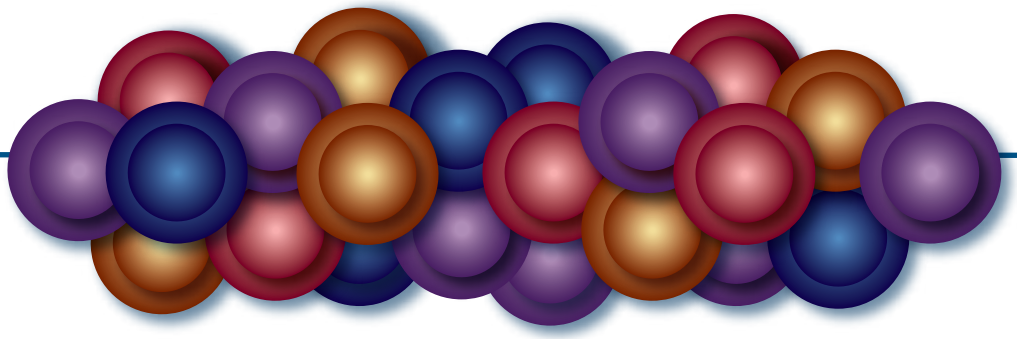
FOURTH EDITION
Revised & Expanded

GMP in Practice

Regulatory Expectations for the Pharmaceutical Industry



James L. Vesper

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REGULATORY EXPECTATIONS FOR THE PHARMACEUTICAL INDUSTRY

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10 9 8 7 6 5 4 3 2 1

ISBN: 1-933722-54-1

PDA

Bethesda Metro Center
Suite 1500
Baltimore, MD 20814
United States
301-986-0293

Davis Healthcare International Publishing, LLC
2636 West Street
River Grove
IL 60171
United States
www.DHIBooks.com

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ACKNOWLEDGEMENTS

This book is the result of working in the pharmaceutical industry nearly thirty years and learning from countless people from around the world. Every consulting project or workshop has been an opportunity to learn. Thanks to all those who have asked a challenging question or described a solution they've had to a vexing problem.

Some other friends and colleagues have answered questions, clarified requirements, and given invaluable suggestions. These include Dick Sands, Jerry Lanese, Mike Anisfeld, Dave Chesney, Joseph Horvath, Ümit Kartoğlu, Jim Carroll, and Thomas Peither.

And, thanks to Gray Brown for his continuing patience and support.

FOREWORD

To say that the pharmaceutical industry is globalized as never before is an understatement. Through partnerships, outsourcing relationships and as a result of economic pressure, the industry now faces unprecedented challenges, not the least of which is how to maintain quality standards and balance different regulatory requirements in today's globally diversified manufacturing environment.

In this book, Jim Vesper consolidates and correlates the key references from the most important global GMP standards into a cohesive and readable reference. He clearly distinguishes between requirements and expectations across the different standards – US, European, Canadian, World Health Organization and International Conference on Harmonization – and makes both the scientific and business case for a unified global approach to compliance and quality management.

The result is a reference that contains something worthwhile for everyone, from the student of basic GMP principles to the most senior management personnel. Jim is to be commended for this contribution to the body of GMP knowledge. I am certain readers will find it to be among the most valuable learning and reference tools currently available in GMP literature.

David L. Chesney
Vice President and Practice Lead,
Strategic Compliance Services,
PAREXEL Consulting
Waltham, Massachusetts

INTRODUCTION

In the workshops I present to technical, quality, and management groups, one of the most frequent questions asked is, "where in the Good Manufacturing Practices (GMPs) does it say I have to do _____?" You can fill in the blank with items such as error correction on a document, or cleaning validation, or including certain things in an investigation report. Often, you won't find specific requirements in a given regulation, like the US FDA's Current Good Manufacturing Practice regulations. For example, 21 CFR 211, originally published in 1978 and updated several times since then does not specifically require errors to be corrected with one line through the original entry, initials and date of the person making the correction, the new entry, and a reason for the correction. Nor does the US cGMP specifically require that GMP/quality audits be performed. (Other, more recent requirements published by Health Canada and the European Union do have these requirements.)

A key to understanding how GMP concepts and expectations change and evolve is from a Warning Letter the US FDA wrote to a pharmaceutical manufacturer in 1998 explaining their philosophy. At issue was stability testing – the firm was contesting some specific expectations that FDA had. FDA said this in the Warning Letter:

> We acknowledge that the cGMP regulations are not explicit about annual stability testing; however, it should be noted that the cGMP regulations are not all inclusive and that what determines a manufacturing practice to be "current" and "good" is if it can be considered feasible and valuable. In the case of annual stability testing, the agency has determined that such a practice is feasible and valuable and, thus, enforceable under Section 501(a)(2)B) of the Food, Drug & Cosmetic Act (FDA, 1998).

Two words are important to notice: "feasible" and "valuable." We can define them this way:

> **Feasible** – you can do it; reasonably available technology exists that allows it to be performed.
>
> **Valuable** – the practice contributes to the safety, identity, strength, purity, and quality of the product; you are going to have more control over the product, the process, or the information you are using to make a decision concerning the product or process.

Informal conversations that I've recently had with FDA drug experts have confirmed that these concepts are as valid today as they were in 1998.

As our industry's manufacturing and distribution practices are getting more complex and more global, manufacturers cannot just focus on one or two sets of requirements – it is too difficult to operate a quality system that has a multitude of variations to meet the individual requirements of a particular national authority. Most multinational firms and those supplying global markets have done what national authorities have not – they have created quality systems and quality system elements that internally harmonize GMP expectations. Yes, there still are some unique requirements that need to be met, but having a majority of requirements harmonized reduces duplication and increases flexibility.

GMP in Practice is intended to help with that harmonization. In it, we will look at more than 30 elements that are typically included in a modern pharmaceutical quality system. Each quality system element has an overview section, some risk-related questions, and 3-10 expectations. Each expectation is explored in a bit more detail and examples of GMP references from the US FDA, Health Canada, the European Union, the World Health Organization, and the International Conference on Harmonization (ICH) are presented. (More on these references below.)

It's been my experience that, in order to get a rich understanding of GMP, a person needs to have knowledge of what various national authorities expect. Often, these individual expectations give slightly different perspectives that, when put together, provide a more detailed, robust sense of "feasible and valuable."

In using this book, there are some cautions:

First, before setting up a system or defending a practice based on something you read here, go to the source documents (you will see these listed below and at the end of each chapter) and read the reference in context.

Second, requirements are very dynamic, so look at the most currently available reference.

Third, keep current with how interpretations change and what inspectors are looking for. Meetings, newsletters, websites and blogs are useful tools.

Fourth, there are other requirements that may apply – as described below, this book is not a comprehensive collection of all expectations. Other guidances may be pertinent.

Fifth, keep in mind seven key essentials of GMP:

1. Product the product from contamination.
2. Prevent mix-ups.
3. Know what to do before you do it – and have a rationale to support it.
4. Document what really occurred.
5. Strive for consistency and control.
6. Have management that supports a person and/or group that makes independent, final decisions on documents, products, and processes, and materials.
7. Learn from what has happened, investigate problems, monitor and continually improve.

Having an effective, robust quality system in place helps you accomplish these essentials and produce products that are consistently safe, identified, of the proper strength, pure, and meet the regulatory requirements wherever they are marketed.

References Cited in this Book

The regulatory references used come from five different sources and were selected because of their applicability to the industry and that "official" English versions were available. There are a number

of other useful guidelines from national authorities and standard-setting bodies that could have been included but were not because of available time and resources.

The following table shows the organization producing the document, the name and date of issue of the document used, an example of the citation, and also the website where the document can be found (at least when this was written).

References cited in the chapters reflect the spelling in the original document. If a section of a larger citation was used, an ellipse ("…") was placed before and/or after the missing text.

As mentioned earlier, always go to the current, original document before establishing, modifying, or defending a practice or decision.

James Vesper

US Food and Drug Administration

Document:
Current Good Manufacturing Practice Regulations, 21 CFR Parts 210–211
Example Citation: § 211.110 (b)
Publication Date: April 2010

Website:
www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm
(Note – use this search tool to find "(211)".

Document:
Process Validation: General Principles and Practices
Example Citation: FDA Validation Guidance, II.B
Publication Date: January 2011

Website:
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070336.pdf

Document:
Guidance to Industry Quality Systems Approach to Pharmaceutical Good Manufacturing Practice Regulations
Example Citation: FDA Quality Systems Guidance, 2.4
Publication Date: September 2006

Website:
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070337.pdf

Document:
Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice
Publication Date: September 2004

Website:
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070342.pdf

CA – Health Canada Health Products and Food Branch Inspectorate

Document:
Good Manufacturing Practices (GMP) Guidelines – 2009 Edition, Version 2
Example Citation: C.02.029 (1) – a regulation; C.02.029 #1 – an interpretation; CA Quality Elements, 4.2.3.1 – a citation that found in Chapter 4 of the Canadian GMPs prior to the regulations in Chapter 5
Publication Date: March 2011

Website:
www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php

Document:
Guidelines for Temperature Control of Drug Products During Storage and Transportation (GUI–0069)
Example Citation: CA GDP 3.2.1
Publication Date: January 2011

Website:
www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0069-eng.php

CA – Health Canada… (continued)

Document:
Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029)
Example Citation: CA Validation Guidelines, 6. Validation protocol
Publication Date: August 2009

Website:
www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/validation/gui_29-eng.php

EU – European Commission

Document:
Volume 4, EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Part I

Chapter 1 Quality Management
Publication Date: February 2008
Example Citation: EU Chapter 1, Principle; EU 1.1

Chapter 2 Personnel
Publication Date: February 2008
Example Citation: EU 2.2

Chapter 3 Premise and Equipment
Publication Date: February 2008
Example Citation: EU 3.2

Chapter 4 Documentation
Publication Date: January 2011
Example Citation: EU 4.1

Chapter 5 Production
Publication Date: Draft Dated November 2010
Example Citation: EU 5.1

Chapter 6 Quality Control
Publication Date: February 2008
Example Citation: EU 6.1

Chapter 7 Contract Manufacture and Analysis (DRAFT)
Publication Date: February 2008
Example Citation: EU 7.1

Chapter 8 Complaints and Product Recall
Publication Date: February 2008
Example Citation: EU 8.1

Chapter 9 Self Inspection
Publication Date: February 2008
Example Citation: EU 9.1

Annex 1 Manufacture of Sterile Medicinal Products
Publication Date: November 2008
Example Citation: EU Annex 1, 3

Annex 8 Sampling of Starting and Packaging Materials
Publication Date: December 1998
Example Citation: EU Annex 8,1

EU – European Commission (continued)

Annex 11 Computerized Systems
Publication Date: January 2011
Example Citation: EU Annex 11, 3

Annex 15 Qualification and Validation
Publication Date: July 2001
Example Citation: EU Annex 15, 1

Annex 16 Certification by a Qualified Person and Batch Release
Publication Date: July 2001
Example Citation: EU Annex 16, 1

Annex 19 Reference and Retention Samples
Publication Date: December 2005
Example Citation: EU Annex 19, 1

Website:
http://ec.europa.eu/health/documents/eudralex/vol–4/index_en.htm

Document:
Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C 63/03)
Example Citation: EU GDP, #32
Publication Date: 1994

Website:
http://ec.europa.eu/health/files/eudralex/vol-4/gdpguidelines1.pdf

WHO – World Health Organization

Document:
WHO Good Manufacturing Practices – Main Principles for Pharmaceutical Products (WHO Technical Report Series 961, 45th Report, Annex 3)
Example Citation: WHO Annex 3 GMP, 16.4
Publication Date: 2011

Website:
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf

Document:
WHO Good Manufacturing Practices for Sterile Pharmaceutical Products (WHO Technical Report Series 961, 45th Report, Annex 6)
Example Citation: WHO Annex 6, Sterile Products, 5
Publication Date: 2011

Website:
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf

Document:
Model Guidance for the Storage and Transport of Time- and Temperature-Sensitive Pharmaceutical Products (jointly with the Expert Committee on Biological Standardization) (WHO Technical Report Series 961, 45th Report, Annex 9)
Example Citation: WHO Annex 9 TTSPP, 4.1
Publication Date: 2011

Website:
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf

WHO – World Health Organization (continued)

WHO Good Distribution Practices [GDP] for Pharmaceutical Products (WHO Technical Report Series 957, 45th Report, Annex 5)
Example Citation: WHO GDP, 3
Publication Date: 2010

Website:
http://whqlibdoc.who.int/trs/WHO_TRS_957_eng.pdf#page=249

Document:
Quality Assurance of Pharmaceuticals: A Compendium of Guidelines and Related Materials. Volume 2, 2nd Updated Edition. Good Manufacturing Practices and Inspections. Chapter 1, Validation
Example Citation: WHO Chapter 1–Validation
Publication Date: 2007

Website:
http://apps.who.int/medicinedocs/index/assoc/s14136e/s14136e.pdf

Document:
Quality Assurance of Pharmaceuticals: A Compendium of Guidelines and Related Materials. Volume 2, 2nd Updated Edition. Sampling Operations: Sampling of Pharmaceutical Products and Related Materials
Example Citation: WHO Chapter 6–Sampling Operations, 2.3
Publication Date: 2007

Website:
http://apps.who.int/medicinedocs/index/assoc/s14136e/s14136e.pdf

Document:
Quality Assurance of Pharmaceuticals: A Compendium of Guidelines and Related Materials. Volume 2, 2nd Updated Edition. Water for Pharmaceutical Use
Publication Date: 2007

Website:
http://apps.who.int/medicinedocs/index/assoc/s14136e/s14136e.pdf

ICH – International Conference on Harmonization

Document:
Q7A – Good Manufacturing Practice for Active Pharmaceutical Ingredients
Example Citation: Q7A 1.2
Publication Date: November 2000

Document:
Q8(R2) – Pharmaceutical Development
Example Citation: Q8(R2) 3.1
Publication Date: August 2009

Document:
Q9 – Quality Risk Management
Example Citation: Q9 1.1; Q9 II.2 – Annex II
Publication Date: November 2005

ICH – International Conference… (continued)

Document:
Q10 – Pharmaceutical Quality Systems
Example Citation: Q10 2.1 (a)
Publication Date: June 2008

Website:
http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html

US Food and Drug Administration

US FDA (1998), Warning Letter to Merck & Company, *Available at* www.fda.gov/downloads/ICECI/EnforcementActionsWarningLetters/1998/UCM066569.pdf. Accessed on 25 May 2011.

9

LEARNING, TRAINING, AND PERFORMANCE

Overview

Training is one of the most important investments a firm can make as it produces products that meet GMP expectations. Training is not done just for the sake of doing it – if so, your firm would be an educational institution and not a manufacturer. Rather, training must be linked with the goals of the organization. Through training, people develop the knowledge and skills so that they can safely, effectively, and consistently, perform their jobs.

If the performance is the desired outcome, training is only part of the equation. The person needs to have the underlying capacity and capability to do the assigned task. Also, the person needs to have the right tools to support the performance. This would include the wrenches and instruments that a repair technician would use, but it also includes "job aids" and "performance supports" – often incorporated into controlled documents like batch records or made available as short demonstration videos in new, integrated electronic batch records that use notebook computers or iPads®. These informational tools can change the training model from "just in case" to "just in time."

Since around 2005, some pharma and biopharma organizations have been changing the name of their "training" departments, incorporating the word, "learning." For example, one large firm formerly called their corporate group, "Training and Continual Improvement;" now it is "Organizational Learning." A unit in the World Health Organization (WHO) changed its name from "Global Training Network" to "Global Learning Opportunities."

Some may see this as a trivial play on words. Others, like the organizations noted above, have realized that if the change from "training" to "learning" is accompanied by a fundamental change in philosophy, focusing on learning will have a significant positive affect on their future.

Some of the differences between a more traditional "training" model and a more progressive "learning" approach includes:

- Training is a "top down" and localized; learning is distributed and occurs everywhere;
- Training presentations are replaced with learning opportunities; trainers become facilitators;
- Training is a "push" system; learning is a "pull" system;
- Trainees become learners;
- Mentors become learners; learners become mentors;
- Formal training expands to include informal learning.

Curricula or learning plans are an important component of a well-functioning learning (or training program), showing learners, supervisors, and regulatory inspectors the path of learning events that the individual is to take as he or she develops knowledge and skills. A well-defined curriculum will cover a person from the point of entry into a position (with a new employee orientation, for example) to when the person has achieved and is enhancing his or her competence and expertise.

From the curricula, training courses and learning opportunities can be developed. These training courses need to be approved before being used. The learning opportunities need to cover the tasks the person performs as well as the applicable GMPs. Training on safety and other mandated-training topics would be included in the curricula.

Key people such as heads of the production, quality assurance, and quality control laboratories; those who release or certify products (e.g., "Responsible Person" or "Qualified Person"); and consultants may need to have special, documented qualifications or licenses.

An important part of developing a competent performer is for the person to have a "mental model" of what they are doing. Simply put, they need to have the big picture of the process and how their work fits into that picture. That picture needs to include a clear vision of what they are specifically doing and what a "good" product looks like and also how they can negatively impact the product or process.

Instructors, trainers, and mentors need to be qualified. This qualification, in practice, considers two things: knowledge and skills in the domain to be trained (e.g., aseptic technique, calibrating a scale, setting up a packaging line) and also practical knowledge and skills of training, coaching, and mentoring.

Assessment and evaluation need to be part of a training effort. Learning professionals usually use "assessment" when looking at someone's performance as shown by a paper test or by demonstration of performance. Evaluation is used when looking at things – like the learner's acceptance of a training course or the effectiveness of a learning program.

The learning program needs to be defined in a procedure setting out roles and responsibilities, the requirements for developing courses, how instructors are qualified, how formal and informal learning is documented, and when formal, structured learning opportunities are to be provided.

The Canadian GMPs say it best in its Rationale summary; these are the only GMPs that emphasize an intangible quality, attitude:

> People are the most important element in any pharmaceutical operation, without the proper personnel with the appropriate attitude and sufficient training, it is almost impossible to fabricate, package/label, test, or store good quality drugs.
>
> It is essential that qualified personnel be employed to supervise the fabrication of drugs. The operations involved in the fabrication of drugs are highly technical in nature and require constant vigilance, attention to details and a high degree of competence on the part of employees. Inadequate training of personnel or the absence of an appreciation of the importance of production control, often accounts for the failure of a product to meet the required standards [C.02.006, Rationale].

Relevant Risk Questions

Some examples of risk questions related to learning, training, and performance include:

- What are the risks if a "just in time" training approach is used instead of a "just in case" model?
- What are the risks to proper task performance if procedures use a "read and understand" training model?
- What are the risks of using predominantly web-based/e-learning programs?
- What are risks in using pen and paper tests to assess a person's knowledge?
- What are the risks to the organization of not having competent trainers in-house?
- What are the risks in changing from a "training" model to a "learning" model?
- What are the risks in not moving to a learning and performance model?

GMP Expectations

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1. ***There are an adequate number of qualified people to safely and effectively perform the required tasks.***

   - People are the most important part in manufacturing, packaging, testing, and controlling drug products. Without people who have the education, training, and experience it is impossible to produce products that are safe, pure, and effective. GMPs require that there are enough qualified, skilled people to get the work done.
   - It is easy to determine if there are not enough people: investigations not being completed in a timely way, preventive maintenance and calibration schedules that are not met, stability samples not quickly analyzed, real-time verifications not being performed, supervisors not available to answer questions, and procedures that take a long time to be revised, approved, and distributed.

GMP Reference Examples

US

There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product [§ 211.25(c)].

CA

An adequate number of personnel with the necessary qualifications and practical experience appropriate to their responsibilities are available on site. The responsibilities placed on any one individual are not so extensive as to present any risk to quality. When key personnel are absent, qualified personnel are appointed to carry out their duties and functions [C.02.006 #5, 5.1, 5.3].

EU

The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality [EU 2.1].

WHO

Principle. The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible… [WHO Annex 3–GMP, 9.1].

The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive so as to present any risk to quality [WHO Annex 3–GMP, 9.2].

ICH

Management should provide the appropriate resources and training to achieve the quality objectives [Q9 2.3(d)].

2. ***Tasks, roles, and responsibilities are defined in job descriptions and organization charts.***

   - For people to perform, they need to know what is expected. Well-written, complete job descriptions and organization charts are a way to communicate this.
   - Organization charts are able to clearly show reporting structures and lines of responsibility and control.
   - The EU and WHO GMPs contain details about the duties of key positions.

GMP Reference Examples

US

(There are no references in § 210-211 for this specific expectation.)

CA

All responsible personnel have their specific duties recorded in a written description and have adequate authority to carry out their responsibilities [C.02.006, #5.2].

EU

The manufacturer must have an organisation chart. People in responsible positions should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of Good Manufacturing Practice [EU 2.2].

The head of the Production Department generally has the following responsibilities:

i. to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
ii. to approve the instructions relating to production operations and to ensure their strict implementation;

iii. to ensure that the production records are evaluated and signed by an authorised person before they are sent to the Quality Control Department;

iv. to check the maintenance of his department, premises and equipment;

v. to ensure that the appropriate validations are done;

vi. to ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need [EU 2.5].

The head of the Quality Control Department generally has the following responsibilities:

i. to approve or reject, as he sees fit, starting materials, packaging materials, and intermediate, bulk and finished products;

ii. to evaluate batch records;

iii. to ensure that all necessary testing is carried out;

iv. to approve specifications, sampling instructions, test methods and other Quality Control procedures;

v. to approve and monitor any contract analysts;

vi. to check the maintenance of his department, premises and equipment;

vii. to ensure that the appropriate validations are done;

viii. to ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

Other duties of the Quality Control Department are summarised in [EU GMPs] Chapter 6 [EU 2.6].

WHO

…Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions [WHO Annex 3–GMP, 9.1].

Responsible staff should have its specific duties recorded in written descriptions and adequate authority to carry out its responsibilities. Its duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of

GMP. The manufacturer should have an organization chart [WHO Annex 3–GMP, 9.3].

The manufacturer should provide training in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories (including the technical, maintenance and cleaning personnel) and for other personnel as required [WHO Annex 3–GMP, 10.1].

The heads of the production and quality unit(s) generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, depending on national regulations:

a) authorization of written procedures and other documents, including amendments;

b) monitoring and control of the manufacturing environment;

c) plant hygiene;

d) process validation and calibration of analytical apparatus;

e) training, including the application and principles of quality assurance;

f) approval and monitoring of suppliers of materials;

g) approval and monitoring of contract manufacturers;

h) designation and monitoring of storage conditions for materials and products;

i) performance and evaluation of in-process controls;

j) retention of records;

k) monitoring of compliance with GMP requirements;

l) inspection, investigation and taking of samples in order to monitor factors that may affect product quality [WHO Annex 3–GMP, 9.8].

ICH

(There are no references in Q8(R2), Q9, or Q10 for this specific expectation.)

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3. Personnel are trained and/or otherwise qualified in the procedures and methods they use and in the tasks they perform.

- It is up to the firm to define what procedures, methods, protocols, work instructions, and related functional documents personnel use and to then ensure the people can perform according to the written documents.
- Some firms differentiate between those who execute the procedure (e.g., a technician who performs equipment cleaning) and those who just need to know that the procedure exists (e.g., managers in a production area).
- People must be trained in procedures before they perform them.
- Training about procedures would include demonstrations, hands-on work, simulations, and/or structured on-the-job training.
- The practice of reading a procedure and signing that it has been understood has only a very limited use in terms of training, as it does not give any information that the person can actually perform the procedure as written.
- "Competency-based training" considers all the procedures, knowledge, and skills a person uses in doing a task and is a more holistic approach.
- Always keep in mind that the goal is correct performance according to the procedure or methods.
- People need to understand how their work fits into the larger picture and the impact of their job on the product, organization, and customer.

GMP Reference Examples

US

Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs… [§ 211.25(a)].

Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform

assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess [§ 211.25(b)].

CA

All personnel are aware of the principles of GMP that affect them, and all personnel receive initial and continuing training relevant to their job responsibilities [C.02.006, #6].

Training is provided prior to implementation of new or revised Standard Operating Procedures (SOPs) [C.02.006, #6.3].

EU

The manufacturer should provide training for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product [EU 2.8].

Besides the basic training on the theory and practice of Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programmes should be available, approved by either the head of Production or the head of Quality Control, as appropriate… [EU 2.9].

Personnel working in areas where contamination is a hazard, e.g., clean areas or areas where highly active, toxic, infectious or sensitising materials are handled, should be given specific training [EU 2.10].

WHO

Besides basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness periodically assessed. Approved training programmes should be available. Training records should be kept [WHO Annex 3–GMP, 10.2].

Personnel working in areas where contamination is a hazard, e.g., clean areas or areas where highly active, toxic, infectious or sensitizing materials are handled, should be given specific training [WHO Annex 3–GMP, 10.3].

ICH

[Quality Risk Management can be used:] To determine the appropriateness of initial and/or ongoing training sessions based on education, experience and working habits of staff, as well as on a periodic assessment of previous training (e.g., its effectiveness); To identify the training, experience, qualifications and physical abilities that allow personnel to perform an operation reliably and with no adverse impact on the quality of the product [Q9, I.1].

---

4. Personnel learn the GMP concepts and regulations that apply to what they do.

- Everyone must know what they do in their job or position that directly or indirectly contributes to GMP compliance and products that have safety, identity, strength, purity, and quality.
- GMP training is not just a one-time event. *Meaningful* learning events need to be provided on a regular basis. Each firm can define this for itself in its learning/training procedure; most firms do this at least annually.
- Discussing changes in regulatory expectations and quality events such as rejections, deviations, recalls, and trends can be a useful focus of an on-going learning event.

GMP Reference Examples

US

Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing

practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with cGMP requirements applicable to them [§ 211.25(a)].

CA

All personnel are aware of the principles of GMP that affect them, and all personnel receive initial and continuing training relevant to their job responsibilities [C.02.006 #5].

EU

Besides the basic training on the theory and practice of Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed… [EU 2.9].

The concept of Quality Assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions [EU 2.12].

WHO

Besides basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness periodically assessed… [WHO Annex 3–GMP, 10.2].

ICH

(There are no references in Q8(R2), Q9, or Q10 for this specific expectation.)

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5. ***Key personnel (including consultants and contractors) have the professional, educational, and experiential credentials required.***

    - Some regulatory authorities have specific requirements for those who head production, quality assurance, and quality control laboratories.

- Those who release or certify products may also need to have special credentials. For example, authorities in the EU require that a "Qualified Person" or "QP" certify products while other countries may use the term "authorized person;" some countries that require that people in this position are a licensed pharmacist.
- Consultants and contractors must have the qualifications to perform the work they are hired to do.
- A resumé or curriculum vitae may help document a person's qualifications and background. These records need to be retained by the hiring/contracting firm.

GMP Reference Examples

US

Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess [§ 211.25(b)].

Consultants advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide [§ 211.34].

CA

The individual in charge of the quality control department of a fabricator, packager/labeller, tester, importer, and distributor; and the individual in charge of the manufacturing department of a fabricator or packager/labeller;

1.1) holds a Canadian university degree or a degree recognized as equivalent by a Canadian university or Canadian accreditation body in a science related to the work being carried out;

1.2) has practical experience in their responsibility area;

1.3) directly controls and personally supervises on site, each working shift during which activities under their control are being conducted; and

1.4) may delegate duties and responsibility (e.g., to cover all shifts) to a person in possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a course of study at a university, college or technical institute in a science related to the work being carried out combined with at least two years of relevant practical experience, while remaining accountable for those duties and responsibility [C.02.006 #1, 1.1-1.4].

The individual in charge of the quality control department of a wholesaler;

2.1) is qualified by pertinent academic training and experience; and

2.2) may delegate duties and responsibility to a person who meets the requirements defined under interpretation 2.1. [C.02.006 #2, 2.1-2.2].

The individual responsible for packaging operations, including control over printed packaging materials and withdrawal of bulk drugs;

3.1) is qualified by training and experience; and

3.2) is directly responsible to the person in charge of the manufacturing department or a person having the same qualifications [C.02.006 #3, 3.1-3.2].

For secondary labellers, individuals in charge of labelling operations and individuals in charge of the quality control department;

4.1) are qualified by pertinent academic training and experience; and

4.2) can delegate their duties and responsibilities to a person who meets the requirements defined under 4.1 [C.02.006 #4, 4.1-4.2].

Consultants and contractors have the necessary qualifications, training, and experience to advise on the subjects for which they are retained [C.02.006 #7].

EU

A Qualified Person must certify in a register or equivalent document, as operations are carried out and before any release, that each production batch satisfies the provisions of Article 51. The persons responsible for these duties must meet the qualification requirements laid down in Article 493 of the same Directive [Directive 2001/83/EC], they shall be permanently and continuously at the disposal of the holder of the Manufacturing Authorisation to carry out their responsibilities. Their responsibilities may be delegated, but only to other Qualified Person(s) [EU 2.4(c)].

WHO

Key personnel responsible for supervising the manufacture and quality units(s) for pharmaceutical products should possess the qualifications of a scientific education and practical experience required by national legislation. Their education should include the study of an appropriate combination of:

a) chemistry (analytical or organic) or biochemistry;
b) chemical engineering;
c) microbiology;
d) pharmaceutical sciences and technology;
e) pharmacology and toxicology;
f) physiology;
g) other related sciences.

They should also have adequate practical experience in the manufacture and quality assurance of pharmaceutical products. In order to gain such experience, a preparatory period may be required, during which they should exercise their duties under professional guidance. The scientific education and practical experience of experts should be such as to enable them to exercise independent professional judgement, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and quality control of pharmaceutical products [WHO Annex 3–GMP, 9.7].

ICH

(There are no references in Q8(R2), Q9, or Q10 for this specific expectation.)

6. ***The learning program is defined by a procedure and learning plan. Learning events and assessments are documented; effectiveness is evaluated.***

   - A drug firm should have a procedure that describes who gets trained, when the training occurs, what topics/courses are covered by the training program, who is qualified to train, who approves training materials, and how training is documented.
   - Recently, regulatory agencies have been looking for evidence that people have learned something during the training. This is considered by trainers to be "assessment." For training that covers knowledge, the assessment can be performed using pen/paper (or e-learning) tests. For motor skills (e.g., setting up equipment or performing an assay) and some cognitive tasks (e.g., reviewing batch records prior to release), assessment can be done by a demonstration of performance. Some firms record actual assessment scores, others just document that the person is qualified/not qualified to perform.
   - Evaluation looks at *things* – the functioning of a training system, for example. When performing an evaluation, you are looking for evidence, not necessarily "proof." For example, if there are very no product rejections or failures, few deviations, and other important things are under control, these facts provide evidence that people (as well as equipment and processes) are performing well.

GMP Reference Examples

US

(There are no references in § 210 or 211 for this specific expectation.)

CA

The effectiveness of continuing training is periodically assessed [C.02.006 #6.2].

Records of training are maintained [C.02.006 #6.4].

The performance of all personnel is periodically reviewed [C.02.006 #6.6].

EU

Continuing training should also be given, and its practical effectiveness should be periodically assessed…Training records should be kept [EU 2.9].

WHO

…Continuing training should also be given, and its practical effectiveness periodically assessed. Approved training programmes should be available. Training records should be kept [WHO Annex 3–GMP, 10.2].

ICH

Management review should provide assurance that process performance and product quality are managed over the lifecycle. Depending on the size and complexity of the company, management review can be a series of reviews at various levels of management and should include a timely and effective communication and escalation process to raise appropriate quality issues to senior levels of management for review. The management review system should identify appropriate actions, such as: (1) Improvements to manufacturing processes and products; (2) Provision, training and/or realignment of resources; (3) Capture and dissemination of knowledge [Q10, 3.2.4(b)].

The outcome of management review of the pharmaceutical quality system and monitoring of internal and external factors can include: …(e) Improvements to the pharmaceutical quality system and related processes; (f) Allocation or reallocation of resources and/or personnel training; (g) Revisions to quality policy and quality objectives; (h) Documentation and timely and effective communication of the results of the management review and actions, including escalation of appropriate issues to senior management [Q10, 4.3].

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7. Learning events are conducted by qualified personnel.

- Instruction can be no better than those who provide it. Each firm can define in its learning/training procedures who is qualified to be an instructor.

- This qualification, in practice, considers two things: knowledge and skills in the domain to be trained (e.g., aseptic technique, calibrating a scale, setting up a packaging line) and also knowledge and skills in instructing.
- Studies have shown that many experts have difficulty communicating how they make decisions – for example, the subtle cues and signals they use in diagnosing the problems with a chromatographic column or a clean-in-place (CIP) skid. Also, subject matter experts (SMEs) tend to overload a learning session with too much detail – much more than the learner can absorb early on. A good instructor needs practical knowledge and skills in both the technical subject matter and how best to teach it and support a learner's development.
- Instructors who provide leader-led (e.g., classroom) training need different skills than those who give on-the-job (OJT) training.
- Generally, GMP training is given by someone in the firm's quality or compliance unit. In some situations, the firm may use outside training or quality experts to provide training to personnel to cover advanced or special topics.
- Characteristics of qualified instructors would include those who have had significant experience in the industry and remain current with trends and expectations. Another key characteristic of a qualified trainer is the ability to communicate information effectively to the learners.

GMP Reference Examples

US

Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis… [§ 211.25(a)].

CA

Training is provided by qualified personnel having regard to the function and in accordance with a written program for all personnel involved in the fabrication of a drug, including technical, maintenance, and cleaning personnel [C.02.006 #6.1].

EU

The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture of medicinal products relies upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer [EU 2, Principle].

WHO

The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience… [WHO Annex 3–GMP, 9.2].

ICH

(There are no references in Q8(R2), Q9, or Q10 for this specific expectation.)

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8. Supervisors and management have training that is appropriate to their functions.

- Supervisors and managers cannot be forgotten when it comes to training. These are the people who must make critical–and often difficult–decisions about GMP and product quality issues and allocating critical resources.
- As with other types of learning events, those given to supervisors and managers should be adapted to their specific needs, such as interpreting GMPs, current trends and expectations, and what can happen if GMPs are not fully followed.

GMP Reference Examples

US

Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, purity, and quality that it purports or is represented to possess [§ 211.25(b)].

CA

Every lot or batch of a drug shall be fabricated, packaged/labelled, tested and stored under the supervision of personnel who, having regard to the duties and responsibilities involved, have had such technical, academic, and other training as the Director considers satisfactory in the interests of the health of the consumer or purchaser [C.02.006].

All personnel are aware of the principles of GMP that affect them, and all personnel receive initial and continuing training relevant to their job responsibilities [C.02.006 #6].

EU

The manufacturer should provide training for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance, and cleaning personnel) and for other personnel whose activities could affect the quality of the product [EU 2.8].

WHO

Key personnel responsible for supervising the manufacture and quality unit(s) of pharmaceutical products should possess the qualifications of a scientific education and practical experience required by national legislation… [WHO Annex 3–GMP, 9.7].

ICH

(There are no references in Q8(R2), Q9, or Q10 for this specific expectation.)

REFERENCE TABLE

Regulatory References Used in this Chapter.
(All links to websites were accessed on 1 June 2011.)

US Food and Drug Administration

Document:
Current Good Manufacturing Practice Regulations, 21 CFR Parts 210-211
Publication Date: April 2010

Website:
www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm
(Note – use this search tool to find "(211)".)

CA – Health Canada Health Products and Food Branch Inspectorate

Document:
Good Manufacturing Practices (GMP) Guidelines – 2009 Edition, Version 2
Publication Date: March 2011

Website:
www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php

EU – European Commission

Document:
Volume 4, EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Part I

Chapter 2 Personnel
Publication Date: February 2008

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www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php

WHO – World Health Organization

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WHO Good Manufacturing Practices – Main Principles for Pharmaceutical Products (WHO Technical Report Series 961, 45th Report, Annex 3)
Publication Date: 2011

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ICH – International Conference on Harmonization

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Q9 – Quality Risk Management
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http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html