GMP & cGMP

1

GMP – history

Why are we interested in GMP history?

F. Nietzsche once said: *If you know the why of living, you can endure any how*

Everyone should know the story of how the GMPs have come to be.

Most requirements were put in place as response to tragic circumstances and to prevent future tragedies.

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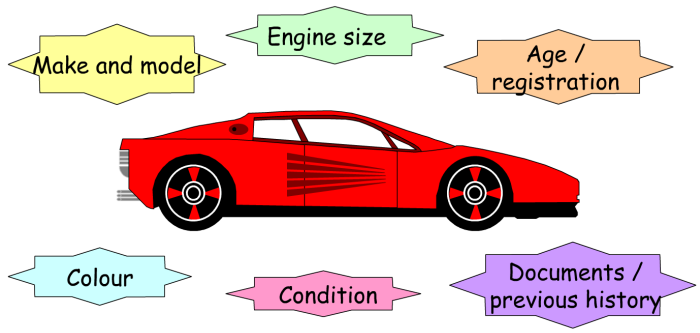
GMP – history

We can choose it by looking:



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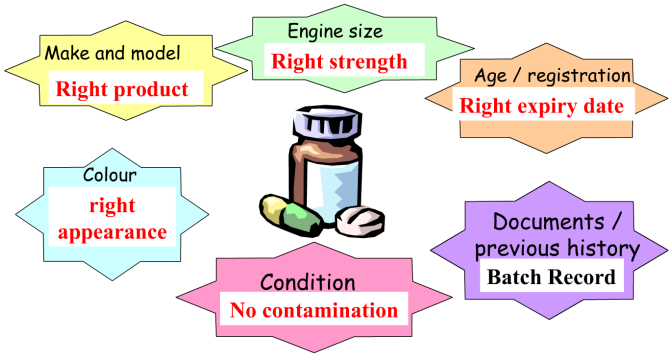
GMP – history

We can not choose it by looking:



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GMP – history

We have to trust in the supply chain and in the manufacturer:

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GMP – history

1937 – sulfanilamide

-Sulfa drugs were introduced in 1935 as anti-infectives;

-one company used diethylene glycol (a poisonous solvent) in an oral elixir of sulfanilamide;

-108 deaths, many of them children;

- company was charged with misbranding (=inaccurate and false labeling →it is illegal…..over the years the word has been replaced with the word adulterated).

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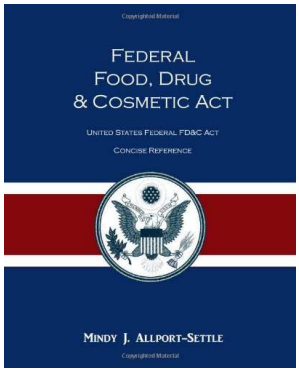
GMP – history

1938 – in USA, Congress enforced the Federal Food, Drug and Cosmetic (FD&C) Act.

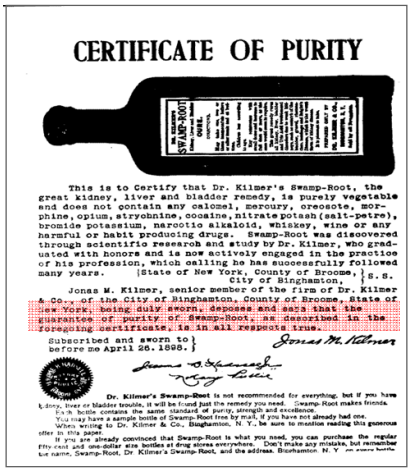
Companies were required to prove that their products were safe before marketing them.



GMP – history

1941 – kick-off of GMP

- Sulfathiazole tablets contaminated with phenobarbital (a sedative);
- 300 people died or were injured;
- FDA enforced and revised manufacturing and quality control requirements, leading to what would later be called GMP;
- During the second world war, batch certification by FDA became a requirement for certain drugs (i.e. 1941 for insulin; 1945 for penicillin).



CERTIFICATE OF PURITY

This is to Certify that Dr. Kilmer's Swamp-Root, the great kidney, liver and bladder remedy, is purely vegetable and does not contain any calomel, mercury, creosote, morphine, opium, strychnine, cocaine, nitrate potash (salt-petre), bromide potassium, narcotic alkaloid, whiskey, wine or any harmful or habit producing drugs. Swamp-Root was discovered through scientific research and study by Dr. Kilmer, who graduated with honors and is now actively engaged in the practice of his profession, which calling he has successfully followed many years. {State of New York, County of Broome, } S.S. City of Binghamton, }

Jonas M. Kilmer, senior member of the firm of Dr. Kilmer & Co., of the City of Binghamton, County of Broome, State of New York, being duly sworn, deposes and says that the guarantee of purity of Swamp-Root, as described in the foregoing certificate, is in all respects true.

Subscribed and sworn to } before me April 26. 1898. }

Jonas M. Kilmer

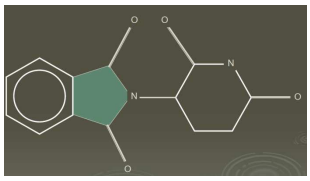
Dr. Kilmer's Swamp-Root is not recommended for everything, but if you have kidney, liver or bladder trouble, it will be found just the remedy you need. Swamp-Root makes friends. Each bottle contains the same standard of purity, strength and excellence. You may have a sample bottle of Swamp-Root free by mail, if you have not already had one. When writing to Dr. Kilmer & Co., Binghamton, N. Y., be sure to mention reading this generous offer in this paper. If you are already convinced that Swamp-Root is what you need, you can purchase the regular fifty-cent and one-dollar size bottles at drug stores everywhere. Don't make any mistake, but remember the name, Swamp-Root, Dr. Kilmer's Swamp-Root, and the address, Binghamton, N. Y.

1906 – certificate of purity signed by doctor

GMP – history

1960 – Thalidomide drug

- Thalidomide was marketed in Europe as a sleeping pill and to treat morning sick-ness;
- regulatory agencies that gave the permission to sell this drug, knew nothing of its side-effects: it was teratogenic;
- it caused deformities in developing fetuses;
- children whose mother took thalidomide in the first three months were born with deformed arms and legs;
- an estimated 10 000 cases were linked to thalidomide use.



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GMP – history

1962 – Kefauver-Harris Drug Amendments

- Two legislators (Kefauver and Harris) pushed more stringent legislation;
- FDA's regulation required companies to test not only to ensure that products were safe but that they were efficacious for their intended use ("proof of efficacy" law);
- regulating clinical trials, the amendments required drugs to be tested in animals before people;
-manufacturers were required to report unexpected harm (adverse events);
- GMP for drugs (21 CFR parts 210 & 211) were made final in 1970.

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GMP – history

1962 – World Health Assembly set out resolutions on drug safety and monitoring.

1968 – The Medicines Act (UK) (an Act of Parliament) governs the manufacture and supply of medicines.

It introduced system for:
- product licensing covering old (pre 1968) and new medicines;
- licensing of manufacturing sites;
- licensing of clinical trials.

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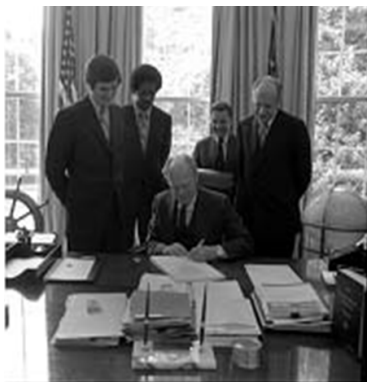
GMP – history

1976 – Medical Device Amendments

- 1972 and 1973 were reported some pacemaker failures;
- 1975 incidents involving a contraceptive intrauterine device caused thousands of injuries (pelvic infections, infertility and some deaths) and the product was taken off the market;
- a Medical Device Amendments required manufacturers to provide FDA with safety and effectiveness data before marketing medical devices.



President Gerarl Ford signs the Medical Device Amendments

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GMP – history

1980 – Infant Formula Act (FDA)

- 1978 manufacturer of infant formula re-formulated two of its soy-based products;
- 1979 infants diagnoses with lack of chlorides (hypochloremic);
- greater regulatory control over the formulation and production of nutritional for infant formula;
- manufacturers are required to analyze each batch of formula for nutrient, code each container with a slot number, keep detailed records of production and analysis;
- the food GMPs (21 CFR part 110) were finalized in the 1980s.

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GMP – history

Beyond 1980s

- FDA began publishing a series of guidance documents that have had a major effect on interpretation of current good manufacturing practices;
- such documents provide guidance only on principles and practices that are not legal requirements;
- however, typically they reflect current agency thinking and expectations.

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1

GMP – history

We can learn from these lessons or can mankind educate itself only by disaster and tragedy?

(by sen. Paul Douglas on the acceptance of the Senate's 1962 drug bill)

Quality / Safety / Efficacy requirements

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2

GMP – definition

- What GMPs are?
- What GMPs are for?
- Who is responsible to apply / to control GMP ?

Good Manufacturing Practices are a set of regulations, codes and guidelines for the manufacture of drug substances and drug products, in vivo and in vitro diagnostic products and food.

GMPs are promulgated by the Authority (EMA, FDA, TGA, Japan, …) and have the force of law.

GMPs require that manufacturers and packagers of drugs, medical devices, some food, and blood have to ensure that their products are safe, pure, and effective before marketing them.

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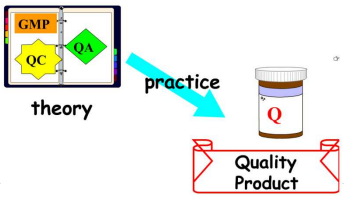
GMP – definition

GMP regulations require a quality approach to manufacturing in order to minimize or eliminate contamination, mix-ups, and errors and produce a “quality product”. This protects the consumer from purchasing a product which is not effective or even dangerous.

Failure of firms to comply with GMP regulations can result in very serious consequences including recall, seizure, fines, and …. injures / death for patients.

Most GMP requirements are very general and open-ended, allowing each manufacturer to decide individually how to best implement the necessary controls….and meet the technological improvements.



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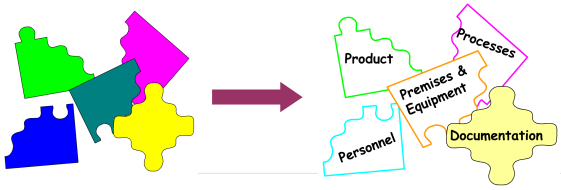
GMP – definition

This provides much flexibility, but also requires that the manufacturer has to apply the requirements in a manner which makes sense for each individual business.

GMP regulations address issues including record-keeping, personnel qualifications and training, sanitation, cleanliness, equipment verification, process validation, complaint handling, ….

Facilities that are in good condition, equipment that is properly maintained and calibrated, employees who are qualified and fully trained, and processes that are validated and reproducible, …. are a few examples of how cGMP requirements help to assure the safety and efficacy of drug products.



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GMP – definition

GMPs are also sometimes referred to as "cGMPs". The "c" stands for "current," reminding manufacturers that they must employ technologies and systems which are up-to-date in order to comply with the regulation.

Inspectors' definition:

Good Manufacturing Practice ensures that drug products are manufactured batch upon batch, year upon year to the appropriate and consistent quality standards in a reproducible way and in accordance with regulatory requirements.

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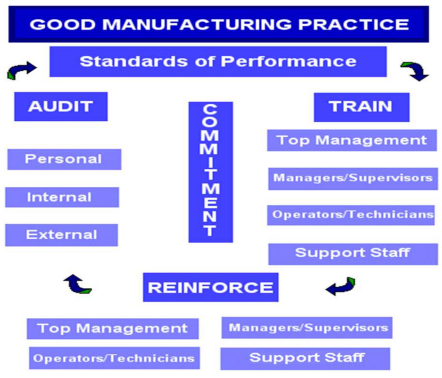
2

GMP – definition

Maintaining GMP is everyone's responsible (Regulatory Authorities & manufacturers).
Maintaining GMP is a continuous (cyclic) process:



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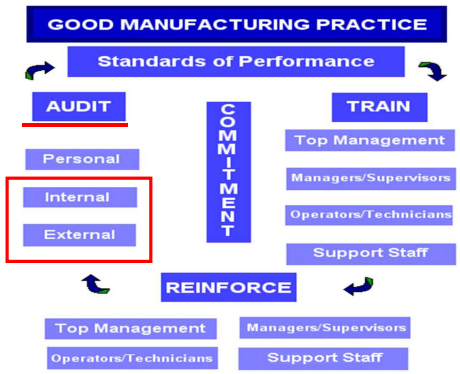

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3

GMP – structure

GMP ~~Great Mountain of Paper~~ ⟹ it is a systematic collection of guidelines

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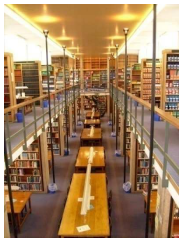
3

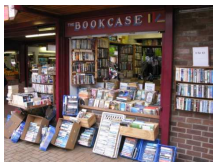
GMP – structure

Where can we find the Good Manufacturing Practices?



Library

Bookshop



Photocopies

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GMP – structure

http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm
(internet website of the European community)

3

GMP – structure

EU Legislation - Eudralex

The body of European Union legislation in the pharmaceutical sector is compiled in Volume 1 and Volume 5 of the publication "The rules governing medicinal products in the European Union":

Volume 1 - EU pharmaceutical legislation for medicinal products for human use

Volume 5 - EU pharmaceutical legislation for medicinal products for veterinary use

The basic legislation is supported by a series of guidelines that are also published in the following volumes of "The rules governing medicinal products in the European Union":

Volume 2 - Notice to applicants and regulatory guidelines for medicinal products for human use

Volume 3 - Scientific guidelines for medicinal products for human use

Volume 4 - Guidelines for good manufacturing practices for medicinal products for human and veterinary use

Volume 6 - Notice to applicants and regulatory guidelines for medicinal products for veterinary use

Volume 7 - Scientific guidelines for medicinal products for veterinary use

Volume 8 - Maximum residue limits

Volume 9 - Guidelines for pharmacovigilance for medicinal products for human and veterinary use

Volume 10 - Guidelines for clinical trial

Medicinal products for paediatric use, orphan, herbal medicinal products and advanced therapies are governed by specific rules.

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GMP – structure

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GMP – structure

Volume 1 of the publications "The rules governing medicinal products in the European Union" contains the body of European Union legislation in the pharmaceutical sector for medicinal products for human use.

Namely:

- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Consolidated version : 05/10/2009).
- Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products.

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GMP – structure

Volume 4 of "The rules governing medicinal products in the European Union" contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC respectively.

- Commission Directive 2003/94/EC, of 8 October 2003, laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use Replacement of Commission Directive 91/356/EC of 13 June 1991 to cover good manufacturing practice of investigational medicinal products.
- Commission Directive 91/412/EEC of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products.

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GMP – structure

2011: GMP vol. 4 restyling in structure

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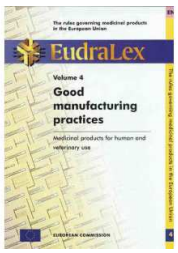
3

GMP – structure



2011: new structure (three parts)

- **Introduction**
- **Part I - Basic Requirements for Medicinal Products**

Chapter 1 - Quality Management
Chapter 2 - Personnel
Chapter 3 - Premise and Equipment
Chapter 4 - Documentation
Chapter 5 - Production
Chapter 6 - Quality Control
Chapter 7 - Contract Manufacture and Analysis
Chapter 8 - Complaints and Product Recall
Chapter 9 - Self Inspection

- **Part II - Basic Requirements for Active Substances used as Starting Materials**

Basic requirements for active substances used as starting materials

- **Part III - GMP related documents**

Site Master File
Q9 Quality Risk Management
Q10 Note for Guidance on Pharmaceutical Quality System
MRA Batch Certificate

- **Annexes**
- **Glossary**

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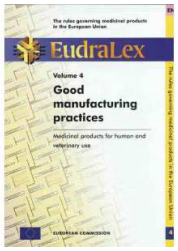
3

GMP – structure



2011: new structure (18 annexes)

- Annex 1 Manufacture of Sterile Medicinal Products
- Annex 2 Manufacture of Biological Medicinal Products for Human Use
- Annex 3 Manufacture of Radiopharmaceuticals
- Annex 4 Manufacture of Veterinary Medicinal Products other than Immunological Veterinary Medicinal Products
- Annex 5 Manufacture of Immunological Veterinary Medicinal Products
- Annex 6 Manufacture of Medicinal Gases
- Annex 7 Manufacture of Herbal Medicinal Products
- Annex 8 Sampling of Starting and Packaging Materials
- Annex 9 Manufacture of Liquids, Creams and Ointments
- Annex 10 Manufacture of Pressurised Metered Dose Aerosol Preparations for Inhalation
- Annex 11 Computerised Systems (revision January 2011)
- Annex 12 Use of Ionising Radiation in the Manufacture of Medicinal Products
- Annex 13 Manufacture of Investigational Medicinal Products
- Annex 14 Manufacture of Products derived from Human Blood or Human Plasma
- Annex 15 Qualification and validation
- Annex 16 Certification by a Qualified person and Batch Release
- Annex 17 Parametric Release
- Annex 19 Reference and Retention Samples

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GMP – structure

Discussion, **still pending** (future Part 4?):
Separate section for GMP on excipients:

The IPEC-PQG Excipients GMPs Guide proposes GMP appropriate for the manufacture of excipients and is a joint initiative between the International Pharmaceutical Excipients Council (IPEC), as IPEC-Americas and IPEC Europe and the Pharmaceutical Quality Group (PQG). It incorporates the IPEC Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients, 2001 with the PQG's PS 9100:2002 Pharmaceutical Excipients.
The Guide makes an essential contribution to the wider understanding of good manufacturing practice appropriate for the excipient supply industry. Excipient manufacturers and their customers can be assured that excipients manufactured according to this Guide will meet internationally accepted good manufacturing practice principles.

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GMP – structure

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GMP – structure

Part III

It is intended to host a collection of GMP related documents, which are not detailed guidelines on the principles of GMP laid down in Directives 2003/94/EC and 91/412/EC.

The aim of Part III is to clarify regulatory expectations and it should be viewed as a source of information on current best practices. Details on the applicability will be described separately in each document. It includes:

- the former annex 20 on ICH Q9 Quality Risk Mangement;
- ICH Q10 guideline on Pharmaceutical Quality System;
- Site master file (a guidance for manufacturers);
- EU Format for batch certification (in the framework of Mutual recognition agreements).

Note: GMP part II is the former annex 18 on API manufacture.

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GMP – structure

First edition of GMP was issued in year 1989

Some chapters and annexes have been revised and updated and others have been drafted as new

Latest entries ?

Latest revisions ?

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GMP – structure

Latest **entries:**

	ENTRY IN FORCE
Annex 15 – qualification & validation	September 2001
Annex 16 – certification by QP & batch release	January 2002
Annex 17 – parametric release	January 2001
Annex 19 – reference & retention samples	January 2006

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GMP – structure

Latest **revisions:**

	ENTRY IN FORCE
INTRODUCTION	December 2010
CHAPTER 1 – Quality Management	Revision February 2008, in force 1 July 2008
CHAPTER 4 - Documentation	Revision January 2011, in force 30 June 2011
CHAPTER 6 – Quality control	Revision October 2005, in force 1 June 2006
CHAPTER 8 – Complaints and product recall	Revision December 2005, in force 1 February 2006
BASIC REQUIREMENTS FOR ACTIVE SUBSTANCES USED AS STARTING MATERIALS (part II)	Revision February 2010, in force 31 July 2010

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GMP – structure

Latest **revisions**:

	ENTRY IN FORCE
Annex 1 – sterile medicinal products	Revision 25 November 2008, in force 1 March 2009 & 1 March 2010 for freeze dried
Annex 3 - radiopharmaceuticals	Revision September 2008, in force 1 March 2009
Annex 6 – medicinal gases	Revision 3 February 2010, in force 31 July 2010
Annex 11 – computerized Systems	Revision January 2011, in force 30 June 2011
Annex 13 – investigational medicinal products	Revision 3 February 2010 , in force 31 July 2010
Annex 14 – products derived from human blood or human plasma	Revision May 2011, in force 30 November 2011

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GMP – updates

Details for:

• Introduction / site master file	December 2010
• chapter 4	June 2011
• annex 11	June 2011
• annex 14	November 2011
• annex 6	July 2010
• annex 1	March 2009

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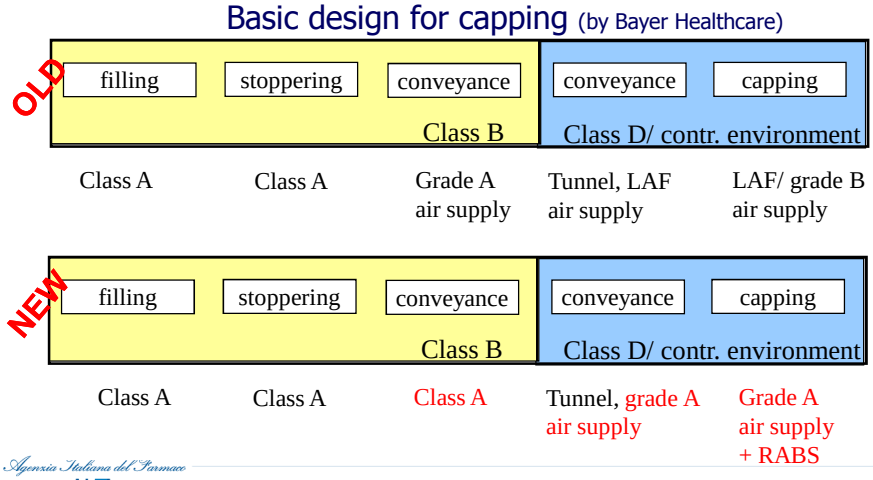
GMP – updates

Basic design for capping (by Bayer Healthcare)



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GMP guidelines

- GMP as per Schedule “M”
  www.cdsco.nic.in
- GMP as per WHO
  www.who.int
- GMP as per MCA now known as MHRA
  www.mca.gov.uk
- GMP as per TGA
  www.tga.gov.au
- GMP as per US FDA
  www.fda.gov
- GMP as per ICH guidelines
  www.ich.org

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GMP

- GMP in solid dosage forms
- GMP in semisolid dosage forms
- GMP in Liquid orals
- GMP in Parenterals Production
- GMP in Ayurvedic medicines
- GMP in Bio technological products
- GMP in Nutraceuticals and cosmeceuticals
- GMP in Homeopathic medicines

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GMP

- Good Manufacturing Practice
- Good Management Practice
- Get More Profit
- Give more Production
- GMP Training with out tears

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GMP

- All past GMPs are history….It is looking like in rear view mirror and driving

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Ten Principles of GMP

1. Design and construct the facilities and equipments properly
2. Follow written procedures and Instructions
3. Document work
4. Validate work
5. Monitor facilities and equipment
6. Write step by step operating procedures and work on instructions
7. Design ,develop and demonstrate job competence
8. Protect against contamination
9. Control components and product related processes
10. Conduct planned and periodic audits

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Beyond GMP

- Reduce pollution -→ Zero discharge
- Adaptation of environment friendly methods
- Consideration for better and healthier life tomorrow
- Consideration of ethics in life
- One should begin with end in mind otherwise it will be the beginning of the end

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Cost of effective GMP

- In fact Cost benefits – positive cost benefits of GMP/QA
- Good plant layout, Smooth work flows, Efficient documentation systems, well controlled process, good stores lay outs and stores records- These are Good manufacturing practices
- Reduction in work in process and inventory holding costs
- Avoidance of cost of Quality failure (cost of waste, of rework, of recall, of consumer compensation and of loss of company reputation)

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List of important documents in GMP

- **Policies**
- **SOP**
- **Specifications**
- **MFR (Master Formula Record)**
- **BMR**
- **Manuals**
- **Master plans/ files**
- **Validation protocols**
- **Forms and Formats**
- **Records**

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10 attributes of a good document

1. Accurate
2. Clear
3. Complete
4. Consistent
5. Indelible
6. Legible
7. Timely
8. Direct
9. Authentic
10. Authorized

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Certifying agencies

- ICH. www.ich.org
- WHO. www.who.int
- US FDA. www.fda.gov
- EU/EMEA. www.emea.europa.eu

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How do GMPs of different countries compare?

At a high level, GMPs of various nations are very similar; most require things like:

- Equipment and facilities being properly designed, maintained, and cleaned
- Standard Operating Procedures (SOPs) be written and approved
- An independent Quality unit (like Quality Control and/or Quality Assurance)
- Well trained personnel and management

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cGMP For Finished Pharmaceuticals

1. General Provision
2. Organization & Personnel
3. Building & Facilities
4. Equipment
5. Control of Components & Drug Product Containers & Closures
6. Production & Process Control
7. Packaging & Labeling Control
8. Handling & Distribution
9. Laboratory Control
10. Records & Reports
11. Returned & Salvaged Drugs

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Organization & Personnel

1. Responsibilities of quality control unit.
2. Personnel qualifications.
3. Personnel responsibilities.
4. Consultants.

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Building & Facilities

1. Design and construction features.
2. Lighting.
3. Ventilation, air filtration, air heating and cooling.
4. Plumbing.
5. Sewage and refuse.
6. Washing and toilet facilities.
7. Sanitation.
8. Maintenance.

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Equipment

1. Equipment design, size, and location.
2. Equipment construction.
3. Equipment cleaning and maintenance.
4. Automatic, mechanical, and electronic equipment.
5. Filters.

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Control of Components & Drug Product Containers & Closures

1. General requirements.
2. Receipt & storage of untested components, drug product containers, and closures.
3. Testing and approval or rejection of components, drug product containers, and closures.
4. Use of approved components, drug product containers, and closures.
5. Retesting of approved components, drug product containers, and closures.
6. Rejected components, drug product containers, and closures.
7. Drug product containers and closures.

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Production & Process Control

1. Written procedures;
2. Charge-in of components.
3. Calculation of yield.
4. Equipment identification.
5. Sampling and testing of in-process materials and drug products.
6. Time limitations on production.
7. Control of microbiological contamination.
8. Reprocessing.

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Packaging & Labeling Control

1. Materials examination and usage criteria.
2. Labeling issuance.
3. Packaging and labeling operations.
4. Tamper-evident packaging requirements for over-the-counter (OTC) human drug products.
5. Drug product inspection.
6. Expiration dating.

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Handling & Distribution

1. Warehousing procedures.
2. Distribution procedures.

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Laboratory Control

1. General requirements.
2. Testing and release for distribution.
3. Stability testing.
4. Special testing requirements.
5. Reserve samples.
6. Laboratory animals.
7. Penicillin contamination.

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Records & Reports

1. General requirements.
2. Equipment cleaning and use log.
3. Component, drug product container, closure, and labeling records.
4. Master production and control records.
5. Batch production and control records.
6. Production record review.
7. Laboratory records.
8. Distribution records.
9. Complaint files.

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Returned & Salvaged Drug Products

1. Returned drug products.
2. Drug product salvaging.

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