USP and IPEC guidelines.

Audits of manufacturing sites are performed worldwide. Audit Reports provide a basis for confirming that the quality systems used to produce the audited excipient meets appropriate cGMP.

Through audits, deficiencies in manufacturing and packaging can be identified early and potential industry tragedies can be avoided.

# Status

- Completed ~21 Site Audits for >30 Excipients
- Conducted:
  - 6 Public Excipient Auditing Workshops including 2 Overseas
  - 3 On-Site
- Performed 7 Gap Assessments



# Audit Report Sharing

- Audit Sponsor: Either Maker or User
- Audit Report: Available for Sale to other Users
  - With Maker Approval
- Confidentiality: Strictly Enforced



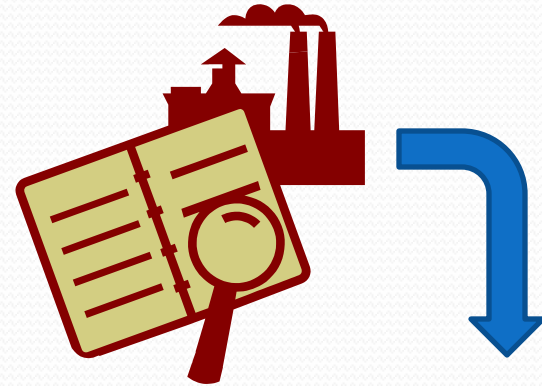
# IPEA Audit Process



Application



Planning



Audit



IPEA Report Review



Excipient Supplier Review



# Excipient Certification

- Assess Conformance of Site Quality System to Excipient GMP Expectations
- Comprehensive Site Audit to Excipient GMPs
- Certify Conformance
  - Issue Certificate
  - Post to Website
    - ❖ Make audit report available

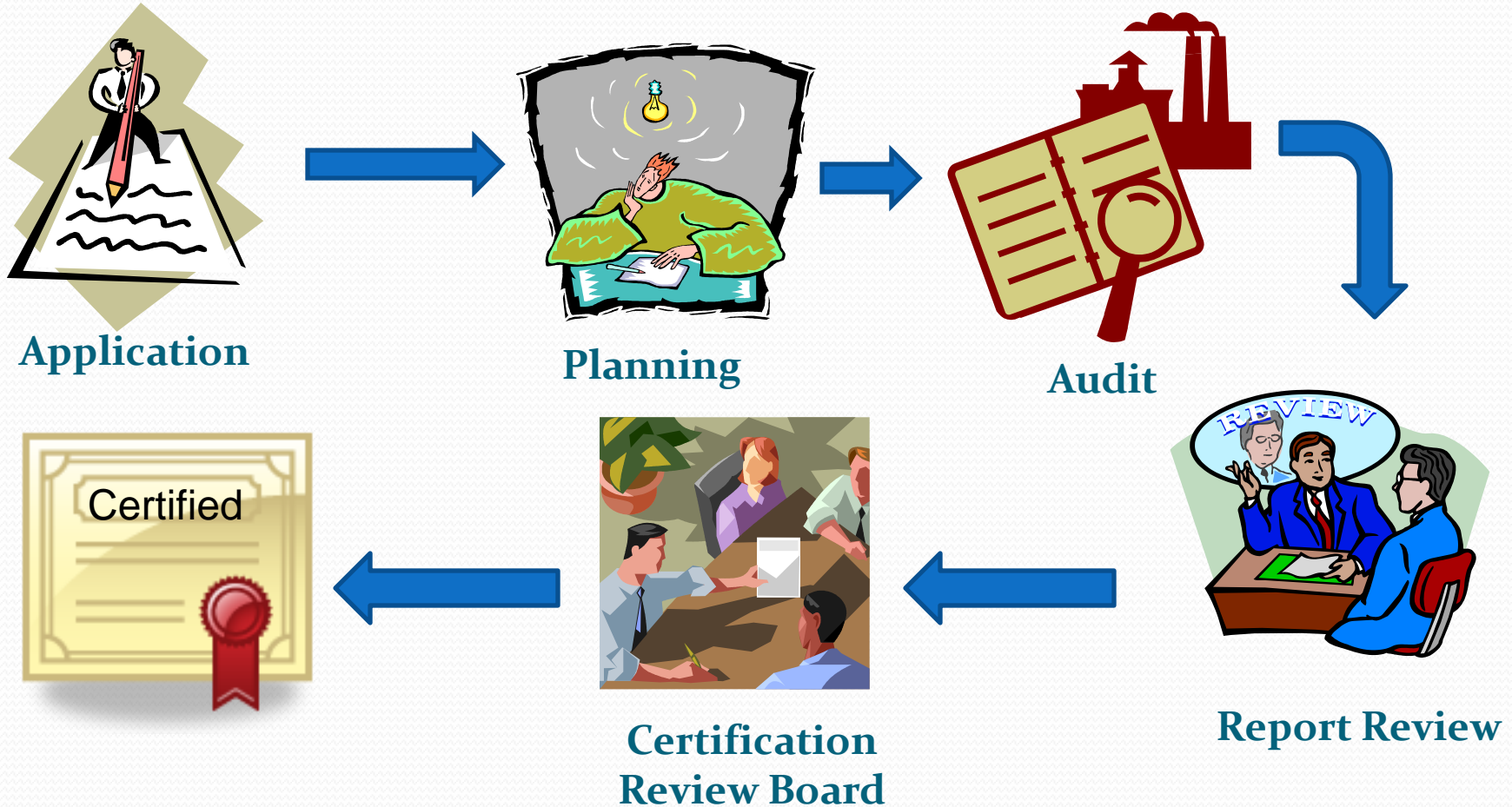


# Excipient Certification

- Accredit to American National Standards Institute
  - Develop Auditable Standard
  - Document Certification Program
  - Create Program Administration
  - Establish Objective Expectations
  - Create Certification Body
  - Prepare Quality Manual
  - Host ANSI Assessment



# IPEA Certification Process



# Auditor Qualification

- Education and Experience
- Training by IPEA
  - 3-Day Workshop, or
  - 1-Day Excipient GMP Expectations



# Auditor Qualification

- Supervised Qualification Audit
  - On-site Performance
  - Audit Report
- Continuing Oversight



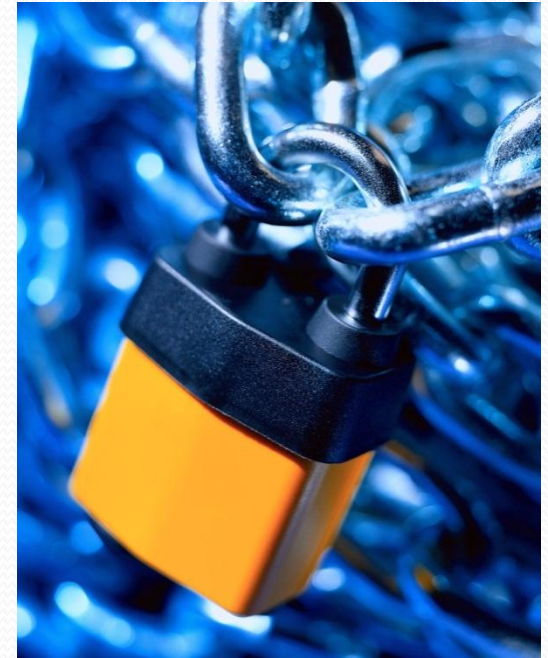
# Objectivity

- Conflict of Interest
  - Disclosure of:
    - ❖ Employment by Applicant
    - ❖ Consulting for Applicant
    - ❖ Significant Financial Interest



# Supply Chain Controls

- FDA Concerned About Ingredients
  - Panama Glycerin Poisoning
  - Contaminated Toothpaste
  - Contaminated Pet Food
  - Heparin
- Excipient Pedigree
  - Do you know where your ingredients are produced?
  - Do you know how they were distributed?



# Improving Supply Chain Security

- Tamper Evident Seals
  - Boxes
    - Embossed Tape
  - Drums
    - Embossed Tape
    - Imprinted Dust Caps
  - Bulk
    - Numbered Seals



# Supply Chain Security

Using an excipient without knowing the manufacturing location and the excipient path to your front door is like using a toothbrush you find lying in a public restroom!



# IPEC Proposal

- Verified Paper Trail
  - Already in-use
    - All movements require paperwork (e.g. BOL)
  - Site audit
    - Excipient manufacturer
    - Distributor
  - Verify distribution
    - Shipping papers back to original manufacturer
    - Periodically confirm



# Quality Approval

- Verify:
  - Package
  - Label
  - Tamper-evident Seal
- Sample:
  - ID test on each sample
  - Manufacturers COA or
  - Full testing



Not knowing excipient pedigree is like accepting currency without verifying its authenticity.



The image shows a \$10 Federal Reserve Note with three callout boxes highlighting security features. The note is a Series 2004 A, featuring Alexander Hamilton. The callouts are: 1. Security Thread: A vertical strip to the right of the portrait. 2. Color-Shifting Ink: The number '10' in the lower right corner. 3. Watermark: A faint image of Alexander Hamilton's portrait on the right side of the note.

**SECURITY THREAD**  
Hold the bill up to the light and look for the security thread, or plastic strip, that is embedded in the paper and runs vertically to the right of the portrait. If you look closely, the words "USA TEN" and a small flag are visible along the thread from both sides of the note. This thread glows orange when held under ultraviolet light. In the redesigned \$10 note, the thread has shifted slightly to the right of its location on older series \$10 notes.

**COLOR-SHIFTING INK**  
Look at the number "10" in the lower right corner on the front of the note. When you tilt the note up and down, the color-shifting ink changes color from copper to green.

**WATERMARK**  
Hold the bill up to the light and look for the watermark, or faint image, similar to the large portrait of Treasury Secretary Alexander Hamilton. The watermark is part of the paper itself and can be seen from both sides of the note. A blank oval has been incorporated into the new \$10 design to highlight the watermark's location.



# Reported FDA Position

CRN: “Industry will be asked to bear a greater and greater burden in the effort to ensure safety of the supply chain in all aspects of the life sciences related industry. Just as sobering is the expected enforcement environment. "We couldn't possibly have known" will no longer be accepted as a defense. Companies will be expected to know everything about not only what their suppliers are providing, but also what their suppliers' suppliers are providing.”

# Thank you for your attention

**[www.ipeainc.com](http://www.ipeainc.com)**

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