A Brief History of USFDA Good Manufacturing Practices (GMPs)

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Agenda

• Introduction – What are “the GMPs”?
• Pre-GMP History (<1963)
• GMP History (1963-2007)
• Making GMP History (2007-Present)
• Conclusion
What are the GMPs?

- **Good Manufacturing Practices (GMPs)**
  - Minimum manufacturing and control practices
    - Sometimes prefixed “c” (for “current”)
  - Focus on “what” to do, not “how” to do
  - Apply to food, human & animal drugs, biologics, devices, processed tissues, and (most recently) dietary supplements
  - Failure to comply = adulteration
    - Products subject to regulatory action
List of USFDA cGMPs

• “Canonical List” of USFDA cGMPs (by publication year):
  – Part 210: cGMP in Manufacturing, Processing, Packing, or Holding of Drugs; General (1963; revamped 1978)
  – Part 211: cGMPs for Finished Pharmaceuticals (1963; revamped 1978)
  – Part 226: cGMPs for Type A Medicated Articles (1975)
  – Part 606: cGMPs for Blood and Blood Components (1975)
  – Part 225: cGMPs for Medicated Feeds (1976)
  – Part 110: cGMP in Manufacturing, Packing, or Holding Human Food (1986)
  – Part 216: Pharmacy Compounding (1999)
  – Part 1271.145-320: Current Good Tissue Practice [for HCT/Ps] (2001)
  – Part 111: cGMP in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements (2007)
GMPs are Everywhere!

- World Health Organization (WHO)
  - [http://www.who.int/topics/pharmaceutical_products/en/](http://www.who.int/topics/pharmaceutical_products/en/)
  - [http://www.fda.gov/cder/dmpq/cgmpregs.htm](http://www.fda.gov/cder/dmpq/cgmpregs.htm)
- ICH Q7: GMPs for Active Pharmaceutical Ingredients 
- European Union (in the EUDRALEX) 
- UK Medicines & Healthcare Regulatory Agency (MHRA) “Orange Book”:
I Repeat, GMPs are Everywhere!

- Buildings & Facilities
- Manufacturing
- Packaging & Labeling
- Product Development Laboratory
- Quality Control & Laboratories
- Quality Assurance
- Receiving & Shipping
- Regulatory Affairs
- Training Department
- Validation Department
Why Review GMP History?

• “Those who cannot remember the past are condemned to repeat it.”
  – George Santayana

• We live in a reactive, not proactive, society
  – Laws & regulations born of tragedies, & catastrophes to prevent recurrence
  – Federal agencies formed or strengthened in their wake
Reactive Government…

- FEMA – 1802; assistance to NH town after a fire
- FTC – 1914; anti-trust & monopolies; Black Tuesday
- OSHA – 1971; coal mining and other disasters
- USDHS – 09/11/2001
- FCC – Janet Jackson’s 2004 “wardrobe malfunction”
- FDA – today’s discussion
1880s-1900s – Progressive Movement

- Decades of lobbying, mounting pressure
  - Consumer groups, mostly women activists
- Muckraking journalism exposes corruption
  - Food and drugs exposed
  - Raised public awareness
  - Led to first laws governing their life cycles
- Events that can still make a person wince today…
1902 – The Poison Squad

• Harvey Wiley’s “Hygienic Table Trials”
  – Congress approved testing of preservatives
  – “Poison Squad” of 12 DA volunteers informed & given free, high-quality (but dosed) meals
  – ½ gram to 4 grams daily over 5-year study
  – first five subjects were:
    • Na₂B₄O₇·10H₂O (borax)
    • C₆H₄(OH)COOH (salicylic acid)
    • H₂SO₄ (sulfuric acid)
    • NaC₆H₅CO₂ (sodium benzoate)
    • CH₂O (formaldehyde)
1902 – The Poison Squad (cont.)

• National controversy & bad publicity:
  – Reporters interviewed chef through basement window
  – Wiley started giving reports to newspapers
  – Experiments stopped after major side-effects
    • nausea, vomiting, stomach aches, inability to work
  – Poison Squad even made the minstrel shows
    • See next slide

• Effects were fortunately reversible
1902 – The Poison Squad (cont.)

- "O, they may get over it but they'll never look the same,
- That kind of bill of fare would drive most men insane.
- Next week he'll give them mothballs, a la Newburgh or else plain;
- O, they may get over it, but they'll never look the same."

- From "Song of the Poison Squad"
  - Lew Dockstader's Minstrels, 1903
1905 – “The Great American Fraud”

• 11-part patent medicine series in Collier’s
  – Exposed “quackery”, “nostrums”, & “ephemera”
  – False claims by mfrs.
  – Raised real health concerns
  – Lack of quality control
  – Many contained alcohol, addictive drugs, or worse!
  – Led to public outrage and significant pressure on Congress
Patent Medicines –
Need a Little Pick-me-Up?

“Carry this package with you always”

http://theodoregray.com/PeriodicTable/PopularScience/2004/08/2/image3.jpg
1906 – “The Jungle” by Upton Sinclair

• Corruption of US meat packing industry

• Attempting to promote socialism over capitalism, but became best-seller (to Sinclair’s lament)
  – "not because the public cared anything about the workers, but simply because the public did not want to eat tubercular beef”

• Nevertheless critical to shaping first food & drug control laws
“The Jungle”, Chapter 14 (Excerpts)

• Jonas had told them how the meat that was taken out of pickle would often be found sour, and how they would rub it up with soda to take away the smell, and sell it to be eaten on free-lunch counters…

• There was never the least attention paid to what was cut up for sausage; there would come all the way back from Europe old sausage that had been rejected, and that was moldy and white – it would be dosed with borax and glycerine, and dumped into the hoppers, and made over again for home consumption…
“The Jungle”, Chapter 14 (Excerpts)

There would be meat that had tumbled out on the floor, in the dirt and sawdust, where the workers had tramped and spit uncounted billions of consumption germs. There would be meat stored in great piles in rooms; and the water from leaky roofs would drip over it, and thousands of rats would race about on it. It was too dark in these storage places to see well, but a man could run his hand over these piles of meat and sweep off handfuls of the dried dung of rats. These rats were nuisances, and the packers would put poisoned bread out for them; they would die, and then rats, bread, and meat would go into the hoppers together. This is no fairy story and no joke; the meat would be shoveled into carts, and the man who did the shoveling would not trouble to lift out a rat even when he saw one – there were things that went into the sausage in comparison with which a poisoned rat was a tidbit…
1906: Pure Food & Drug (Wiley) Act

- Foremost concern: correct product labeling
  - Prohibited mfr & sale of *adulterated, misbranded, poisonous,* or *deleterious* foods, drugs, medicines
  - Banned their interstate transport
- Authorized legal *enforcement of USP standards*
- Often considered origin of modern FDA
- Required *Rx from licensed doctors* for some drugs
- Several flaws, however:
  - Therapeutic claims were not limited
  - Did not require pre-market inspections or approvals
A Step Back: US Pharmacopeia (USP)

• 1820 – 217 “most fully established & best understood” drugs published:
  – Standards (ultimately, GMPs)
  – QC system
  – national formulary (NF)

• 1846 – recognized by Drug Import Act

• 1906 – standards became enforceable as law by Bureau of Chemistry
  – BoC becomes FDA in 1926
1933: America’s Chamber of Horrors

- FDA exhibited real products to pressure fixing the 1906 law’s flaws, including:
  - A weight loss drug that caused death
  - A hair remover that caused baldness, even if not used on the head
  - An eyelash dye that blinded women (next slide)
  - Lotions & creams that caused mercury poisoning
  - First Lady Eleanor Roosevelt took this exhibit to the White House and appealed to America's women to campaign for stronger protections for consumers
1933: America’s Chamber of Horrors

Lash Lure – “the New and improved Eye Brow and Eye Lash Dye”

However, it took another tragedy to change the law…

http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118458.htm
1937 – Elixir Sulfanilimide

- 1932 – 1st sulfa antimicrobial
- 1937 – S. E. Massengill devised liquid dosage form for children:
  - Chief Chemist Watkins’ creation: 10% sulfanilamide, 72% diethylene glycol, 16% water, “elixir flavor”, raspberry extract, saccharin solution, amaranth, and caramel
- 107 deaths, 248 survivors
- No regulation required toxicity testing – only one law was broken. What was it?
1937: Tragedy Aftermath

• CEO: "We have been supplying a legitimate professional demand and not once could have foreseen the unlooked-for results. I do not feel that there was any responsibility on our part”

• Watkins: committed suicide awaiting the trial

• Massengill: minimum fine – guilty only of labeling this an “elixir” when it contained no alcohol
  – Product seizure by FDA by near “technicality”

• Result: Highlighted need for pre-market drug safety testing
1938: Food, Drug & Cosmetic (FD&C) Act

- Requires new drug pre-marketing **safety studies**
  - Origin of what is now the NDA process
- Prohibits **false therapeutic claims**
- Authorizes factory **inspections**
- Allows FDA to request court **injunctions**
  (previously: only seizures & prosecutions)
- Extends control to **cosmetics and devices**
- Requires **safe tolerances** for unavoidable poisonous substances
1941: Sulfathiazole Tragedy

- Winthrop Chemical markets sulfathiazole tablets contaminated with phenobarbital
  - Hundreds of deaths and injuries resulted
- FDA's investigation revealed plant control deficiencies and irregularities
  - In both production & recall processes
- Result: FDA drastically revises rules on manufacturing & quality controls
  - Hailed as “the birth of GMPs”, though GMP regulations won’t be issued for 23 more years
1953-1962: Thalidomide Tragedy

- 1953 – synthesized by Chemie Grünenthal
  - No side effects, high animal dose tolerances
- 1956 – given freely to employees to help determine what it could do
- One brought it home to his pregnant wife – child born without ears!
- Drug soon approved & sold in >40 countries
  - antiemetic (morning sickness)
  - sleeping aid
1953-1962: Thalidomide Tragedy

- 1956 - Richardson-Merrell applies to sell as Kevadon in US
  - Frances Kelsey, new FDA inspector rejected application:
    - Fetal safety background from working with quinone (malaria drug) in the 1940s
    - Application reflected major dearth of safety data and no mechanism of action, as required by 1938 FD&C Act
    - Despite political pressure and 6 reapplications, Kelsey refused to approve the drug for sale
1953-1962: Thalidomide Tragedy

- 1956-1962 – approx. 10,000 Europeans born with phocomelia
- Kevadon kept off US market
- Kelsey earns highest Congressional honor

[Image: http://www.thalidomide.ca/fr/informations/images/baby.jpg]
1962: Tragedy Aftermath

• **Kefauver-Harris Amendment**
  - “Proof of Efficacy” required
  - Adverse events reporting to FDA required
  - “Informed consent” for clinical studies
  - Drug ads must disclose side effects
  - 2-year inspection mandate
  - Authorized FDA to issue **GMP rules**
    - For “manufacturing, packaging, or holding of finished pharmaceuticals”
1963: First Drug GMPs (28 FR 6385)

- Foundation for today’s GMPs

- For “manufacturing, processing, packing or holding finished pharmaceuticals”
1970-1980s: Signs of Effectiveness…

… Led to increased scope and control:

- 1975 – cGMPs for blood & blood components finalized
- 1976: Proposed GMPs for LVPs (next slide)
- 1976: Medical Device Amendment
  - Dalkon Shield incident – IUD marketed as safe by AH Robins
  - Aggressive marketing despite knowledge of safety problems led to the “largest tort liability case since asbestos”!
    - Billions of dollars in settlements! Bought out by AHP (now Wyeth)
  - By 1978, device GMPs (21 CFR 820) finalized
- 1978: Drug GMPs (21 CFR 210-211) expanded
- 1986: Food GMPs (21 CFR 11) finalized
1976: GMPs for Low Volume Parenterals

• Stemmed from 1970-1971 and 1973 epidemics of septicemia in US hospitals due to contaminated IV fluids
  – FDA questioned manufacturers’ abilities in ensuring sterility
  – In response, FDA proposed LVP regulations (21 CFR 212)

• Contrary to other GMPs, particularly explicit process standards were proposed:
  – Limits for lethality factors
  – Laminar flow of air, heat distribution & penetration
  – Water quality

• Many manufacturers objected, and FDA withdrew draft LVP and pre-draft SVP regulations as a result
  – Most standards were voluntarily applied, anyway
1978 Human & Veterinary Drug GMP Revision (43 FR 45013; 45076-45077)

- Resulted from FDA Task Force studying GMPs
- Main source of modern-day 21 CFR 210 & 211
- Largely considered a “writer’s revision”
  - Overhauled section numbering (see next page)
  - Emphasized writing SOPs
  - Large expansion of regulations
    - 1963 GMPs = 3 pages in FR; 1978 GMPs = 76 pages in FR
    - Exempted “certain OTC products”
- Updated “…in light of current technology for drug manufacturing and [to] delineate requirements more specifically…”

Q PHARMA
Overview of “Modern-Day” GMPs (21 CFR 211)

Subpart A (§1-3)  
- General Provisions
Subpart B (§22-34)  
- Organization and Personnel
Subpart C (§42-58)  
- Buildings and Facilities
Subpart D (§63-72)  
- Equipment
Subpart E (§80-94)  
- Control of Components and Drug Product Containers and Closures
Subpart F (§100-115)  
- Production and Process Controls

Subpart G (§122-137)  
- Packaging and Labeling Control
Subpart H (§142-150)  
- Holding and Distribution
Subpart I (§160-176)  
- Laboratory Controls
Subpart J (§180-198)  
- Records and Reports
Subpart K (§204-208)  
- Returned and Salvaged Drug Products
1980: FDAMA

• 1980 – Food & Drug Administration Modernization Act (FDAMA)
  – Congress required FDA to "make public a plan that establishes a framework for achieving mutual recognition of good manufacturing practices inspections"
  – Also: prior to this, GMPs were not required for Over-the-Counter (OTC) products
    • OTC products on the market now required testing
    • Products with a safe history were given time to comply
  – FDA furthers pursuit of international harmonization
1980s-1990s: Increased FDA Guidance

• Some Examples:
  – 1987: Guideline on General Principles of Process Validation
    • Note: updated draft made available in 2009
    • Result of the Generic Drug Scandals of the early-mid 90s
  – 1998: Draft Guidance for Industry Manufacture, Processing or Holding Active Pharmaceutical Ingredients
A Step Back: Guidance Documents

- First one issued in 1949, “Procedures for the Appraisal of the Toxicity of Chemicals in Food”

  - Guidance Docs represent FDA’s “current thinking” on a topic

- “Optional for Use” documents – not legally enforceable, but:
  - If there isn’t a good reason for not following the guidance, you are expected to follow the guidance
  - If an alternate practice is not documented as equivalent or better, you are expected to follow the guidance
1980s-1990s: Looking Forward

- Numerous cGMP violations by industry; Generic Drug Scandal
- FDA eventually recognized more direction was necessary:
  - to provide a uniform standard to the entire industry
  - minimize the potential for harm
  - or achieve some other (unspecified) cGMP objective
- By 1996, FDA proposed (61 FR 20104) to:
  - Amend cGMPs to clarify certain manufacturing, quality control, and documentation requirements and
  - ensure regulations more accurately encompassed current industry practice
- This would add new subparts L, M, N, O & P to 21 CFR 211

- §211.220 would define requirements for process validation
  - “To preserve the validated status of a process, measures must be taken that will allow any significant process changes to be recognized and addressed promptly. Such change control measures can apply to equipment, standard operating procedures, manufacturing instructions, environmental conditions, or any aspect of the process system that has an effect on its state of control, and therefore on the state of validation.”

- §211.221 would define requirements for method validation
- §211.240 would define requirements for control of physical & chemical contaminants
- Proposal later (2007) shelved – complete paradigm shift
  - “In light of more recent scientific and technical advances and evolving quality systems and risk management concepts.”
2000: ICH Tripartite Guideline Q7(a)

- **GMP Guide for Active Pharmaceutical Ingredients (API)**
  - Adopted in 2001 by FDA (66 FR 49028-49029) because 21 CFR 210-226 are specifically for “finished pharmaceuticals”
  - Replaced FDA’s 1998 draft guidance
- “API Starting Material” – used in production of an API that becomes a significant structural component
  - Production starts when API Starting Material enters process
- GMPs are applied on a “sliding scale” from the start of the production process through final API stages
- Provides a table illustrating when GMPs should begin (see next page)
<table>
<thead>
<tr>
<th>Type of Manufacturing</th>
<th>Application of this Guide to steps (shown in grey) used in this type of manufacturing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Manufacturing</td>
<td>Production of the API Starting Material</td>
</tr>
<tr>
<td>API derived from animal sources</td>
<td>Collection of organ, fluid, or tissue</td>
</tr>
<tr>
<td>API extracted from plant sources</td>
<td>Collection of plants</td>
</tr>
<tr>
<td>Herbal extracts used as API</td>
<td>Collection of plants</td>
</tr>
<tr>
<td>API consisting of comminuted or powdered herbs</td>
<td>Collection of plants and/or cultivation and harvesting</td>
</tr>
<tr>
<td>Biotechnology: fermentation/ cell culture</td>
<td>Establishment of master cell bank and working cell bank</td>
</tr>
<tr>
<td>“Classical” Fermentation to produce an API</td>
<td>Establishment of cell bank</td>
</tr>
</tbody>
</table>

• Working Group created to analyze related cGMP requirements in effect in the US and internationally, particularly those related to quality systems

• Ultimate goals of updating GMPs:
  – “Encourage timely detection and response to emerging defects or indications that product quality has been compromised”
  – “Further clarity and modernize the regulations”
  – “Harmonize various aspects of parts 210/211 with other Agency and international regulations”

• From final 2004 report: "FDA will take an incremental approach to modifying parts 210/211, while pursuing international harmonization through ICH and PIC/S."
2007-2008: First Incremental Change

- December 4, 2007 – to clarify & modernize GMPs, FDA:
  - Withdrew 1996 proposed rule (72 FR 68111)
  - Published a direct final rule (72 FR 68064)
  - Published a companion proposed rule (72 FR 68113)
- Comment period for direct final rule closed February 19, 2008
- On April 4, 2008, FDA withdrew direct final rule due to significant adverse comments (73 FR 18440)
- After careful consideration of all comments, FDA published new final rule (effective December 8, 2008)
  - First increment of modifications to parts 210 and 211
2008: cGMP Revisions

• The final rule revises the drug cGMP regulations primarily in three areas:
  – Aseptic Processing
    • Made consistent with 2004 “Sterile Drug Products Produced by Aseptic Processing – cGMP”
  – Asbestos Filters
    • Bans limited use of asbestos-containing filters used in processing injectable drug products
  – Verification by a Second Individual
    • Certain operations may be performed by (validated) automated equipment and verified by a person, rather than one person performing an operation and another person verifying that the operation was correctly performed
<table>
<thead>
<tr>
<th>Rank</th>
<th>Category of GMP deficiency</th>
<th>#</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Documentation – QS Elements &amp; procedures</td>
<td>1341</td>
<td>14.1%</td>
</tr>
<tr>
<td>2</td>
<td>Design and maintenance of premises</td>
<td>634</td>
<td>6.7%</td>
</tr>
<tr>
<td>3</td>
<td>Design and maintenance of equipment</td>
<td>594</td>
<td>6.2%</td>
</tr>
<tr>
<td>4</td>
<td>Documentation - manufacturing</td>
<td>526</td>
<td>5.5%</td>
</tr>
<tr>
<td>5</td>
<td>Potential for microbiological contamination</td>
<td>463</td>
<td>4.9%</td>
</tr>
<tr>
<td>6</td>
<td>Documentation - specification and testing</td>
<td>432</td>
<td>4.5%</td>
</tr>
<tr>
<td>7</td>
<td>Status labeling - WIP, facilities &amp; equipment</td>
<td>371</td>
<td>3.9%</td>
</tr>
<tr>
<td>8</td>
<td>Environmental monitoring</td>
<td>323</td>
<td>3.4%</td>
</tr>
<tr>
<td>9</td>
<td>Process validation</td>
<td>317</td>
<td>3.3%</td>
</tr>
<tr>
<td>10</td>
<td>Sampling - procedures and facilities</td>
<td>297</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

# of GMP deficiencies in Top 10  5298  52.5%

# of inspections:  423

# of GMP deficiencies overall  9465
GMPs are **Everyone’s Responsibility!**

- Products can be considered **adulterated!**
- Enforcement Actions – e.g. 483, Warning Letter, Consent Decree; Recalls, Seizures, Injunctions
- For malicious acts, “**persons**” can be fined or incarcerated!
  - A “person” may be the company, the President, CEO, a Director, Manager, Supervisor, or even the Operator / Technician who failed to follow GMPs
  - “Persons” can be **debarred** from working in the industry!
Summary of GMP History

• Regulations over product quality, patient safety, and efficacy were born reactively from tragedies over the past 110 years (or so), and becoming more proactive:
  – 1800s: ingredient/product QC and manufacturing standards
  – Early 1900s: ingredient/product safety & labeling
  – Mid 1900s: increased safety regulation & product efficacy
    • Also: research regulations, GLPs, GCPs *(not discussed here)*
  – Late 1900s: harmonizing & implementing “best practices”
    • Interpretation and understanding production processes
  – 2000s: risk-based design, development, scale-up, and increased scrutiny of these during FDA inspections
ANY ADDITIONAL QUESTIONS?
Acknowledgements & Contact Information

• Thank you to ISPE-NJC and the Chapter Day attendees for allowing me the opportunity to speak today!

• For further reading material on this subject or if you have any questions, please do not hesitate to contact me!

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