

Draft: Guide to Master Formulae.

GUIDE TO MASTER FORMULAE

Table of Contents:

	page
1) Introduction	3
2) Terms for Master Formula (MF)	3
3) Definitions of Batch / Lot	4
4) Master Formulae needed	4
5) GMP guidelines on master documentation	5
6) Required Contents of a MF	6
7) MF and corresponding Batch Records	10
8) Formats for MF	10
9) Issuing of MF copy as a blank batch record	11
10) Electronic MF and Batch Records	12
11) Batch Records versus Master Formula	13
12) Batch record review checklist	13
Appendix 1: Extract from: World Health Organization, Technical Report Series, No. 908, 2003; Annex 4: Good Manufacturing Practices for pharmaceutical products: main principles	
Appendix 2: Extract from: EUDRALEX; Volume 4 - Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice: Chapter 4 Documentation.	
Appendix 3: Extract from: Pharmaceutical Inspection Convention Co-operation Scheme PE 009-3, 1 January 2006; Guide to Good Manufacturing Practice for Medicinal Products; Documentation.	

Draft: **Guide to Master Formulae.**

Appendix 4: Extract from Canadian GMP Guidelines, Health Canada, Health Products and Food Branch Inspectorate. Good Manufacturing Practices Guidelines, 2002 Edition, Version 2.

Appendix 5: Extracts from US Code of Federal Regulations (CFR) and US FDA Guidelines.

App 5-1) US Regulations for Master Production Records for Finished Pharmaceuticals. Extract from:

CFR 21, Chapter I, Subchapter F: Biologics, Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals; Subpart F--Production and Process Controls, Sec. 211.100 Written procedures; deviations; and Subpart J--Records and Reports; Sec. 211.186 Master production and control records.

App 5-2) US Regulations for Batch Records for Finished Pharmaceuticals: Extract from:

CFR 21, Chapter I, Subchapter F: Biologics; Subchapter C: Drugs General; Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals; Subpart J--Records and Reports; Sec. 211.188 Batch production and control records.

App 5-3) US Regulations for Batch Records for Biological Products: Extract from:

CFR 21, Chapter I, Subchapter F: Biologics, Part 600 Biological Products: General; subpart B Establishment Standards, Sec 600.12 Records

App 5-4) US FDA Guidelines for Batch Records for Sterile Products: Extract from:

Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER); Office of Regulatory Affairs (ORA). September 2004 (Pharmaceutical cGMPs).

Appendix 6: [Sample master formula for a hypothetical biological product](#)

Appendix 7: [Example one of a Master Formula](#)

Appendix 8: [Example two of a Master Formula](#)

Appendix 9: [Example three of a Master Formula](#)

Draft: Guide to Master Formulae.

1) Introduction

In the 1997 WHO guidance document: “WHO/VSQ/97.01: (A WHO guide to good manufacturing practice (GMP) requirements. Part 1: Standard operating procedures and master formulae)” some basic explanations and instructions were given for preparing various documents required by Good Manufacturing Practice guidelines from WHO and from several regulatory authorities.

GMP guidelines include the requirements for documents (individual), documentation (the systems and formats for documents), and documenting (recording) of production and control activities. Most GMP guidelines provide the same or very similar information as the principles of Good Manufacturing Practice are now international in scope.

In this guidance document, the requirement for master manufacturing instructions and the requirements as given in different GMP documents, different names for these documents, and various forms that they can take will be described. This is to guide vaccine manufacturers who are applying for pre-qualification or re-qualification of their product(s) in the preparation or improvement of current documents for manufacturing operations.

2) Terms for Master Formula (MF)

WHO identifies manufacturing instructions as “Master Formula. Other terms used in GMP guidelines and regulations are “Manufacturing Formula”, “Master Production and Control Record”, but all mean the same thing – an approved master document that describes the full process of manufacturing for the batch of product with at least cross-reference to the support operations for a batch of a specific product. Individual companies may give internal names to these documents (manufacturing instructions, monographs, etc). In this guidance document the WHO term Master Formula (or MF) will be used.

The following are the extracted definitions from several guidelines:

- WHO GMP Guidelines: A formally authorized **master formula** should exist for each product and batch size to be manufactured.
- EU and PIC GMP guidelines: “Formally authorised **Manufacturing Formula and Processing Instructions** should exist for each product and batch size to be manufactured. They are often combined in one document.”
- Health Canada GMP guidelines. **MASTER FORMULA** (formule-type) - A document or set of documents specifying the raw materials with their quantities and the packaging materials, together with a detailed description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls

Draft: Guide to Master Formulae.

- US CFR. To assure uniformity from batch to batch, **master production and control records** for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person. The preparation of master production and control records shall be described in a written procedure and such written procedure shall be followed.

3) Definitions of Batch / Lot:

A Master Formula is required for each batch and batch size. A “batch” or “lot” as defined in the WHO GMP guideline (TRS 908 Annex 4) is”

“batch (or lot)

A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.”.

In general, the term “batch” more often refers to intermediates or final formulated bulks which are in one or a few large containers, while “lot” usually refers to the final product in the final container. They are, however, interchangeable as indicated in WHO’s GMP guideline glossary.

4) Master Formulae needed:

As above, batch or lot will refer to all production intermediates, final formulated bulks and final vialled product. Each master cell bank, viral seed lot, bulk concentrate, or viral harvest if stored and tested before release for further processing is a batch and a master formula for its production is written and approved. Also, for different scales of production of any batch or lot, a distinct master formula is prepared.

For final container product, as explained in the WHO definition above, a final “lot” will be the product that is filled during the same continuous fill-run, and in the case of freeze-dried products, the filled vials lyophilized in the same lyophilizer at the same time. These should have unique numbers to identify them as having been processed exactly the same way at the same time. On occasion, when only a part of a large final bulk is filled, the lot numbers for these bulks may have a common identifier with a suffix (“-1” or “a”)

Draft: Guide to Master Formulae.

to show the separate fills. Similarly, a large fill lot with a unique lot number may be lyophilized in different lyophilizers and the suffix would indicate the different freeze-dryer. A master formula for a batch/lot of product with the possibility to select one of several approved equipment items (e.g a freeze dryer) should clearly indicate this choice and provide space for the unique lot number designation.

5) GMP guidelines on master documentation

To show the consistency of requirements for Master Formulae, the sections on master documents and batch records have been extracted from various guidelines/regulations. The extracted texts are provided in Appendices 1-5:

1) WHO:

World Health Organization Technical Report Series, No. 908, 2003, Annex 4.
Good Manufacturing Practices for Pharmaceutical Products: Main Principles

2) EU:

EUDRALEX; Volume 4 - Medicinal Products for Human and Veterinary Use:
Good Manufacturing Practice: Chapter 4: Documentation.

3) Pharmaceutical Inspection Convention (PIC):

Pharmaceutical Inspection Co-operation Scheme PE 009-3, 1 January 2006:
Guide to Good Manufacturing Practice for Medicinal Products. (© PIC/S January 2006)

4) Canada:

Health Canada, Health Products and Food Branch Inspectorate. Good
Manufacturing Practices Guidelines, 2002 Edition (Version 2).

5) USA:

US Code of Federal Regulations: Chapter 21, subparts 211 and 600

And

US FDA: Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Office of Regulatory Affairs (ORA), September 2004. Pharmaceutical cGMPs.

Draft:

Guide to Master Formulae.

6) Required Contents of a MF

Each of the regulation or guidelines above give a list of the requirements for the contents of the MF. These are given in Table A for the Master (Production) Formula and Table B for the Master Packaging Formula for WHO, EU, PICs and Health Canada. Table C gives the contents Master Production and Control Records required by the USA.

From Table A and B it is clear that the guidelines are harmonized and the requirements are formatted the same way and with the same or very similar text. The USA regulations cover the same information but in a different format and do not distinguish between production and packaging master formulae.

Draft: Guide to Master Formulae.

Table A: Contents of Master Formulae

WHO TRS 908 Annex 4 section 15.23	EU GMP Guideline (Jan 06) Section 4.14 and 4.15	PICs document PE099 (Jan 06) section 4.14 and 4.15	Health Canada GMP Guideline Version 2 (2002), section 24.
The master formula should include	The Manufacturing Formula/Processing Instructions should include	The Manufacturing Formula/Processing Instructions should include	Master Manufacturing Formula: Master formula are written to provide not less than 100% of label claim and include the following
name of the product, with a product reference code relating to its specification;	the name of the product, with a product reference code relating to its specification;	the name of the product, with a product reference code relating to its specification	the name of the product, with a reference code relating to its specifications
a description of the dosage form, strength of the product and batch size	a description of the pharmaceutical form, strength of the product and batch size	a description of the pharmaceutical form, strength of the product and batch size	a description of the dosage form, strength of the product, and batch size
a list of all starting materials to be used (if applicable, with the INNs), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);	a list of all starting materials to be used, with the amount of each, described using the designated name and a reference which is unique to that material; mention should be made of any substance that may disappear in the course of processing	a list of all starting materials to be used, with the amount of each, described using the designated name and a reference which is unique to that material; mention should be made of any substance that may disappear in the course of processing;	a list of all raw materials to be used, along with the amount of each, described using the designated name and a reference that is unique to that material (mention is made of any processing aids that may not be present in the final product);
a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;	a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable	a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.	a statement of the expected final yield, along with the acceptable limits, and of relevant intermediate yields, where applicable
a statement of the processing location and the principal equipment to be used;	a statement of the processing location and the principal equipment to be used;	a statement of the processing location and the principal equipment to be used;	a statement of the principal equipment to be used;
the methods, or reference to the methods, to be used for preparing and operating the critical equipment, e.g. cleaning (especially after a change in product), assembling, calibrating, sterilizing, use;	the methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising);	the methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising);	the procedures, or reference to the procedures, to be used for preparing the critical equipment, e.g., cleaning (especially after a change in product), assembling, calibrating, sterilizing, etc.
detailed step-wise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);	detailed stepwise processing instructions (e.g. checks on materials, pre-treatments, sequence for adding materials, mixing times, temperatures);	detailed stepwise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);	detailed stepwise processing instructions (e.g., checks on materials, pretreatment, sequence for adding materials, mixing times or temperatures, etc.)

Draft: Guide to Master Formulae.

the instructions for any in-process controls with their limits;	the instructions for any in-process controls with their limits;	the instructions for any in-process controls with their limits;	the instructions for any in-process controls, along with their limits;
where necessary, the requirements for storage of the products, including the container, the labelling, and any special storage conditions;	where necessary, the requirements for bulk storage of the products; including the container, labelling and special storage conditions where applicable;	where necessary, the requirements for bulk storage of the products; including the container, labelling and special storage conditions where applicable;	where necessary, the requirements for storage of the products, including the container, the labelling and any special storage conditions;
any special precautions to be observed.	any special precautions to be observed.	any special precautions to be observed.	any special precautions to be observed

Table B: Contents of Master Packaging Formulae

WHO TRS 908 Annex 4 (2003) Section 15.24	EU GMP Guideline (Jan 06) Sections 4.16	PICs document PE099 (Jan 06) Sections 4.16	Health Canada GMP Guideline Version 2 (2002), section 25.
Formally authorized packaging instructions should exist for each product, pack size and type. These should normally include, or make reference to:	There should be formally authorised Packaging Instructions for each product, pack size and type. These should normally include, or have a reference to, the following	There should be formally authorised Packaging Instructions for each product for pack size and type. These should normally include, or have a reference to, the following:	In the case of a packaged product, the master formula also includes for each product, package size and type, the following:
the name of the product;	a) name of the product	name of the product;	
a description of its pharmaceutical form, strength and, where applicable, method of application;	b) description of its pharmaceutical form, and strength where applicable;	description of its pharmaceutical form, and strength where applicable;	
the pack size expressed in terms of the number, weight or volume of the product in the final container;	c) the pack size expressed in terms of the number, weight or volume of the product in the final container;	the pack size expressed in terms of the number, weight or volume of the product in the final container;	
a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications for each packaging material;	d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;	a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;	
where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have	e) where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of	where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf-life of	

Draft: Guide to Master Formulae.

been marked;	the product;	the product;	
special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after packaging operations;	f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;	special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin	special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before operations begin;
a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;	g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;	a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;	a description of the packaging operations, including any significant subsidiary operations and the equipment to be used
details of in-process controls with instructions for sampling and acceptance limits.	h) details of in-process controls with instructions for sampling and acceptance limits	details of in-process controls with instructions for sampling and acceptance limits	details of in-process controls, with instructions for sampling and acceptance limits.

Table C: USA: Master Production and Control Records

USA 21 CFR 211.186
Master production and control records shall include
The name and strength of the product and a description of the dosage form
The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit
A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic;
An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records;
A statement concerning any calculated excess of component;
A statement of theoretical weight or measure at appropriate phases of processing
A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to 211.192 is required;
A description of the drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling;
Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed.

Draft:

Guide to Master Formulae.

7) MF and corresponding Batch Records

Master Formula give the complete production instructions for a specific batch and batch size of cell banks, virus seed lots, intermediates, final bulks, final formulated bulks or final container product that are made in one production run with definite start to finish steps. Blank spaces are provided for the entry of data as the production run progresses. Identification or cross-reference to required supporting data is included in the step-by-step instructions.

The batch production record (BPR) is the approved copy of the master document with filled in data entries, signatures, dates, production locations, operators, and lot number, records of all supporting data (autoclave records, cleaning records, equipment identification and calibration dates, in-process test results, and QC results) appended. For cell banks, intermediates and final bulks that are stored for significant periods, the BPR is for that product. Once a final product has been produced, batch records (BR) is comprised of a single document of the sequential batch records for the starting cell banks or virus seed lots, the intermediates, the final bulks, final formulated bulks and the final container with all the supporting documents. If the product is a pool of several intermediates or final bulks then the full batch record includes the individual batch records of all the components. For combined vaccines, the complete batch record of the final product is the composite of the batch records of the complete batch record of the final bulks of each component, the final formulated bulk and the final product, again including all the supporting data.

For vaccines that have large long shelf life intermediates or final bulks that are used for several final formulated bulks/final products, the

8) Formats for MF.

The generally recommended MF format is to prepare a single continuous document that provides step-by-step production instructions, raw materials, equipment used, locations of production, dates, operators, etc for the product, with blank spaces to record the data and sign and date all entries, and at least cross-references to all supporting SOPs and operations. (See Tables A, B and C above).

An example of a Master Formula for a hypothetical biological product was provided [in the WHO Guidance document: WHO/VSQ/97.01: A WHO guide to good manufacturing practice \(GMP\) requirements. Part 1: Standard operating procedures and master formulae, Appendix 6: Sample master formula for a hypothetical biological product.](#) A copy of this is reproduced in Appendix 6 in this document. Many other formats are possible for a MF and will depend on the production process and supporting activities, as well as on the documentation system in place at the manufacturing company. [Appendix](#)

Draft: Guide to Master Formulae.

7, 8 and 9 provide examples of actual master formulae from several manufacturers with details revised to protect confidential information.

For individual batches/lots of intermediates and bulks the MF is a complete document. However, for the final container product, the full MF is the total of MF of each step. Therefore, for any final vaccine, a Master Formula Summary List is recommended. This would be a listing of each MF document number and title for each batch size of final product and would also include the options for any intermediates that are produced in different batch sizes and for the individual bulk components of a combined antigen vaccine.

Such a Master Formula Summary List would include as applicable:

MFs for:

- Master Cell Bank
- Working Cell Bank
- Fermentation or Culture harvests
- Harvest pool, or bulk concentrate
- Purified intermediate
- Final bulk
(The above would be duplicated for each antigen in a combined vaccine)
- Final formulated bulk (if stored)
- Filling or filling/lyophilization
- Labelling/Packaging

In some companies, manufacturing instructions have been prepared as a series of SOPs which describe each step and each providing a record sheet for the data to be entered. In this format, there is no continuous production instruction and recording document. If this is the case, then the Master Formula will be a Master SOP List of the production SOPs in order of their use is required to describe the overall master production process, with all the SOPs and record sheets appended. A separate list would be required for each batch size. Although many of the SOPs might be the same, some SOPs for various batch sizes may be different. In this case, rather than the cross-referencing supporting SOPs in a continuous MF, the SOPs for facility and equipment preparation, supporting sterilization runs, in-process tests, etc would be included in the Master SOP List.

9) Issuing of MF copy as a blank batch record

While Master Formulae are almost invariably stored on the computer, the official signed form is a paper copy. When a production order is made, QA is responsible to generate a copy, usually adds the lot number and stamps each page of the reproduced MF which is now the blank batch record for the production data for the assigned batch or lot. The MF

Draft: Guide to Master Formulae.

should make reference to in process tests, QC tests, production parameters that are computer recorded (e.g. fermentation or lyophilization printouts), environmental monitoring or water testing, autoclave run charts or depyrogenation oven charts, etc but generally these supporting operations and records are not within a MF. The batch record, however, includes the record sheets of all the production records and support records.

Master formulae, once approved and signed, should remain under the control of QA. Copies are not stored in the production areas for uncontrolled use. When revisions are made (following the change control process, and document control process) a new version is assigned a revision (or edition) number, the approval signatures and effective dates are added, and the previous version is archived. Unlike routine testing SOPs which have a fairly general distribution and are available in each laboratory or production area using them, a copy of the currently approved MF is issued batch by batch on production orders. When a series of SOPs are used for production operations, then the corresponding SOPs record sheets should also be controlled by QA and issued on production orders. Master copies of the MF (each numbered and recorded on a QA distribution list) can be distributed to relevant departments if needed, but the MF issued for a production run should be stamped by QA to ensure that the currently valid version is used. There will obviously be company-by-company differences in the details of the procedures for QA approval and issuing of MF.

10) Electronic MF and Batch Records.

As mentioned above, the MF is invariably (in this electronic age) on the computer, and should be under pass-word control of QA. Because the MF master copy is a signed document, the approved and signed original hard-copy of the MF becomes the official copy and should remain with QA. Photocopies – stamped, numbered, and on a distribution list - may be issued (see above) as reference copies to the relevant department head. The electronic version may have the signature and date fields typed in, e.g. “official copy signed by XXX”; “official copy dated ddmmyy”. If the electronic copy is printed out as the blank batch record for each production run, the QA department must stamp each page of the printout and sign that it is the approved current MF. The lot number can be added electronically or by hand on each page by the responsible person in QA. Alternately, the hard-copy can be photocopied for the production run, but will also be stamped and the lot number added. Whatever method is decided by a company, the MF must be issued by QA for each production run and controlled to ensure that only an approved copy of the current MF (or series of SOP record sheets) is issued on a production order.

Computerized batch records – ie filling in the blank MF– are more complicated. The computer programme for permitting the entering of production data at the time of performance of the production step will require computer access inside the cleanroom. In this case, the MF would be issued electronically with safeguards to ensure that no

Draft: Guide to Master Formulae.

unofficial copies can be made, or pages replaced. Passwords for entering data, verifying data or correcting data will need to be implemented. Specific procedures for recording any changes made to data records or the recording of deviations to production procedures must be validated and fully traceable retaining the original data and the corrected data. The review of batch records should include the full review of all changes and corrections made on the electronic forms. All of this process must be defined in SOPs for the procedures to be followed for electronic batch records. Specific guidelines on computer data entry and validation have been published by PIC and the US which can be consulted for detailed guidance.

For electronic batch records prepared by transcription from a hand-written record to a computer batch record requires additional verification that the computerized entries have been checked and are correct. This would require confirmation at the time of entry and again verified by QA.

11) Batch Records versus Master Formula:

In the regulations and guidelines (see appendices 1-4) there are also requirements for completed batch records (for some reason never called “lot records”). The MF is essentially the blank batch record for the production operations as discussed in 7) above. The batch record (BR often called Batch Processing Record BPR) is the MF with all data entered plus all the results of the supporting operations (in-process test results, environmental monitoring, autoclave records, etc).

[Details of the contents of the Batch Record are found in Appendix 1 \(WHO\); Appendix 2 \(EU\); Appendix 3 \(PIC\); and Appendix 4 \(Health Canada\) and Appendix 5 \(US\).](#)

12) Batch record review checklist

For a continuous production instruction MF, all the supporting operations are included as data fields or as cross-references within the document. For such a document, a list of the records sheets that are expected to be present in the batch record are itemized in a checklist which can also be a table of contents of the batch record.

For a production document using various SOPs to define the production process, the Master SOP List may be essentially the same as the batch record checklist.

Draft: **Guide to Master Formulae.**

Appendix 1: Extract from World Health Organization

WHO Technical Report Series, No. 908, 2003

Annex 4: Good Manufacturing Practices for pharmaceutical products: main principles

From the Glossary

batch records

All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

master formula

A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

master record

A document or set of documents that serve as a basis for the batch documentation (blank batch record).

standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

15. Documentation

15.1 *Principle.* Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a drug for sale, to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer. In some cases some or all of the documents described below may be brought together, but they will usually be separate.

Draft: Guide to Master Formulae.

General

15.2 Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.

15.3 Documents should be approved, signed and dated by the appropriate responsible persons. No document should be changed without authorization and approval.

15.4 Documents should have unambiguous contents: the title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

15.5 Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specific period of time.

15.6 Where documents require the entry of data, these entries should be clear, legible and indelible. Sufficient space should be provided for such entries.

15.7 Any alteration made to a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

15.8 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records should be retained for at least one year after the expiry date of the finished product.

15.9 Data (and records for storage) may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed standard operating procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently checked. Batch records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs or other means. It is particularly important that, during the period of retention, the data are readily available.

Documents required

Draft: Guide to Master Formulae.

Labels (sections 15.10-15.12 not extracted)

Specifications and testing procedures (sections 15.13-15.17 not extracted)

Specifications for starting and packaging materials (sections 15.18-15.21 not extracted)

Master formulae

15.22 A formally authorized master formula should exist for each product and batch size to be manufactured.

15.23 The master formula should include:

- (a) the name of the product, with a product reference code relating to its specification;
- (b) a description of the dosage form, strength of the product and batch size;
- (c) a list of all starting materials to be used (if applicable, with the INNs), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);
- (d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;
- (e) a statement of the processing location and the principal equipment to be used;
- (f) the methods, or reference to the methods, to be used for preparing and operating the critical equipment, e.g. cleaning (especially after a change in product), assembling, calibrating, sterilizing, use;
- (g) detailed step-wise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
- (h) the instructions for any in-process controls with their limits;
- (i) where necessary, the requirements for storage of the products, including the container, the labelling, and any special storage conditions;
- (j) any special precautions to be observed.

Packaging instructions

15.24 Formally authorized packaging instructions should exist for each product, pack size and type. These should normally include, or make reference to:

- (a) the name of the product;
- (b) a description of its pharmaceutical form, strength and, where applicable, method of application;
- (c) the pack size expressed in terms of the number, weight or volume of the product in the final container;
- (d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications for each packaging material;

Draft:

Guide to Master Formulae.

- (e) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;
- (f) special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after packaging operations;
- (g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
- (h) details of in-process controls with instructions for sampling and acceptance limits.

Batch processing records

15.25 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved specifications on the record. The method of preparation of such records should be designed to avoid errors. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)

15.26 Before any processing begins, a check should be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. This check should be recorded.

15.27 During processing, the following information should be recorded at the time each action is taken, and after completion the record should be dated and signed by the person responsible for the processing operations:

- (a) the name of the product;
- (b) the number of the batch being manufactured;
- (c) dates and times of commencement, of significant intermediate stages, and of completion of production;
- (d) the name of the person responsible for each stage of production;
- (e) the initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g. weighing);
- (f) the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
- (g) any relevant processing operation or event and the major equipment used;
- (h) the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;

Draft:

Guide to Master Formulae.

- (i) the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield;
- (j) notes on special problems including details, with signed authorization for any deviation from the master formula.

Batch packaging records

15.28 A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the approved packaging instructions, and the method of preparing such records should be designed to avoid errors. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)

15.29 Before any packaging operation begins, checks should be made that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks should be recorded.

15.30 The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password:

- (a) the name of the product, the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;
- (b) the date(s) and time(s) of the packaging operations;
- (c) the name of the responsible person carrying out the packaging operation;
- (d) the initials of the operators of the different significant steps;
- (e) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;
- (f) details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area;
- (g) whenever possible, samples of the printed packaging materials used, including specimens bearing the approval for the printing of and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting;
- (h) notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;

Draft:

Guide to Master Formulae.

(i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

Draft: Guide to Master Formulae.

Appendix 2: Extract from: EUDRALEX; Volume 4 - Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice:

CHAPTER 4 DOCUMENTATION

Principle

Good documentation constitutes an essential part of the quality assurance system. Clearly written documentation prevents errors from spoken communication and permits tracing of batch history. Specifications, Manufacturing Formulae and instructions, procedures, and records must be free from errors and available in writing. The legibility of documents is of paramount importance.

General

4.1 Specifications describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Manufacturing Formulae, Processing and Packaging Instructions state all the starting materials used and lay down all processing and packaging operations.

Procedures give directions for performing certain operations e.g. cleaning, clothing, environmental control, sampling, testing, equipment operation.

Records provide a history of each batch of product, including its distribution, and also of all other relevant circumstances pertinent to the quality of the final product.

4.2 Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorisation dossiers.

4.3 Documents should be approved, signed and dated by appropriate and authorised persons.

4.4 Documents should have unambiguous contents; title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

4.5 Documents should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.

4.6 Documents should not be handwritten; although, where documents require the entry of data, these entries may be made in clear, legible, indelible handwriting. Sufficient space should be provided for such entries.

4.7 Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

4.8 The records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable. They should be retained for at least one year after the expiry date of the finished product.

4.9 Data may be recorded by electronic data processing systems, photographic or other reliable means, but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data processing methods, only authorised persons should be able to enter or modify data in the computer and there should be a record of changes and deletions; access should be restricted by passwords or other means and the result of entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper or other means. It is particularly important that the data are readily available throughout the period of retention.

Documents required

Specifications (sections 4.10 to 4.13 not extracted)

Manufacturing Formula and Processing Instructions

Formally authorised Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured. They are often combined in one document.

4.14 The Manufacturing Formula should include:

- a) the name of the product, with a product reference code relating to its specification;
- b) a description of the pharmaceutical form, strength of the product and batch size;
- c) a list of all starting materials to be used, with the amount of each, described using the designated name and a reference which is unique to that material; mention should be made of any substance that may disappear in the course of processing;

d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

4.15 The Processing Instructions should include:

- a) a statement of the processing location and the principal equipment to be used;
- b) the methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising);
- c) detailed stepwise processing instructions (e.g. checks on materials, pre-treatments, sequence for adding materials, mixing times, temperatures);
- d) the instructions for any in-process controls with their limits;
- e) where necessary, the requirements for bulk storage of the products; including the container, labelling and special storage conditions where applicable;
- f) any special precautions to be observed.

Packaging Instructions

4.16 There should be formally authorised Packaging Instructions for each product, pack size and type. These should normally include, or have a reference to, the following:

- a) name of the product;
- b) description of its pharmaceutical form, and strength where applicable;
- c) the pack size expressed in terms of the number, weight or volume of the product in the final container;
- d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;
- e) where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product;
- f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
- g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
- h) details of in-process controls with instructions for sampling and acceptance limits.

Batch Processing Records

4.17 A Batch Processing Record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions. The method of preparation of such records should be designed

Draft:

Guide to Master Formulae.

to avoid transcription errors. The record should carry the number of the batch being manufactured. Before any processing begins, there should be recorded checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use.

During processing, the following information should be recorded at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person responsible for the processing operations:

- a) the name of the product;
- b) dates and times of commencement, of significant intermediate stages and of completion of production;
- c) name of the person responsible for each stage of production;
- d) initials of the operator of different significant steps of production and, where appropriate, of the person who checked each of these operations (e.g. weighing);
- e) the batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
- f) any relevant processing operation or event and major equipment used;
- g) a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
- h) the product yield obtained at different and pertinent stages of manufacture;
- i) notes on special problems including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions.

Batch Packaging Records

4.18 A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions and the method of preparation of such records should be designed to avoid transcription errors. The record should carry the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained. Before any packaging operation begins, there should be recorded checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use.

The following information should be entered at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person(s) responsible for the packaging operations:

- a) the name of the product;
- b) the date(s) and times of the packaging operations;
- c) the name of the responsible person carrying out the packaging operation;
- d) the initials of the operators of the different significant steps;

Draft:

Guide to Master Formulae.

- e) records of checks for identity and conformity with the packaging instructions including the results of in-process controls;
- f) details of the packaging operations carried out, including references to equipment and the packaging lines used;
- g) whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;
- h) notes on any special problems or unusual events including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions;
- i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation.

Procedures and records (sections 4.19 to 4.29 not extracted)

Draft:

Guide to Master Formulae.

**Appendix 3: Extracted from PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME PE 009-3, 1
January 2006**

GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS.
© PIC/S January 2006 (Reproduction prohibited for commercial purposes. Reproduction for internal use is authorised, provided that the source is acknowledged).

DOCUMENTATION

PRINCIPLE

Good documentation constitutes an essential part of the quality assurance system. Clearly written documentation prevents errors from spoken communication and permits tracing of batch history. Specifications, Manufacturing Formulae and instructions, procedures, and records must be free from errors and available in writing. The legibility of documents is of paramount importance.

GENERAL

4.1.

Specifications describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Manufacturing Formulae, Processing and Packaging Instructions state all the starting materials used and lay down all processing and packaging operations.

Procedures give directions for performing certain operations e.g. cleaning, clothing, environmental control, sampling, testing, equipment operations.

Records provide a history of each batch of product, including its distribution, and also of all other relevant circumstances pertinent for the quality of the final product.

DOCUMENTS REQUIRED

MANUFACTURING FORMULA AND PROCESSING INSTRUCTIONS

Formally authorised Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured. They are often combined in one document.

4.14. The Manufacturing Formula should include:

- a) the name of the product, with a product reference code relating to its specification;
- b) a description of the pharmaceutical form, strength of the product and batch size;
- c) a list of all starting materials to be used, with the amount of each, described using the designated name and a reference which is unique to that material;

Draft:**Guide to Master Formulae.**

mention should be made of any substance that may disappear in the course of processing;

- d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

4.15. The Processing Instructions should include:

- a) a statement of the processing location and the principal equipment to be used;
- b) the methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising);
- c) detailed stepwise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
- d) the instructions for any in-process controls with their limits;
- e) where necessary, the requirements for bulk storage of the products; including the container, labelling and special storage conditions where applicable;
- f) any special precautions to be observed.

PACKAGING INSTRUCTIONS**4.16. There should be formally authorised Packaging Instructions for each product for pack size and type. These should normally include, or have a reference to, the following:**

- a) name of the product;
- b) description of its pharmaceutical form, and strength where applicable;
- c) the pack size expressed in terms of the number, weight or volume of the product in the final container;
- d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;
- e) where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf-life of the product;
- f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
- g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
- h) details of in-process controls with instructions for sampling and acceptance limits.

BATCH PROCESSING RECORDS**4.17. A Batch Processing Record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions. The method of preparation of such records should be**

Draft:

Guide to Master Formulae.

designed to avoid transcription errors. The record should carry the number of the batch being manufactured.

Before any processing begins, there should be recorded checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use. During processing, the following information should be recorded at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person responsible for the processing operations:

- a) the name of the product;
- b) dates and times of commencement, of significant intermediate stages and of completion of production;
- c) name of the person responsible for each stage of production;
- d) initials of the operator of different significant steps of production and, where appropriate, of the person who checked each of these operations (e.g. weighing);
- e) the batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
- f) any relevant processing operation or event and major equipment used;
- g) a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
- h) the amount of product yield obtained at different and pertinent stages of manufacture;
- i) notes on special problems including details, with signed authorization for any deviation from the Manufacturing Formula and Processing Instructions.

BATCH PACKAGING RECORDS

4.18. A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions and the method of preparation of such records should be designed to avoid transcription errors. The record should carry the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained.

Before any packaging operation begins, there should be recorded checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use.

The following information should be entered at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person(s) responsible for the packaging operations:

- a) the name of the product;
- b) the date(s) and times of the packaging operations;
- c) the name of the responsible person carrying out the packaging operation;
- d) the initials of the operators of the different significant steps;

Draft:

Guide to Master Formulae.

- e) records of checks for identity and conformity with the Packaging Instructions including the results of in-process controls;
- f) details of the packaging operations carried out, including references to equipment and the packaging lines used;
- g) whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;
- h) notes on any special problems or unusual events including details with signed authorization for any deviation from the Manufacturing Formula and Processing Instructions;
- i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation.

Draft: Guide to Master Formulae.

Appendix 4: Extract from Canadian GMP Guidelines

**Health Canada, Health Products and Food Branch Inspectorate
GOOD MANUFACTURING PRACTICES GUIDELINES, 2002 EDITION, Version 2**

From the GLOSSARY:

MANUFACTURING BATCH DOCUMENT (fiche de lot de fabrication) - Instructions that outline in detail the materials and procedures required to fabricate, prepare, and preserve a single lot or batch of a drug in dosage form.

MASTER FORMULA (formule-type) - A document or set of documents specifying the raw materials with their quantities and the packaging materials, together with a detailed description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

MASTER PRODUCTION DOCUMENT (document-type de production) - a document that includes specifications for raw material, for packaging material and for packaged dosage form, master formula, sampling procedures, and critical processing related SOPs, whether or not these SOPs are specifically referenced in the master formula.

MANUFACTURING CONTROL

REGULATION

C.02.011

(1) Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(b) and importer of a drug shall have written procedures, prepared by qualified personnel, in respect of the drug to ensure that the drug meets the specifications for use of that drug.

(2) Every person required to have written procedures referred to in subsection (1) shall ensure that each lot or batch of the drug is fabricated, packaged/labelled and tested in compliance with those procedures.

RATIONALE

This Regulation requires that a number of measures be taken to maintain the integrity of a drug product from the moment the various raw materials enter the plant to the time the finished dosage form is released for sale. These measures seek to ensure that all manufacturing processes are clearly defined, systematically reviewed in light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their established specifications.

MANUFACTURING MASTER FORMULA

Draft:

Guide to Master Formulae.

23. Processing operations are covered by master formulae, that are prepared by, and are subject to independent checks by, persons who have the qualifications described under Regulation C.02.006 Interpretation 1.

24. Master formulae are written to provide not less than 100% of label claim and include the following:

- 24.1 the name of the product, with a reference code relating to its specifications;
- 24.2 a description of the dosage form, strength of the product, and batch size;
- 24.3 a list of all raw materials to be used, along with the amount of each, described using the designated name and a reference that is unique to that material (mention is made of any processing aids that may not be present in the final product);
- 24.4 a statement of the expected final yield, along with the acceptable limits, and of relevant intermediate yields, where applicable;
- 24.5 a statement of the principal equipment to be used;
- 24.6 the procedures, or reference to the procedures, to be used for preparing the critical equipment, e.g., cleaning (especially after a change in product), assembling, calibrating, sterilizing, etc.;
- 24.7 detailed stepwise processing instructions (e.g., checks on materials, pretreatment, sequence for adding materials, mixing times or temperatures, etc.);
- 24.8 the instructions for any in-process controls, along with their limits;
- 24.9 where necessary, the requirements for storage of the products, including the container, the labelling and any special storage conditions; and
- 24.10 any special precautions to be observed.

PACKAGING MASTER FORMULA

25. In the case of a packaged product, the master formula also includes for each product, package size and type, the following:

- 25.1 the package size, expressed in terms of the number, weight, or volume of the product in the final container;
- 25.2 a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types with the code or reference number relating to the specifications for each packaging material;
- 25.3 an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product are to be positioned;
- 25.4 special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before operations begin;
- 25.5 a description of the packaging operations, including any significant subsidiary operations and the equipment to be used; and
- 25.6 details of in-process controls, with instructions for sampling and acceptance limits.

Draft:

Guide to Master Formulae.

MANUFACTURING BATCH DOCUMENT

26. Each batch processed is effectively governed by an individually numbered manufacturing order prepared by qualified personnel from the master formula by such means as to prevent errors in copying or calculation and verified by qualified personnel.

27. As it becomes available during the process, the following information is included on or with the manufacturing order:

27.1 the name of the product;

27.2 the number of the batch being manufactured;

27.3 dates and times of commencement and completion of significant intermediate stages, such as blending, heating, etc., and of production;

27.4 the batch number and/or analytical control number, as well as the quantity of each raw material actually weighed and dispensed (for active raw material, the quantity is to be adjusted if the assay value is less than 98% calculated on "as is" basis and on which the master formula was based);

27.5 confirmation by qualified personnel of each ingredient added to a batch;

27.6 the identification of personnel performing each step of the process; and of the person who checked each of these steps;

27.7 the actual results of the in-process quality checks performed at appropriate stages of the process and the identification of the person carrying them out;

27.8 the actual yield of the batch at appropriate stages of processing and the actual final yields, together with explanations for any deviations from the expected yield;

27.9 detailed notes on special problems with written approval for any deviation from the master formula; and

27.10 after completion, the signature of the person responsible for the processing operations.

28. Batches are combined only with the approval of the quality control department and according to pre-established written procedures.

28.1 The introduction of part of a previous batch, conforming to the required quality, into the next batch of the same product at a defined stage of fabrication is approved beforehand. This recovery is carried out in accordance with a validated procedure and is recorded.

PACKAGING BATCH DOCUMENT

29. Packaging operations are performed according to comprehensive and detailed written operating procedures or specifications, which include the identification of equipment and packaging lines used to package the drug, the adequate separation and if necessary, the dedication of packaging lines that are packaging different drugs and disposal procedures for unused printed packaging materials. Packaging orders are individually numbered.

30. The method of preparing packaging orders is designed to avoid transcription errors.

Draft:

Guide to Master Formulae.

31. Before any packaging operation begins, checks are made that the equipment and work station are clear of previous products, documents, and materials that are not required for the planned packaging operations and that equipment is clean and suitable for use. These checks are recorded.

32. All products and packaging materials to be used are checked on receipt by the packaging department for quantity, identity and conformity with the packaging instructions.

33. Precautions are taken to ensure that containers to be filled are free from contamination with extraneous material.

34. The name and batch number of the product being handled is displayed at each packaging station or line.

35. Packaging orders include the following information (recorded at the time each action is taken):

35.1 the date(s) and time(s) of the packaging operations;

35.2 the name of the product, the batch number, and the quantity of bulk product to be packaged, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;

35.3 the identification of the personnel who are supervising packaging operations and the withdrawal of bulks;

35.4 the identification of the operators of the different significant steps;

35.5 the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;

35.6 the general appearance of the packages;

35.7 whether the packages are complete;

35.8 whether the correct products and packaging materials are used;

35.9 whether any on-line printing is correct;

35.10 the correct functioning of line monitors;

35.11 handling precautions applied to a partly packaged product;

35.12 notes on any special problems, including details of any deviation from the packaging instructions with written approval by qualified personnel;

35.13 the quantity, lot number, and/or analytical control number of each packaging material and bulk drug issued for use; and

35.14 a reconciliation of the quantity of printed packaging material and bulk drug used, destroyed or returned to stock.

36. To prevent mix-ups, samples taken away from the packaging line are not returned.

37. Whenever possible, samples of the printed packaging materials used, including specimens bearing the batch number, expiry date, and any additional overprinting, are attached to packaging orders.

38. Filling and sealing are followed as quickly as possible by labelling. If labelling is delayed, procedures are applied to ensure that no mix-ups or mislabelling can occur.

39. Upon completion of the packaging operation, any unused batch-coded packaging materials are destroyed, and their destruction is recorded. A procedure is followed if non-coded printed materials are returned to stock.

Draft:

Guide to Master Formulae.

40. Outdated or obsolete packaging materials are destroyed and their disposal is recorded.
41. Products that have been involved in non-standard occurrences during packaging are subject to inspection and investigation by qualified personnel. A detailed record is kept of this operation.
42. Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units packaged is investigated and satisfactorily accounted for before release. Validated electronic verification of all printed packaging materials on the packaging line may obviate the need for their full reconciliation.
43. Printed packaging materials are
 - 43.1 stored in an area to which access is restricted to designated personnel who are supervised by persons who have the qualifications outlined under Regulation C.02.006 Interpretation 2;
 - 43.2 withdrawn against a packaging order;
 - 43.3 issued and checked by persons who have the qualifications outlined under Regulation C.02.006 Interpretation 2; and
 - 43.4 identified in such a way as to be distinguishable during the packaging operations.
44. To prevent mix-ups, roll-fed labels are preferred to cut labels. Gang printing is avoided.
45. Cut labels, cartons, and other loose printed materials are stored and transported in separate closed containers.
46. Special care is taken when cut labels are used, when overprinting is carried out off-line and in hand-packaging operations. On line verification of all labels by automated electronic means can be helpful in preventing mix-ups. Checks are made to ensure that any electronic code readers, label counters or similar devices are operating correctly.
47. The correct performance of any printing (e.g., of code numbers or expiry dates) done separately or in the course of the packaging is checked and recorded.
48. Raw materials, packaging materials, intermediates, bulk drugs and finished products are (a) stored in locations that are separate and removed from immediate manufacturing areas, and (b) transported under conditions designated by the quality control department to preserve their quality and safety.
49. All intermediate and finished products are held in quarantine and are so identified in accordance with Interpretation 21, until released by the quality control department.
50. Every package of a drug is identified by a lot number.

Draft: Guide to Master Formulae.

Appendix 5: Extracts from US Code of Federal Regulations (CFR) and US FDA Guidelines.

App 5-1) US Regulations for Master Production Records for Finished Pharmaceuticals. Extract from:

CFR 21, Chapter I, Subchapter F: Biologics, Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals;

Subpart F--Production and Process Controls:

Sec. 211.100 Written procedures; deviations.

(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.

(b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.

Subpart J--Records and Reports

Sec. 211.186 Master production and control records

(a) To assure uniformity from batch to batch, master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person. The preparation of master production and control records shall be described in a written procedure and such written procedure shall be followed.

(b) Master production and control records shall include:

(1) The name and strength of the product and a description of the dosage form;

(2) The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit;

(3) A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic;

Draft:

Guide to Master Formulae.

- (4) An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records;
- (5) A statement concerning any calculated excess of component;
- (6) A statement of theoretical weight or measure at appropriate phases of processing;
- (7) A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to 211.192 is required;
- (8) A description of the drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling;
- (9) Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed.

Database Updated April 1, 2005

App 5-2) US Regulations for Batch Records for Finished Pharmaceuticals:

CFR 21, Chapter I, Subchapter F: Biologics; Subchapter C: Drugs General; Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals;

Subpart J--Records and Reports.

Sec. 211.188 Batch production and control records

Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch. These records shall include:

- (a) An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed;
- (b) Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including:

Draft: Guide to Master Formulae.

- (1) Dates;
- (2) Identity of individual major equipment and lines used;
- (3) Specific identification of each batch of component or in-process material used;
- (4) Weights and measures of components used in the course of processing;
- (5) In-process and laboratory control results;
- (6) Inspection of the packaging and labeling area before and after use;
- (7) A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;
- (8) Complete labeling control records, including specimens or copies of all labeling used;
- (9) Description of drug product containers and closures;
- (10) Any sampling performed;
- (11) Identification of the persons performing and directly supervising or checking each significant step in the operation;
- (12) Any investigation made according to 211.192.
- (13) Results of examinations made in accordance with 211.134.

Database Updated April 1, 2005

App 5-3) US Additional Regulations for Batch Records for Biological Products:

CFR 21, Chapter I, Subchapter F: Biologics, Part 600 Biological Products: General;

Subpart B Establishment Standards,

Sec 600.12 Records

(a) *Maintenance of records.* Records shall be made, concurrently with the performance, of each step in the manufacture and distribution of products, in such a manner that at any time successive steps in the manufacture and distribution of any

Draft:

Guide to Master Formulae.

lot may be traced by an inspector. Such records shall be legible and indelible, shall identify the person immediately responsible, shall include dates of the various steps, and be as detailed as necessary for clear understanding of each step by one experienced in the manufacture of products.

(b) *Records retention*--(Not extracted)

(2) *Records of recall*. (Not extracted)

(3) *Suspension of requirement for retention*. (Not extracted)

(c) *Records of sterilization of equipment and supplies*. Records relating to the mode of sterilization, date, duration, temperature and other conditions relating to each sterilization of equipment and supplies used in the processing of products shall be made by means of automatic recording devices or by means of a system of recording which gives equivalent assurance of the accuracy and reliability of the record. Such records shall be maintained in a manner that permits an identification of the product with the particular manufacturing process to which the sterilization relates.

(d) *Animal necropsy records*. (Not extracted)

(e) *Records in case of divided manufacturing responsibility*. If two or more establishments participate in the manufacture of a product, the records of each such establishment must show plainly the degree of its responsibility. In addition, each participating manufacturer shall furnish to the manufacturer who prepares the product in final form for sale, barter or exchange, a copy of all records relating to the manufacturing operations performed by such participating manufacturer insofar as they concern the safety, purity and potency of the lots of the product involved, and the manufacturer who prepares the product in final form shall retain a complete record of all the manufacturing operations relating to the product.

[38 FR 32048, Nov. 20, 1973, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 70 FR 14982, Mar. 24, 2005]

Database Updated April 1, 2005

App 5-4) Extract from US FDA Guidelines for Batch Records for Sterile Products:

Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice: U.S. Department of Health and Human Services, Food and Drug Administration; Center for Drug Evaluation and Research (CDER);

Draft:

Guide to Master Formulae.

Center for Biologics Evaluation and Research (CBER); Office of Regulatory Affairs (ORA). September 2004)Pharmaceutical cGMPs)

Manufacturers should build process and environmental control activities into their aseptic processing operation. It is critical that these activities be maintained and strictly implemented on a daily basis. The requirement for review of all batch records and data for conformance with written procedures, operating parameters, and product specifications prior to arriving at the final release decision for an aseptically processed product calls for an overall review of process and system performance for that given cycle of manufacture. All in-process and laboratory control results must be included with the batch record documentation in accordance with section 211.188. Review of environmental and personnel monitoring data, as well as other data relating to acceptability of output from support systems (e.g., HEPA / HVAC, WFI, steam generator) and proper functioning of equipment (e.g., batch alarms report; integrity of various filters) are considered essential elements of the batch release decision.

While interventions and/or stoppages are normally recorded in the batch record, the manner of documenting these occurrences varies. In particular, line stoppages and any unplanned interventions should be sufficiently documented in batch records with the associated time and duration of the event. In addition to lengthened dwell time of sterile product elements in the critical area, an extensive intervention can increase contamination risk. Sterility failures have often been attributed to atypical or extensive interventions that have occurred as a response to an undesirable event during the aseptic process. Written procedures describing the need for line clearances in the event of certain interventions, such as machine adjustments and any repairs, should be established. Such interventions should be documented with more detail than minor events. Interventions that result in substantial activity near exposed product or container closures or that last beyond a reasonable exposure time should, where appropriate, result in a local or full line clearance.

Any disruption in power supply, however momentary, that could affect product quality is a manufacturing deviation and must be included in batch records (211.100, 211.192).

Draft:

Guide to Master Formulae.

Appendix 6: WHO/VSQ/97.01: A WHO guide to good manufacturing practice (GMP) requirements. Part 1: Standard operating procedures and master formulae, Appendix 6: Sample master formula for a hypothetical biological product

To be added

Appendix 7: Example one of a Master Formula

To be added

Appendix 8: Example two of a Master Formula

To be added

Appendix 9: Example three of a Master Formula

To be added