PURDUE UNIVERSITY

Weldon School of Biomedical Engineering

The Convergence of Differences, The Future of Excellence

BME 695N

Engineering Nanomedical Systems

Lecture 20

GMP and issues of quality control manufacture of nanodelivery systems

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I A. What does cGMP mean?

Good Manufacturing Practice or **GMP** (also referred to as 'cGMP' or 'current Good Manufacturing Practice') is a term that is recognized worldwide for the control and management of manufacturing and quality control testing of foods and pharmaceutical products.

Source: Wikipedia

Why GMP? Controlling processes means more predictable outcomes…

Since sampling products will statistically only ensure that the samples themselves (and perhaps the areas adjacent to where the samples were taken) are suitable for use, and end-point testing relies on sampling, GMP takes the holistic approach of regulating the manufacturing and laboratory testing environment itself. An extremely important part of GMP is documentation of every aspect of the process, activities, and operations involved with drug and medical device manufacture. If the documentation showing how the product was made and tested (which enables traceability and, in the event of future problems, recall from the market) is not correct and in order, then the product does not meet the required specification and is considered *contaminated* (*adulterated* in the US). Additionally, GMP requires that all manufacturing and testing equipment has been qualified as suitable for use, and that all operational methodologies and procedures (such as manufacturing, cleaning, and analytical testing) utilized in the drug manufacturing process have been validated (according to predetermined specifications), to demonstrate that they can perform their purported function(s). ***Source: Wikipedia***

GMP is world-wide

The World Health Organization (WHO) version of GMP is used by pharmaceutical regulators and the pharmaceutical industry in over one hundred countries worldwide, primarily in the developing world. The European Union's GMP (EU-GMP) enforces more compliance requirements than the WHO GMP, as does the Food and Drug Administration's version in the US. Similar GMPs are used in other countries, with Australia, Canada, Japan, Singapore and others having highly developed/sophisticated GMP requirements. In the United Kingdom, the Medicines Act (1968) covers most aspects of GMP in what is commonly referred to as "The Orange Guide", because of the color of its cover, is officially known as *The Rules and Guidance for Pharmaceutical Manufacturers and Distributors*.

Source: Wikipedia

Enforcement

GMPs are enforced in the United States by the FDA; within the European Union, GMP inspections are performed by National Regulatory Agencies (e.g., GMP inspections are performed in the United Kingdom by the Medicines and Healthcare products Regulatory Agency (MHRA); in Australia by the Therapeutical Goods Administration (TGA); in India by the Ministry of Health and by similar national organizations worldwide). Each of the inspectorates carry out routine GMP inspections to ensure that drug products are produced safely and correctly; additionally, many countries perform Pre-Approval Inspections (PAI) for GMP compliance prior to the approval of every new drug for marketing.

Regulatory agencies (including the FDA in the US and regulatory agencies in many European nations) are legally entitled to turn up unannounced to conduct inspections, if they believe that there are suitable grounds for doing this.

Source: Wikipedia

What can be learned from the semi-conductor industry clean-room and manufacturing?

What doesn’t fit this paradigm?

II. cGMP-level manufacturing

A. Predictable methods lead to predictable products

B. The CFR (Code of Federal Regulations) sections on GMPs

C. What is covered under cGMP?

What is covered under cGMP?

Code of Federal Regulations: Parts 210 & 211

cGMP in Manufacturing, Processing, Packing or Holding of Drugs and Finished Pharmaceuticals

A. General Provisions

B. Organization and personnel

C. Buildings and facilities

D. Equipment

E. Control of Components and Drug Product Containers and Closures

F. Production and Process Controls

G. Packaging and labeling Control

H. Holding and Distribution

I. Laboratory Controls

J. Records and Reports

K. Returned and Salvaged Products

GLP and the FDA

The US FDA has rules for GLP in 21CFR58. These are the rules used for preclinical trials on animals prior to clinical research in humans. Research that is not conducted under these restrictions might be inadmissable in support of a New Drug Application in the US.

Source: Wikipedia

Good Laboratory Practice (GLP)

Good Laboratory Practice generally refers to a system of management controls for laboratories and research organizations to ensure the consistency and reliability of results as outlined in the OECD Principles of GLP and national regulations. GLP applies to non-clinical studies conducted for the assessment of the safety of chemicals to man, animals and the environment. The internationally accepted definition is as follows:

Good Laboratory Practice (GLP) embodies a set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived. These studies are undertaken to generate data by which the hazards and risks to users, consumers and third parties, including the environment, can be assessed for pharmaceuticals, agrochemicals, cosmetics, food and feed additives and contaminants, novel foods and biocides. GLP helps assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments.

Source: Wikipedia

III. Bionanomanufacturing

A. So what is special about biomanufacturing?

B. Nano-clean water necessary for nano-pharmaceuticals

C. Contaminants at the nano-level

D. Can you scale up the process?

IV.Some quality control issues and how to test

A. Correctness of size – size matters!

B. Composition – atomic level analyses

C. Monodispersity versus agglomeration

D. Order and correctness of layers

E. Correctness of zeta potentials

F. Does the nanomedical system contain the correct payload?

G. Targeting (and mis-targeting) specificity and sensitivity

References

CFR (Code of Federal Regulations) sections on GMPs.
http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=200421

Go into the "Browse Parts" column and select Parts 200-299. The GMP sections are 210 and 211.