BEST PRACTICE GUIDELINES

For Pharmaceutical Secondary Packaging

EUROPEAN
CARTON MAKERS
ASSOCIATION

ECMA Best Practice Guidelines for

Pharmaceutical Secondary Packaging

Developed by the ECMA Pharma Forum with the involvement of Willem Otte Consultancy

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TABLE OF CONTENTS

Introduction **5**

Terms and Definitions **6**

Chapter 1 – Order Receipts & Pre-Press **7**

1.1 Customer Onboarding 7

1.2 Order Receipt 8

1.3 Planning / Preparation 9

1.4 Artwork Management / Pre-press 9

Chapter 2 – Production processes **10**

2.1 Printing 10

2.2 Die-Cutting 16

2.3 Folding & Gluing 20

2.4 Braille Embossing 23

2.5 Final Inspections 24

Chapter 3 – Post-Production & Logistics **26**

3.1 Labelling & Packaging 26

3.2 Storage 27

3.3 Stock Management 29

3.4 Sampling 31

3.5 Order Picking / Packing 31

3.6 Customer Requirements 32

3.7 Transportation Controls 33

3.8 Returns / Sort / Rework 34

3.9 External Warehousing 34

Chapter 4 – Quality Systems 35
4.1 Management Review 35
4.2 Documented Information 35
4.3 Equipment Management 35
4.4 Facilities 36
4.5 Training 36
4.6 Product Status Management 37
4.7 Recall / Traceability 39
4.8 Deviation Management 41
4.9 CAPA Management 42
4.10 Customer Complaints 43
4.11 Audit Observations 44
4.12 Data Integrity 45
4.13 Risk Management 46
4.14 Qualification / Validation 46
4.15 Vendor Management 48
4.16 Change Management 48
4.17 Sampling 49

INTRODUCTION

As the representative body for the folding carton industry, the European Carton Makers Association (ECMA), is delighted to release these **Best Practice Guidelines for Pharmaceutical Secondary Packaging**.

These guidelines document Best Practice from 'receipt of order to delivery to the customer' and encompass the latest technology. Those companies that comply with the guidelines are demonstrating their rigorous work practices, dedication and commitment to the Pharma & Healthcare sector. Compliance with the requirements of the **Best Practice Guidelines for Pharmaceutical Secondary Packaging** will be via self-certification and will be recognised with a certificate and quality stamp.

The **Best Practice Guidelines for Pharmaceutical Secondary Packaging** will be relevant to all companies that manufacture cartons used by the Pharmaceutical and Healthcare sector. It is an information and management tool with a clear methodology based on the following principles:

- Senior Management sponsorship of compliance with the BEST PRACTICES standard.
- A Quality Management System such as PS 9000 / ISO 9001 / ISO 15378 and/or a strict workplace hygiene control system needs to be in place and will continue to be the cornerstone quality benchmark.

This new publication was developed in the ECMA Pharma Forum, with the involvement of Willem Otte Consultancy. We would also like to thank the following member companies for their contribution to these guidelines Autajon Packaging Belgium sa/nv, Cömertler Matbaacilik San.ve TIC. A.S., Edelmann GmbH, Eson Pac AB, Essentra Packaging, Faller Packaging, Graphic Packaging International, Intergrafipak B.V., Jaakkoo Taara Oy, LGR Packaging, Medica Packaging Ltd, Palladio Group S.p.a., Paperpack S.A., Royal van Eerd bv and WestRock.

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Disclaimer

ECMA has done everything possible to ensure accuracy of the information contained in this document.

ECMA accepts no liability whatsoever for any business decisions based on the contents of this document. These remain the sole responsibility of the users of this information.

TERMS AND DEFINITIONS

The following terms are underlined once per section throughout the document.

	Term	Definition
1.	Artwork	The elements that constitute a mechanism in printing, such as type, proofs and illustrations.
2.	Braille	Braille is a technology with a special alphabet which allows blind or visually impaired people to read. The blind read Braille alphabet, by feeling letters with their fingertips.
3.	Braille embossing technology	The stamping of dots that represent the Braille alphabet on a material using an embossing die and counterpart.
4.	Campaigning	Campaigning is the way to maximise the efficiency of the manufacturing process by producing like for like jobs back to back.
5.	Certificate of Assurance	Document attesting that specific goods have undergone specified testing with specified results agreed between the seller and buyer.
6.	Certificate of Conformance	Official recognition that a product possess the technical specifications alleged by the manufacturer or seller.
7.	Cross contamination	Inadvertent transfer of material from one batch to another.
8.	Digital printing	Is continuous generation of new printing images, using a digital file to print images directly onto a substrate.
9.	Offset printing	Uses permanent plates to transfer an image onto a rubber “blanket” that rolls the image onto a substrate.
10.	ERP system	Enterprise Resource Planning system.
11.	Foil printing	Is performed typically after offset or digital print step is performed by using: - a Hot Stamping method on Press with custom metal dies, or - a Cold Stamp method
12.	4 eye principle	Requirement that some action or decision must be approved by at least two persons.
13.	Gang printing	Gang printing means printing more than one design on a substrate during one production run, also referred to as combo, composite or combination printing.
14.	Intermediate material	A manufactured product that requires additional processing before it becomes finished goods.
15.	Line clearance	Standardized procedure in manufacturing for ensuring equipment and work areas are free of products, documents and materials from the previous process.
16.	Pre-press one up file	An electronic print-ready file that is an accurate representation in terms of content and how the finished piece will appear when produced.
17.	Process aids	Materials used during processing but not present in the final product.
18.	Substrate	An underlying substance or layer, in printing often seen to as a clean or unprinted print sheet.
19.	Tailgate samples	Samples taken according to a pre-approved sampling plan. They represent the batch and are shipped together with the batch.
20.	Varnishing	Varnishing is performed by adding a layer of varnish to the print.

CHAPTER 1

ORDER RECEIPT & PRE-PRESS

1.1 Customer Onboarding

A successful business relationship is based on proactive and professional cooperation. In terms of leadership, a well-organised and practised "customer onboarding" process is the basis for a successful start. This chapter sets out the basic requirements for the integration of new customers.

It is deemed best practice to follow the following guidelines:

- PS 9000:2016 / ISO 9001:2015, chapter 5.1.2 “customer focus”
- PS 9000:2016, chapter 8.2.2 + 8.2.2.3 “Specification/Requirements”
- PS 9000:2016, chapter 8.2.1 “customer communication”
- PS 9000:2016, chapter 5.1.3 “customer audits”

Customer management requires a formal customer onboarding process. With this process, the customer's requirements are systematically determined at the beginning of a new business relationship and compared to those of the supplier. Any differences should be recognised at an early stage and mutually agreed with both parties.

The customer onboarding process shall include a check and match of:

- Material specifications
- Product specifications
- Manufacturing capability e.g., qualification, trials
- Acceptable Quality Levels (AQL’s)
- Delivery requirements inc. documentation

It is also important for the supplier to understand the intended use of the carton and the conditions in which it will be processed and stored.

Once these requirements are verified and differences are mutually agreed, the customer can be formally accepted.

It is best practice to outline the terms of agreement from both parties in a formal contract and or Quality Agreement, and periodically verify if both the customers’ and suppliers’ expectations are fulfilled.

1.2 Order Receipt

1.2.1 Order Processing and Registration

Best Practice requires that the supplier maintains a system in which the administrative information of the customer is linked to the ERP system of the supplier.

1.2.2 Item Specific Requirements

For new items:

Best Practice requires to follow the ISO 9001, where suppliers must ensure that they are able to meet the customers' product and service requirements.

The customers' specifications should be assessed both for content and technical attributes prior to production. Any concerns should be recognised and mutually agreed by both parties before production start.

For unchanged and changed reprints:

Best Practice requires the suppliers to maintain a system for filing:

- Production specific information
- Product specific information
- Order specific information

This information shall be subject to formal change control.

1.2.3 Artwork

The European Carton Makers Association (ECMA) recommends following the ECMA Technical Guidelines for the creation and exchange of artwork files. Refer to section 1.4, "Artwork Management / Pre-press".

1.2.4 Campaigning

To enable efficient production processes, campaigning can be applied.

Best Practice requires to capture campaigning in a Standard Operating Procedure (SOP) or apply it with an appropriate risk assessment.

1.3 Planning / Preparation

It is deemed best practice to follow the following guidelines during planning and preparation of production orders:

- ⇨ ISO 9001:2015 sections 7.1 and 8.1
- ⇨ PS 9000:2016 section 8.1 “Operational planning and control”
- ⇨ PS 9000:2016 section 8.5.1.1 “Print related processes (e) Gang Printing”

1.3.1 Planning

It is recommended to verify availability of at least the following manufacturing elements when planning the production.

For repeat items:

a. Manufacturing tools
b. Raw materials
c. Printing plates
d. Capacity for relevant machinery

For new items:

a. Customer approved artwork
b. New manufacturing tools
c. Raw materials
d. Printing plates
e. Capacity for relevant machinery

1.3.2 Preparation

Based on the availability of these production elements, production can be planned and the production run can be prepared.

It is Best Practice to only communicate the expected lead time to the customer once the timely availability of these manufacturing elements have been verified.

1.4 Artwork Management / Pre-press

The European Carton Makers Association (ECMA) recommends manufacturers of folding cartons for supply to the Pharma industry, to follow the ECMA Technical Guidelines for the creation and exchange of artwork files in the production of folding boxes.

Any modification of customer approved artwork for the purposes of plate making shall be verified prior to plate making. Best practice requires the pre-press one-up file for a particular job to be compared digitally against customer approved artwork.

Once digitally verified, the prepress one-up file is considered approved and may be used as a reference from this point forward for comparison purposes throughout the manufacturing process.

CHAPTER 2

PRODUCTION PROCESSES

2.1 Printing

2.1.1 Printing Techniques

Offset printing and digital printing are both useful printing methods for the pharmaceutical industry. Each have benefits depending on the project. To enhance the appearance of a print or to protect the print, additional techniques such as foil printing and varnishing are applied.

Best Practice requires open communication with the customer about the applied printing technologies. Offset printing can be seen as the standard and wide-spread method for printing folding cartons. In case of switching from one printing method to the other, it is recommended to conduct a risk assessment prior to implementing the change.

In these guidelines, we compare against offset printing as being the standard.

⇨ Refer to the PS9000 Standard, section 8.5.1.1d

A. Offset Printing

- Benefits:
  - High printing quality.
  - Proven technology and industry standard for printing on folding cartons
  - 4 colour CMYK as well as PMS colours or combinations of both possible.
  - Efficient printing process once it has been set-up. Therefore, cost effective for large quantities.
  - Accurate colour reproduction and high level of colour stability.
  - Offers possibilities for custom finishes with different substrates and speciality inks.
  - Wide range of substrate formats and thicknesses possible.
  - Inline printing of coatings commonly used, typically aqueous or UV.
  - Production speed independent of number of colours.

B. Digital printing:

- Benefits:
  - Does not require printing plates and pre-print stages between digital files and the final product. Therefore, low set-up costs and cost effective for short runs.
  - Offers possibilities for printing only the required amount.
  - Low minimum quantities.
  - Offers variable data capability when each piece needs a unique code, such as serialized information.
  - No equipment formatting required such as film plates or chemicals.
  - Typically uses 4 colour processing, more colour utilization is feasible.
  - Aqueous and ultraviolet (UV) coatings commonly used.
  - UV inkjet base for digital printing devices do not require UV over coating.
  - Offer possibilities for metalized colour utilization.

- Controls:
  - Quality Inspections are to be performed, documented and approved at each stage of the process. Including Start-up, In-process and Final inspections.
  - Line Clearance protocols are expected to be deployed to prevent mix of product.
  - Critical to Quality criteria should be clearly communicated through process control plans, work instructions, customer specifications or other methodology.
  - examples are but not limited to:
    - Verification of all job specific materials against the work order.
    - Colour match via Digital Library or other colour reference
    - Registration
    - Copy or image quality
    - Copy position and content
    - Coating coverage
    - Dimensions
    - Barcode / Data Matrix Code

- Potential Risks:

  <u>Maintenance</u>

  Digital printing equipment requires extensive Preventive Maintenance.

  <u>Production</u>

  The digital printing process requires extra measures to eliminate the risk of product mix up and to ensure print quality.
  - There is only one print job allowed waiting in the print queue.
  - A Separator file (i.e. Die Outline) is to be used as a 'lead in' and 'lead out' identifier.
  - The Job File is to be deleted after a run is completed.
  - An automated In-Line inspection system is to be used to ensure all print criteria are properly assessed against an acceptable proof.

- Digital printing versus offset printing:
  - Digital printing shall offer the same level of quality assurance as offset printing.
  - Digital printing generates other risks and requires other inspection methods.
  - Digital printing uses other types of inks and colour substitution, however, the reference for colouring shall be identical to offset printing.

C. Foil Printing

- Benefits:
  - Hot Foil is used for precise applications and small areas.
  - Cold Foil is used for moderate to full coverage applications.
  - Foil printing will add to cost but the appearance benefit is very attractive.
  - Hot foil stamping and other similar enhancements on product packaging can help attract consumer attention faster and keep attention longer than ordinary packaging.

- Equipment:
  - Foil printing requires specific equipment.
  - Hot Foil requires a Hot Stamp Press and custom die with defined pressure/temperature.
  - Cold Foil requires ultraviolet light at defined setting.
  - Foil stamping has specific tolerances for applications, depending on the type and method of application. This should be considered as part of the set up and customer specification agreement.
  - Foil application should be considered as customer artwork. Therefore, it should be subject to the same controls as artwork. Including a verification if the foil is added according to the customers' specifications. This should be controlled by a documented procedure.

D. Varnishing

- Purpose:
  The need for varnishing depends on the printing technology, and the inks. Varnish offers protection to the print, and enhances the appearance of the print. In addition, varnish can be used for anti-counterfeit purposes.

- Process:
  Varnish can be applied using a plate or rubber blanket. Varnish application should be controlled to ensure the varnish is consistently mixed and applied. Inconsistency causes line performance issues either in Finishing or on the customer's packing lines.

  Each plate or blanket should be uniquely identified and checked for damage prior to use. A Standard Operating Procedure, Work Instruction, Batch Record or equivalent should define how to verify the correct version of plate or blanket.

- In Process Checks:
  To ensure varnish application is consistent throughout the manufacture of the whole batch, In Process Checks shall be performed. The In Process Checks shall be defined in a Standard Operating Procedure, Work Instruction, Batch Record or equivalent, for all types of varnishing techniques used. Including anti-counterfeit methods which can be difficult to inspect visually.

⇨ Refer to section 2.1.2, "Printing Process" part D, "In process controls".

2.1.2 Printing Process

A. Preparation of Starting Materials

The operator should have all starting materials listed within the specification:

- Board type
- Number of printing plates
- Plate references
- Coating plate references
- Ink
- Other materials such as varnishes and foil where applicable

All the above materials should be traceable back to origin.

All In Process Controls (IPC) should be documented and outlined in a Standard Operating Procedure (SOP).

Printing plates can either be stored (traceable for usage) or newly generated each time.

B. Line Clearance Verification

Possible sources of product mix-up shall be avoided. It is best practice to verify and document that all materials from the previous run have been removed from the production area before setting up the next run. This includes:

- Raw material
- Work in process material
- Tools
- Samples
- Documents
- Waste
- Computer information

The following activities are expected to be performed during a line clearance activity:

- Line clearance is performed to a defined process.
- Where common materials from the previous run are required for the next run, this shall be documented as part of the line clearance process.
- Evidence of line clearance is documented in the production batch record.
- Line clearance shall be performed just before setting up the next production run.

⇨ Refer to the PS9000 Standard, section 8.1.1.4

C. Set-up and Controls for Production Release

Best Practice requires to define the set-up of a print machine (make-ready) in a Standard Operating Procedure (SOP). The “make ready” should be performed using unprinted stock. The “make ready” should be repeated if more than one set of plates is required for a run.

⇨ Refer to the PS9000 Standard, section 8.5.1.1.c

The machine operator shall:

- Verify the identity of the printing plates against the batch documentation.
- Assure printing plates are allocated to the corresponding ink.
- Ensure colour compliance in accordance with site procedure or customer requirements.
- Ensure compliance with approved artwork.
- Perform an “electronic comparator check” at make ready to support the operator in reviewing register, text, low spots in blankets and blemishes.
- Sign the “make ready process” as completed prior to running.
- Carry out a First Article Inspection (FAI) according to the applicable requirements. The results shall be approved and recorded in the batch record.

D. In-process Controls

As a best practice, it is important to ensure that product conformity is maintained during the production cycle. This is managed through a defined sampling program where critical to quality characteristics are verified against mutual agreed Acceptable Quality Levels (AQL).
The frequency for sampling shall be risk based, depending on process stability/capability data.
The frequency and applicable inspection items are to be defined in a Standard Operating Procedure, Work Instruction, Batch Record or equivalent.

The inspection results shall be verified against the customers’ requirements.

As a best practice Process Control Plans should detail the in-process inspection criteria, including:

- Process definition
- Specifications
- Tolerances
- Sampling criteria
- Inspection methods
- Reaction plan

As a Best Practice, critical to quality characteristics should be verified through electronic detection devices. These devices should be qualified, calibrated and maintained according to pre-determined schedules. The verification process with electronic detection devices should be validated and defined in formal Standard Operating Procedures or Work Instructions.

Any defects identified should be:

- Followed up in terms of containment, root cause analysis and corrective/preventive actions.
- Tabbed/highlighted for removal during the subsequent processes.
- Recorded in the Batch Record, ERP system or equivalent, for traceability at subsequent process steps.
- Periodically evaluated in terms of continuous improvement.

E. Final Control

The quality system should include a Final Control to assure that the printed layout is in accordance with the batch documentation. For every batch the Final Control should include a verification of the “ready to run sheet” against the artwork. The intervals for the inspection process should be determined by a risk approach.

F. Intermediate Material Storage

Best practice requires to design storage of intermediate materials based on a risk assessment. Intermediate materials should be clearly identified and properly segregated to avoid cross contamination.

⇨ Refer to the PS9000 Standard, section 8.1.1.3.

2.1.3 Gang printing

⇨ Refer to the PS9000 Standard, section 8.5.1.1e.

Gang printing is a common method to reduce waste and to produce small quantities in a cost effective way.

Gang printed sheets require die-cutting in one production run. After die-cutting, the designs can be segregated and processed separately.

A. Customer Information

Best Practice requires open communication with the customer when using the gang printing-method. Customers must pre-approve the use of gang printing in production.

B. Requirements for Gang Printing

Best Practice requires to mitigate cross-contamination by applying the following requirements:

- Each design on a gang printed sheet has its own item number that corresponds with the customers’ order.
- Each design on a gang printed sheet has its own different code which is read during the folding/gluing process. Usually the gluing-flap is used for code positioning.
- The embossing system must assure that each position number receives the corresponding braille.
- The identity of braille and printed items should be verified against specifications.
- Different designs should be separated before folding/gluing, either by validated electronic equipment or under the 4 eye principle.
- Gang printed sheets are adequately differentiated by size, shape or colour.

2.2 Die-Cutting

2.2.1 Preparation of Starting Materials

It is vital that all appropriate materials, processing aids and documentation are made available to the personnel performing work. Control of these elements should be defined via a Standard Operating Procedure (SOP).

The following is required to ensure product conformity before starting production;

- Correct material is received from the previous processing step and verified against the job order.
- Die-cutting tools and supporting equipment (including Braille tooling) are verified against job order and die/tooling identification numbers.
- Inspection equipment is correct and in calibration.
- Batch traceability is to be maintained throughout the production cycle which may include multiple pallets of material used.

Best Practice to manage verification of die-cutting tools is to:

- Indicate for each production batch the identification code for the required die-cutting tool.
- Identify each tool with a unique identification code, applying this information on the physical tool.
- Verify the identification codes against the production batch.

Best Practice to manage the braille tool verification (if separated from the die-cutting tool), is to:

- Indicate for each production batch the identification code for the required braille tool.
- Identify each tool with a unique identification code, applying this information on the physical tool.
- Verify the identification codes with the codes required by the production batch.
- Verify the control number of the braille tools against the number of positions in the sheet.

For both die-cutting and braille tool, best practice is to register the identification code in the ERP system or similar and to use a 2D/3D code on the physical tool in order to improve the precision of the checking phase.

2.2.2 Line Clearance Verification

It is deemed best practice to follow the following guidelines:

⇨ Both PS9000:2016 and ISO9001:2015

Possible sources of product mix-up shall be avoided. It is best practice to verify and document that all materials from the previous run have been removed from the production area before setting up the next run. This includes:

- Raw material
- Work In Process material
- Tools
- Samples
- Documents
- Waste
- Computer information

The following activities are expected to be performed during a line clearance activity:

- Line clearance is performed to a defined process.
- Where common materials from the previous run are required for the next run, this shall be documented as part of the line clearance process.
- Evidence of line clearance is documented in the production batch record.
- Line clearance shall be performed just before setting up the next production run.

2.2.3 Set-up and Controls for Production Release

As part of the product release activity, ensuring that product has satisfied all requirements prior to starting the production run, is crucial. Therefore, it is best practice to have a defined process that identifies the activities specific to setup or make-ready and the associated approval requirements.

Elements of an effective setup program:

- Ensure a full line clearance has been performed and approved before starting the setup/make-ready process.
- Production process parameters and critical to quality criteria (including Braille) shall be identified via the job order, through process control plans and/or specific work instructions and shall incorporate specific customer requirements as needed.
- Production equipment (including dies, etc.) shall be managed through a preventive maintenance program/process and shall be fit for use.
- Sampling criteria shall be identified and performed per instructions and/or process control plans and samples shall be kept with the batch record as defined.
- All inspections and testing where required shall be performed and documented and kept with the batch record as defined.
- Where a First Article Inspection (FAI) is required, the inspection shall be carried out according to internal/customer requirements and shall be documented, approved and form part of the batch record.
- Any waste material shall be disposed of per defined procedures.

⇨ Refer to PS9000:2016 and ISO9001:2015

2.2.4 In Process Controls

As a best practice, it is important to ensure that product conformity is maintained during the production cycle. This is managed through a defined sampling program where critical to quality characteristics are verified against mutual agreed Acceptable Quality Levels (AQL).
The frequency for sampling shall be risk based, depending on process stability/capability data.
The frequency and applicable inspection items are to be defined in a Standard Operating Procedure, Work Instruction, Batch Record or equivalent.
The inspection results shall be verified against the customers' requirements.

As a best practice Process Control Plans should detail the in-process inspection criteria, including:

- Process definition
- Specifications
- Tolerances
- Sampling criteria
- Inspection methods
- Reaction plan

As a Best Practice, critical to quality characteristics should be verified through electronic detection devices. These devices should be qualified, calibrated and maintained according to pre-determined schedules. The verification process with electronic detection devices should be validated and defined in formal Standard Operating Procedures or Work Instructions.

Any defects identified should be:

- Followed up in terms of containment, root cause analysis and corrective/preventive actions.
- Tabbed/highlighted for removal during the subsequent processes.
- Recorded in the Batch Record, ERP system or equivalent, for traceability at subsequent process steps.
- Periodically evaluated in terms of continuous improvement.

2.2.5 Final Control

Best practice requires a final control on intermediate product prior to moving it to the next operation. This final control should include a verification of all critical quality requirements against the required procedures, work instructions, process control plans and customer requirements.

Key elements to be considered:

- All inspections completed, documented, and formally approved.
- Inspection records included in the batch record.
- Pallets properly identified and protected against cross contamination.
- Tooling inspected for damage/wear prior to storage.
- Job closed per defined procedures.
- Full line clearance performed as required.

2.2.6 Intermediate Material Storage

Best practice requires to design storage of intermediate materials based on a risk assessment. Intermediate materials should be clearly identified and properly segregated to avoid cross contamination.

⇨ Refer to the PS9000 Standard, section 8.1.1.3.

Specific elements to consider in terms of Die Cutting and Braille tooling:

- Tooling to be inspected on wear or damage prior to returning to its designated storage location.
- Tooling to have a permanent unique identification code.
- Tooling identification code to be linked to the Job Order ensuring correct tooling has been delivered.

Best practice prefers:

- Registration of tooling in the ERP system to enable direct linking to production orders.
- 2D/3D coding techniques for tool identification to improve the precision of tooling verification activities.

2.3 Folding & Gluing

2.3.1 Preparation of Starting Materials

It is vital that all appropriate materials, processing aids and batch documentation are made available to personnel performing work. This includes specifications, operating procedures, work instructions and forms.

Inspection of these starting materials should be defined via a procedure.
The conformity of the following materials shall be verified against the job order before starting production;

- Material coming from previous processing step
- Supporting equipment
- Inspection devices

The inspection on the starting materials shall be defined via a procedure, the inspection results shall be recorded in the batch record.

When a batch requires multiple pallets in the production area, it is imperative to have a system that guarantees full material traceability. Best Practice requires managing the identification and registration of products using the ERP system.

Batch documentation shall include the following information:

- Batch ID of the cartons
- Pharma code, where applicable
- Braille requirements, where applicable
- Measurement specifications for folding
- Packaging and palletization requirements
- Sampling requirements
- Labelling requirements

2.3.2 Line Clearance Verification

It is deemed best practice to follow the following guidelines:

⇨ Both PS9000:2016 and ISO9001:2015

Possible sources of product mix-up shall be avoided. It is Best Practice to verify and document that all materials from the previous run have been removed from the production area before setting up the next run. This includes:

- Raw material
- Work In Process material
- Tools
- Samples
- Documents
- Waste
- Computer information

The following activities are expected to be performed during a line clearance activity:

- Line clearance is performed to a defined process.
- Where common materials from the previous run are required for the next run, this shall be documented as part of the line clearance process.
- Evidence of line clearance is documented in the production batch record.
- Line clearance shall be performed just before setting up the next production run.
- Further detail can be found in PS9000 latest version.

2.3.3 Set-up and Controls for Production Release

It is crucial to verify that all requirements are met prior to starting a production run. Best practice requires a defined process that identifies the activities specific to setting up a new production run. Elements of an effective setup program are noted below.

⇨ In addition, PS9000 and ISO9001 (latest versions) provide further instruction in this area.

- A full line clearance shall be performed and approved before setting up a new order.
- Production process parameters and critical to quality criteria shall be identified via formal documentation such as but not limited to:
  - Job order
  - Process control plans
  - Specific work instructions
  - Specific formal customer requirements
- The calibration/validation/preventive maintenance status of production equipment shall be verified.
- Sampling criteria shall be available.
- All required inspections and testing shall be performed and recorded in the batch record.
- First Article Inspection (FAI) shall be carried out according to the applicable requirements. The results shall be approved and recorded in the batch record.

2.3.4 In Process Controls

As a best practice, it is important to ensure that product conformity is maintained during the production cycle. This is managed through a defined sampling program where critical to quality characteristics are verified against mutual agreed Acceptable Quality Levels (AQL).
The frequency for sampling shall be risk based, depending on process stability/capability data.
The frequency and applicable inspection items are to be defined in a Standard Operating Procedure, Work Instruction, Batch Record or equivalent.
The inspection results shall be verified against the customers' requirements.

As a best practice Process Control Plans should detail the in-process inspection criteria, including:

- Process definition
- Specifications
- Tolerances
- Sampling criteria
- Inspection methods
- Reaction plan

As a Best Practice, critical to quality characteristics should be verified through electronic detection devices. These devices should be qualified, calibrated and maintained according to pre-determined schedules. The verification process with electronic detection devices should be validated and defined in formal Standard Operating Procedures or Work Instructions.

Any defects identified should be:

- Followed up in terms of containment, root cause analysis and corrective/preventive actions.
- Tabbed/highlighted for removal during the subsequent processes.
- Recorded in the Batch Record, ERP system or equivalent, for traceability at subsequent process steps.
- Periodically evaluated in terms of continuous improvement.

2.3.5 Final Control

Best practice requires a final control on final product prior to storing it. This final control should include a verification of all critical quality requirements against the required procedures, work instructions, process control plans and customer requirements.

Key elements to be considered:

- All inspections completed, documented, and formally approved.
- Inspection records included in the batch record.
- Pallets properly identified and protected against cross contamination.
- Tooling inspected for damage/wear prior to storage.
- Job closed per defined procedures.
- Full line clearance performed as required.

NOTE:

- For requirements regarding tailgate sampling, see chapter 4, section 16, "Sampling".
- For storage of folded and glued product see section 3.2 "Product Storage".

2.4 Braille Embossing

It is deemed best practice to follow the following guidelines

- PS9000:2016, section 8.5.1.3 "Braille"
- ISO 17351 Packaging – Braille on packaging for medicinal products
- ECMA Braille Guideline

2.4.1 Technologies

There are two processes for embossing the braille alphabet on cardboard:

A. Application during the die-cutting process

- The female block is placed permanently on the die-cutting tool and the male form is placed on to the counter plate.
- Braille/embossing male and female embossing dies are required for each folding box on a sheet.
- As the sheets passes between the male and female embossing tools, the pressure applied pushes the board to create raised dots onto the cardboard.

B. Application during the folding/gluing process

- Braille embossing by gluing system uses only one male die, custom made for the order and a single universal female tool.
- The folding boxes are pressed against the male cliché as the cylinder rotates and the impressions of the raised dots are transferred on to the cardboard.

2.4.2 Braille Control System

Best Practice requires to include the following aspects in the Braille control system:

- The printing company and the tool maker formally agree on the technical specifications of the embossing tools. The tool maker must be on the company's approved supplier list.
- First Article Inspection (FAI) shall be carried out according to the applicable requirements. The results shall be approved and recorded in the batch record.
  The following inspection items should be verified:
  - Braille position and direction.
  - Braille height to the ISO standard and/or customer specifications.
  - Braille dot quality.
  - Braille is situated in the correct panel.
- Inspection methods must be defined per Standard Operating Procedure or Work Instruction.
- Inspection frequency must be defined per Standard Operating Procedure or Work Instruction (e.g. first sheet inspection, interval in-process control, last sheet inspection).
- The inspections shall be conducted by trained personnel.
- All Braille inspection results should be recorded and retained for a specified period as outlined in site procedures.

2.4.3 Life Cycle Requirements and Retention Process of Braille Tooling

Best Practice requires to define the following Braille tooling aspects per Standard Operating Procedure:

- Registration and traceability
- Life cycle requirements and retention process
- Measures to prevent incorrect Braille
- Management of changes to Braille embossing tooling

2.5 Final Inspection

Final Inspection refers to the tests carried out on the finished product to determine compliance with the customer specification, prior to shipping. These tests can be completed prior to or part of the final product release process.
The final inspection may or may not include checking all parameters of the customer specification. If not all attributes are inspected as part of final release this should be justified, preferably by a formal risk assessment.
The final inspection should be focused on the Critical to Quality (CTQ) attributes defined from the customer quality agreement or internally documented process control plans (Acceptable Quality Levels). The attributes are functional or cosmetic and defined by severity based on the impact the defect could have on the customers packing process or the end patient.

- ⇨ Details for the classification of defects can be found in the Editio Cantor Verlag Aulendorf, General principles and special defect evaluation lists.

With the advancement of technology within the print manufacturing processes, the requirement for final inspection testing at the end of the process is diminishing. Best Practice manufacturing processes are evolving so final inspection becomes a verification inspection. The inspection is designed, based on a formal risk assessment to minimize risk to the end patient. In addition, the inspection shall ensure that the predefined Critical to Quality checks are completed accurately in real time. The CTQ should be defined and documented for the entire manufacturing process. The final inspection verification ensures the products have been produced in accordance with the Customers Quality Agreements/Specifications and any defects are within the agreed tolerances. The final inspection process should be focused on ensuring compliance of the product to all Customer Agreements and to identify any significant defects or process failures which could result in patient risk.

2.5.1 Release Criteria

Best Practice would be to define the sample based on a recognised sampling plan e.g.:

- ⇨ ANSI Z1.4
- ⇨ ISO 3951-2:2013 for inspection by variables
- ⇨ ISO2859-1 for inspection by attributes

These are used to determine an Acceptable Quality Limit (AQL) by which to accept or reject the batch based on a random sampling analysis.

2.5.2 Inspection Items

Best Practice requires to only use final product samples that went through the full manufacturing process, including any specialised processing such as but not limited to Embossing, Brailling and Foiling.

Samples should be inspected on:

- ❖ Print quality for cosmetic and functional defects
- ❖ Cut and crease
- ❖ Compliance with the approved artwork
- ❖ User functionalities
- ❖ Glued samples should be checked on bleeding and glue bond resistance

A. Sample Material

Best practice requires to capture the following in a formal Standard Operating Procedure:

- The number of samples to be inspected.
- The retention period for batch samples.

B. Reference Material

Sample inspections should be conducted against customer approved digital or hard copy files. These Customer Specifications should be part of the batch records. They should also include specific customer requirements, such as but not limited to:

- Product identification
- Tray and shipper quantities
- Pallet type
- Customer specific test analysis

The approved carton design and/or technical specifications should be either cross referenced or defined in the batch records.

C. Inspection Equipment

- Electronic Verifications should be completed at the point of manufacture. Best Practice would be to use these systems to verify the success of the process rather than rely solely on manual checks. These should include bar code scanning, dot scan systems to read Braille, inline camera inspection systems and comparator systems to verify compliance with approved artwork.
- Final inspection should verify if these Critical to Quality checks have been completed correctly to customer requirements, considering all agreed AQL.

D. Documentation – Internal

Final Batch records should be retained. They should be data compliant and include:

- The unique batch number which is held for traceability of the batch/lot.
- Documented evidence of the inspections completed throughout the manufacturing process.

The types and frequency of checks should be defined in a formal document, such as a Standard Operating Procedure, Work Instruction or process control plan.

At Final batch release a verification check should be performed against the Batch record to ensure the checks have been carried out in line with the Standard Operating Procedure.

CHAPTER 3

POST-PRODUCTION & LOGISTICS

3.1 Labelling & Packaging

It is deemed best practice to follow the following guidelines:

- ⇨ PS9000:2016 and ISO9001:2015

For the labelling and packaging processes including pallet labelling, Best Practice requires documented system that will reduce the risk of misidentification, ensure accurate reconciliation, provide full traceability, and prevent customer confusion and dissatisfaction. As part of this activity, it is expected that the manufacturer shall label the shippers with all the information necessary to track the shippers to the product, the order, and the production batch.

In addition, when considering the information that is to be identified for such traceability, a clear understanding of customer expectations/requirements must be identified. This must be part of the labelling/packaging process.

Elements for labelling to be considered are:

- ❖ Unique batch number
- ❖ Name of Manufacturer
- ❖ Customer name/Address
- ❖ Product name
- ❖ Product code
- ❖ Customer order number
- ❖ Shipment Quantity
- ❖ Additional information can be placed within the label depending on the manufacturer's systems and/or customer requirements

3.2 Storage

3.2.1 Conditions – Temperature / Humidity Requirements

Best Practice requires that storage conditions are appropriate for the materials impacted. This can include raw material manufacturer's recommendations, as well as finished product shelf-life requirements.

Additional elements to be considered are:

- Location (Indoor / Outdoor storage)
- Appropriate Pest Control Program
- Associated tolerance ranges that can impact on carton performance
- Monitoring activities for long term storage of cartons

3.2.2 Segregation Controls

A Best Practice approach to segregation control is to ensure there are dedicated storage areas. They will reduce the risk of selecting incorrect material(s) and prevent cross-contamination.

Additional elements to consider are:

- Adequate size allowing for organised storage of raw materials, Work In Progress (WIP) and finished product.
- Clean and dry with provision to store materials, WIP and products off the floor.
- Allowance for the dry storage of pallets.
- Use of physical barriers.
- Use of alternative methods such as but not limited to taped top sheet, shrink wraps and closed cages.
- Appropriate labelling as required.

3.2.3 Security Controls

As a Best Practice, the organisation should control the facility using intrusion systems, perimeter security, and access control to ensure to maintain full product security.

A. Suppression Systems and Impact to Product Quality

As a Best Practice, the organisation should ensure the methods used to protect the facility are through a documented process.

This should include a reaction plan for managing contaminated product in the event of a fire or other accident or catastrophe.

B. Pallets (plastic / wood and associated controls)

The use of Pallets is a fundamental component in warehouse storage and distribution activities. Best Practice is to have a program in place that defines the process for protecting valuable materials from being damaged by improper handling. It should also include plans to prevent injury to employees during the handling activity.

Additional elements to consider are:

- Pallet construction
- Appropriate to the product being handled
- Clean, dry and in good condition
- Pallet storage
- Course of action to be taken when an issue is detected
- How specific customer requirements are incorporated into the organisation's systems

C. Safety of Storage Solution (weight / racking controls / protection)

The organisation as Best Practice shall ensure that the systems used to support storage of product are engineered appropriate to it's use. The system shall meet all local, state and country regulatory requirements. It shall provide safety protocols required to prevent injuries.

This includes:

- Racking systems
- Forklift operation
- Proper positioning of materials
- Pallet utilisation
- Manual lifting/Handling

D. Lighting (natural) – to protect product

Adequate illumination is essential in establishing a safe and productive work environment. As a Best Practice the lighting requirements in warehouse/storage applications should be aligned with the size of the area and the work performed. Lighting requirements should also comply with all regulatory standards.

Additional considerations:

- Lighting should not adversely affect, directly or indirectly, the products during manufacture and storage.
- Where product is exposed, light fixtures/fittings shall have protective safety covers.

3.3 Stock Management

It is deemed best practice to follow the following guidelines:

- ⇨ Refer to PS9000:2016 and ISO9001:2015

3.3.1 Inventory Control

As a Best Practice it is essential that the warehouse has management and inventory control systems in place to support knowing what is in stock, how much is available, and the condition, the age and location of items.

This can include the following:

- ❖ Have a well-organised floor plan
- ❖ Consider the use of “First In First Out (FIFO)” and/or “Earliest Expiry First Out (EEFO)” practices
- ❖ Use of clear and concise labels and signage
- ❖ Cycle counting

3.3.2 Control of Reject (stock on hand after a complaint)

Control of material that has been found to be defective via a customer complaint or internal rejection is a vital part of overall stock management. As a Best Practice, this material is to be removed from inventory, placed into quarantine, and identified as such in the organisation’s ERP system and/or by physical labelling.

3.3.3 Cycle Counts

As part of proper warehouse management, it is critical to know exactly how much inventory is available so that overstock or out of stock conditions can be avoided. This includes both finished goods and raw materials. Therefore, Best Practice is to ensure cycle counting is a regular part of the organisation’s operation.

Additional elements to be considered:

- ❖ Cycle count should be defined based on the needs of the organisation.
- ❖ All discrepancies to be reported / recorded with appropriate actions taken.

3.3.4 Control of Expiry / Shelf Life

The shelf-life of a product is the time that it remains acceptable for use, remains safe and retains the properties required to meet the design requirements as specified by the organisation or the customer. As a Best Practice, the organisation should define the storage conditions and required settings through a documented procedure or policy.

3.3.5 Disposal Controls / Documentation

As a Best Practice, the organisation should have a Disposal Management System to coordinate and control the disposal of waste material which can include excessive or redundant inventory, as well as obsolete or expired goods in a warehouse.

Additional elements to consider:

- Formally documented
- Documents retained for defined period
- Secure and controlled disposal
- Removed and contained until disposal

⇨ Additional guidance regarding Disposal Control can be found in the PS9000:2016 Standard, section 8.7.2, “Waste material”.

3.3.6 Revision Control

Best Practice is to have a process in place that defines how changes for systems, documents, product and processes are managed and controlled to ensure conformity to requirements. This includes a defined revision control program that details the changes made.

This includes:

- Customer notification (where required)
- Documented evidence describing the change(s)
- Results of the review
- Persons authorising and approving the changes
- Actions taken
- Document retention

3.4 Sampling

3.4.1 Sampling Plan

- ⇨ To be carried out in accordance with customer agreements, considering sampling collection timings and representation of the manufactured lot.
- ⇨ An appropriate sampling plan, including a sample size and sampling procedure to be in place e.g. in compliance with Article 4.1.3, ISO 2859 / ANSI Z1.4 or similar.

3.4.2 Traceability

Sampling procedures must provide for accurate traceability of the tailgate samples.

3.4.3 Representation

- ❖ The tailgate samples are to be packaged in the same or similar manner as the production lot, where possible.
- ❖ Tailgate samples to be handled and stored under similar conditions as the production lot.
- ❖ Components should not be manipulated or sorted once placed in the sample box for shipment.

3.4.4 Identification and Shipment

- ❖ Tailgate samples should be identified to ensure that these samples will correlate with the correct production lot shipment.
- ❖ Tailgate samples must be clearly identified and segregated from any other samples to prevent mix up.
- ❖ Tailgate samples should be shipped with a label that clearly distinguishes them from the production batch (e.g. "QC Samples" or “Representative Samples”).

3.5 Order Picking / Packing

3.5.1 Picking of Goods

Depending on the system of each company, produced batches will require picking for delivery. This system may be controlled via a Warehouse Management System (WMS). This constitutes Best Practice and is encouraged. For this, the following must be implemented:

- ❖ The equipment must be verified/validated to ensure compliance.
- ❖ The place and personnel of picking must be defined and described in a procedure.
- ❖ Storage locations and management must be described in a procedure.

3.5.2 Packing of Goods

- ❖ Goods must be packed according to a delivery schedule to meet customer requirements.
- ❖ A delivery plan must be formed and communicated to the finished warehouse team, including pallet positions if available. WMS implementation is encouraged, to increase automation and traceability.
- ❖ Pallet consolidation and picking of stock holding can be done with customer approval.

3.6 Customer Requirements

3.6.1 Execution of Customer Requirements

It is Best Practice to ensure all customer requirements are implemented within the organisation.

This is done through:

- Updating or developing procedures, work instructions and production work orders.
- Training staff on any customer specific requirements.
- Validating compliance through review and Control Plans.
- Verifying effectiveness through defined inspection criteria throughout the production cycle.

3.6.2 Documentation Requirements

Best Practice is to ensure that all customer relevant documented information has been completed, is accurate and verifies that the product meets the customer's requirements and is easily retrievable.

This can include:

- Customer requirements provided for review and acceptance.
- Data relating to the customer's product shall be made available when required by the customer.
- Data related to the production process, in-process, and final control/test equipment.
- Delivery documentation including Certification of product.
- Quality Agreements that determine both customer and supplier responsibilities.
- Validation documentation that, where required, is provided to the customer for review and approval.

3.7 Transportation Controls

Transport of finished materials can be managed in-house, outsourced to an approved supplier and / or controlled by the receiving customer. When outsourcing, Best Practice requires a qualification process of the Logistic Service Providers (LSP).

3.7.1 General Requirements

- Customer delivery requirements should be noted on the batch records. Information relating to customers' address details should be maintained and reviewed regularly.
- Depending on customer requirements, the sampling regime will be defined on the batch records and a certificate will be generated for every batch.
- Transportation vehicles should be clean and supplied by an approved supplier along with qualified drivers.
- Transport shall be secured to avoid exposure of finished materials to damage, loss or theft.
- Consideration is to be given to whether dedicated vehicles are required or not. Where shipments can be combined with other goods, the types of goods that are permitted / prohibited are to be defined.
- Transportation vehicles shall be maintained and cleaned on a regular basis.
  The internal compartments shall be:
  - dry
  - clean, free from litter, dust and pests
  - free of odours

3.7.2 Requirements for Logistic Service Providers

Qualification of LSP's shall include:

- Audit requirements
- Quality Agreement, including requirements for returns
- Service Level Agreement
- Transportation Qualification
- Performance monitoring

Finished materials from other parties present in the same vehicle are packed, identified and separated in such a way that there is no risk of a mix up and selecting incorrect materials.

3.8 Returns / Sort / Rework

3.8.1 Returns

As a Best Practice, returns are to be managed according to a documented process that details at minimum the following elements:

- Responsibilities defined (Who, What, etc.)
- Training requirements
- Mechanism for authorisation of return
- Quarantine/Identification/Access
- Logging of returns and status
- Issuance of Credit
- Appropriate personnel to be notified of returned material/product
- Operating system updated with batch detail
- How approved (sort/rework) product or a new production run is to be re-identified (batch control), labelled and packaged
- Customer communication/approval

3.8.2 Sort / Rework

As a Best Practice, the organisation shall have a documented process to ensure the returned product that is to be sorted/reworked does not result in further complaints and customer dissatisfaction.

To support this, the following elements are expected to be deployed:

- Appropriate working area to conduct inspection to mitigate product mix.
- Full line clearance performed and documented.
- Risk assessment performed prior to sort/rework.
- Formal sort/rework process defined and approved prior to start of activity including how the sort should be executed. Manual inspection or other.
- Acceptable Quality Level (AQL) Sampling Plan defined or as otherwise noted by the customer.
- Quality oversite of all activities, including final release of the inspected batch or authorisation to destroy defectives.
- Formal approval performed and documented by Quality including authorisation of new batch if required.
- Management of waste/defective product.

3.9 External Warehousing

Pharma customers require manufacturers of printed packaging components to ensure that the applicable GMP requirements are in place and applied at the outsourced location.

The outsourced location needs to be qualified. The qualification process should include the following aspects:

- Audit frequency
- Any applicable contracts, such as supply agreement, confidentiality agreement or quality agreement
- Transport requirements
- Security controls
- Environmental requirements
- Reporting requirements

CHAPTER 4

QUALITY SYSTEMS

Introduction

ECMA recommends that packaging suppliers to the Pharma industry base their Quality systems on recognised international quality standards – ISO9001 and PS9000. Accreditation to one or both of these standards is normally a pre-requisite for supplying packaging materials to the pharmaceutical industry.

The Quality System should include the following key element:

4.1 Management Review

Best Practice requires that every packaging supplier conduct an annual management review of the year's quality performance.

- ⇨ Details of the management review requirements can be found within the ISO9001/PS9000 standards.

4.2 Documented Information

Pharma customers require proper control of documentation.

- ⇨ The PS9000 standard contains the Best Practice in this regard as follows:
  - 7.5.2 "Creating and updating documents".
  - 7.5.3 "Control of documented information"
    - 7.5.3.1 "System administration"
    - 7.5.3.2 "Control of records"

4.3 Equipment Management

Best Practice requires that critical to quality equipment be validated on installation, calibrated at an agreed frequency and maintained according to an agreed schedule.

This equipment may include, but not be limited to electronic verification systems, such as:

- ❖ Bar code scanners
- ❖ Dot scan systems to read Braille
- ❖ In-line camera inspection systems
- ❖ Comparators to verify compliance with approved artwork.
- ❖ Measurement equipment used in the batch release process

Critical to Quality equipment should be listed and appropriately identified. In addition, it should be referenced in written validation, calibration and/or maintenance schedules.

4.4 Facilities

Best Practice requires that facilities are secure, properly maintained and free from pests via an appropriate pest control program.

Facilities should not be accessible to unauthorised personnel. Manufacturing areas should be physically separated from areas such as changing rooms, toilets and hand washing. Toilets should not open directly onto manufacturing areas.

Equipment, machines and facilities should be cleaned according to a stated frequency and standard to prevent product contamination.

Best Practice requires the organisation to define requirements for all employees as it relates to health and hygiene practices, including cGMP, Food Safety and other appropriate standards.

4.5 Training

As a Best Practice, the organisation must strive to continuously develop their employees' skills, level of understanding, and associated competencies so that defined objectives and goals are achieved. In addition, providing a strong culture for learning enables the employee to achieve their full potential, delivers job satisfaction/career development, and supports employee retention.

This must be accomplished through a defined procedure that includes the following key elements:

- All functions of the company.
- Detailed approach for identifying the necessary competencies for required tasks.
- Direction on evaluating the effectiveness of training and future training needs, such as refresher training via a scoring system or other appropriate method.
- Job Descriptions and the elements associated within them.
- An approach for New Employee Orientation that includes organisation overview, Health & Safety, cGMP and other introductory criteria as required.
- Job performance reviews that provide an open forum for discussion on progress and development articulated in a formal training plan.
- Training Matrix that;
  - Provides direction on the required documents (Standard Operating Procedures/Work Instruction/other) for each function.
  - Identifies the employee has been trained over multiple skills/processes.
- Details on proficiency level where deemed applicable, e.g. a grading system from entry level to mastery.
- Leverage for absences, work restraints, potential future constraints, etc.
- Direction for both internal and external training events and the approach for formal approvals by both the trainer and trainee once the training event is completed.
- Criteria for the trainer (certifications, experience, etc.).

⇨ PS9000:2016, section 7.2.1

4.6 Product Status Management

4.6.1 Product Final Release

It is considered as Best Practice that products for the pharmaceutical market are subject to a formal documented release process. In addition, the manufacturing site follows the recommendations outlined in PS9000.

Formal documentation should include at least the following key controls:

- Sampling plans and specific customer requirements.
- Access requirements for electronic systems used for batch release. Access should be for authorised personnel only. Each person will have a unique access with electronic signature, that will unambiguously identify them when releasing a batch.
- Electronic signatures should be subject to formal password controls and ensure data integrity. This procedure should follow the principles of ALCOA+.
  Refer to section 4.12, “Data Integrity”.
- Each person performing a batch release should be allocated appropriate access to the software through a documented process.
- Access should only be permitted to appropriately trained personnel.

4.6.2 Hold / Quarantine

It is deemed best practice to establish a procedure for control of hold / quarantine product, this procedure should include the following elements.

- Details on who can place product on hold / quarantine.
- Who is authorized to remove product from hold / quarantine status.
- The establishment of a hold / quarantine area within the facility.
- How product will be identified and segregated whilst in hold / quarantine status.
- The mechanisms in place to prevent hold / quarantine product being further processed or shipped.
- The process to be followed for rework or inspection activities, including any approval requirements.
- How traceability will be maintained during any rework or inspection activities.
- The governance requirements for the control of hold/ quarantine stock including any reconciliation requirements.
- The requirements for documenting status changes.
- How containment activities will be performed (including evaluation of any other potential batches impacted), including a link to the product recall process in the case that product has left the control of the organization.
- Instructions on when a deviation is required.

4.6.3 Destruction

- Destruction or disposal of product should be documented, this should include the reason for disposal, the batch number, the item number, and the quantity to be destroyed.
- It should be clear within the system where the decision has been made to destroy internal Work In Progress and where the customer has requested disposal and potential reprint.

4.6.4 Defect Manual

It is considered Best Practice to establish consistent terminology for process defects and to classify their severity based on the impact to the patient and ongoing supply chain.

A Quality Defect Manual with pictures, associated Acceptable Quality Levels (AQL's) and classifications is a Best Practice approach to identifying the primary process defects.

A. Classification of Defects

It is Best Practice to agree with customers on the classification of defects in advance of purchase orders. Typically, within pharmaceutical packaging, these are defined as Critical, Major and Minor defects.

The severity of the defect is then subject to an agreed Acceptable Quality Level (AQL).

B. Details Classification of Defects

Details for the classification of defects can be found in the Editio Cantor Verlag Aulendorf, General "principles and special defect evaluation lists".

4.6.5 Critical Control plans

Critical control plans or process control plans are a holistic overview of all the key steps in an individual process. They clearly document the control mechanism against process deviations. They should provide an overview to be used for identifying needs for special procedures to mitigate the risk of critical defects.

4.7 Recall / Traceability

It is considered as Best Practice that final products and processing materials used to manufacture a batch are fully traceable throughout the manufacturing process and onward supply chain. This is to ensure in the event of a product recall all products at risk or potentially at risk can be identified and contained. A documented procedure should be established to identify the product recall actions. This should be subject to a verification audit to ensure the recall plan can be executed effectively and in the required timescale (typically within 48 hours of request from customer).

4.7.1 Product Recall Procedure should include as a minimum

- Product recall plan
- Defined responsibilities
- Defined notification / escalation requirements
- Identification of any production order numbers impacted – Customer/Stock/Work In Progress
- Immediate containment/quarantine
- Raw material review
- Batch record review
- Certificate of Analysis review
- Final batch disposition
- Customer communications
- Product recall impact analysis
- CAPA plan
- After Action Review

4.7.2 Raw Materials Traceability

It is deemed best practice to follow the following guideline:

⇨ PS9000:2016, section 8.5.2.1.a

4.7.3 Manufactured Batch identification

All individual production batches should have a unique system generating identification. The production batch should be clearly identified throughout all stages of the manufacturing processes and final delivery.

4.7.4 Batch Records

Batch records can take the form of paper or digital. Where paper records are used, the principles of Good Documentation Practice should be followed. Where digital batch records are utilized then the system in use should be data integrity compliant and follow the principles of ALCOA+.

The batch record should contain traceability of all manufacturing process steps, in process checks, and quality control checks conducted to release the batch. This should also contain all identification of any defects and reconciliation of these defects and subsequent actions taken prior to release. In the event of a product recall the batch record is a key record and should be retrieved for all batches which might be implicated with the defect to evaluate their risk.

4.7.5 Certificate

A Certificate of Conformity (CoC) or Certificate of Assurance (CoA) should be created for each batch produced, confirming that the batch has been manufactured in accordance with all internal, regulatory and customer specifications.

4.7.6 Delivery Notes

All deliveries of finished products shall be subject to the issue of a delivery note containing the elements of the order. At a minimum the delivery note should contain:

- Customer name
- Item code
- Item description
- Customer order number
- Production batch number
- The quantity delivered
- Delivery address

4.8 Deviation Management

4.8.1 Standard Operating Procedure

Deviations should be handled according to a written procedure including purpose, scope, definitions, responsibilities, timelines and CAPAs.

⇨ Best Practice in this regard is contained in the ISO 15378, section 10.2 “Nonconformity and corrective actions”.

The SOP shall define the following aspects:

4.8.2 Definition for Deviations

The SOP shall provide guidelines for qualifying issues as formal deviations.

4.8.3 Deviation Classification

It is Best Practice to classify identified deviations based on a risk assessment.
See section 13, “Risk Assessments".

4.8.4 Root Cause Analysis

Best Practice requires a root cause analysis of all defects and issues leading to customer complaints. The analysis shall be conducted based on dedicated methods such as but not limited to 8D, 4M+P, Fish Bone and 5-Why.

4.8.5 Impact Assessment

Best Practice requires the organisation to investigate the impact of the deviation on processes and product quality.

4.8.6 Follow Up

It is Best Practice to include corrective and preventive actions resulting from deviations into the CAPA management system.
See section 8, “CAPA Management".

4.8.7 Effectiveness Verification

Best Practice requires the organisation to verify the effectiveness of CAPAs resulting from deviations as described under ISO 9000 standard, section 3.7.11, “Effectiveness”.

4.8.8 Customer Notification

The Quality management system of the carton producer should be capable of eliminating all deviations before delivery. The Standard Operating Procedure and/or Quality Agreement shall provide guidance on what deviations to report to the customer.

4.8.9 Filing

Deviations should be listed in a defined system providing oversight and possibilities for tracking and trending.

4.8.10 Periodic Review

The deviation system should be subject to periodic review to analyse for trends.

4.8.11 Reporting

The outcome of the periodic analysis shall be subject to management review and input to a continuous improvement system. The outcome shall also be reported to stakeholders.

4.9 CAPA Management

4.9.1 Standard Operating Procedure

Best Practice requires the organisation to describe their CAPA management system in a written procedure including purpose, scope, definitions, responsibilities and timelines.

4.9.2 Sources

CAPA's can result from the following sources:

- Deviations
- Complaints
- Audits (internal and external)
- Changes

Required actions that do not result from such a source can be registered as a "stand alone" CAPA.

4.9.3 System

The CAPA management system shall include:

- CAPA documentation
- Unique CAPA numbering
- The CAPA origin
- A description of actions
- The CAPA Owner
- The CAPA approver
- CAPA Timelines

4.9.4 Filing

CAPAs should be listed in a defined system providing CAPA oversight and possibilities for tracking and tracing.

4.9.5 Periodic Review

CAPA's should be periodically analysed to verify:

- Timeline adherence
- CAPA effectiveness

⇨ Refer to the ISO 9000 standard, Chapter3.7.11, "Effectiveness".

4.9.6 Reporting

The outcome of the periodic analysis shall be subject to management review and input to a continuous improvement system. The outcome shall also be reported to stakeholders.

4.10 Customer Complaints

Standard Operating Procedure

Best Practice requires the organisation to describe their Customer Complaint system in a written procedure including purpose, scope, definitions, responsibilities and timelines.

The Standard Operating Procedure shall define the following aspects:

4.10.1 Definition for Customer Complaints

The Standard Operating Procedure shall provide guidelines on what defines a formal customer complaint and how to handle informal reporting of events.

4.10.2 Complaint Classification

It is Best Practice to classify identified customer complaints based on a risk assessment. See paragraph 13, “Risk Assessments".

Excursions or deviations to agreed Acceptable Quality Level (AQL) shall be taken into account and a process established for how to document and control these events.

4.10.3 Root Cause Analysis

Best Practice requires a root cause analysis of all defects and issues leading to customer complaints. The analysis shall be conducted based on dedicated methods such as but not limited to 8D, 4M+P, Fish Bone and 5-Why.

4.10.4 Systematic and Accidental Issues

Best Practice prefers the organisation to differentiate between systematic issues and accidental issues causing customer complaints.

Systematic issues require an inspection of the system that might result in more systemic or holistic changes to the system.

4.10.5 Follow Up

It is Best Practice to include corrective and preventive actions resulting from customer complaints into the CAPA management system. See section 4.9, “CAPA Management".

4.10.6 Right of Rework

The Standard Operating Procedure shall include requirements for the right to rework at the supplier’s site.

4.10.7 Effectiveness Verification

Best Practice requires the organisation to verify the effectiveness of CAPAs resulting from customer complaints as described under ISO 9000 standard, section 3.7.11, “Effectiveness”.

4.10.8 Filing

Customer complaints should be listed in a defined system providing oversight and possibilities for tracking and tracing.

4.10.9 Periodic Review

Customer complaints should be periodically analysed.

4.10.10 Reporting

The outcome of the periodic analysis shall be subject to management review and input to a continuous improvement system. The outcome shall also be reported to stakeholders.

4.11 Audit Observations

Standard Operating Procedure

Best Practice requires the organisation to describe handling of audit observations in a written procedure including purpose, scope, definitions, responsibilities and timelines.

The Standard Operating Procedure shall define the following aspects:

4.11.1 Definition

According to ISO 9001 standard, section 3.13.9, audit observations are results of the evaluation of collected audit evidence against audit criteria.

4.11.2 CAPAs

It is Best Practice to include the handling of audit observations in the CAPA system.

This will ensure adherence to requirements in terms of:

- Responsibilities
- Documentation
- Track and trace
- Timelines
- Periodic evaluation
- Effectiveness verification

⇨ See section 4.9, “CAPA Management”.

4.11.3 Categorisation

To establish proper prioritisation and timelines, it is common practice to classify audit observations in the following categories:

- Recommendation / opportunity for improvement
- Minor
- Major
- Critical

4.11.4 Acceptance

It is expected that audit observations are accepted by the audited organization, but may be challenged when evidence is provided after an audit is completed.

4.11.5 Filing

Audit observations should be listed in a defined system providing oversight and possibilities for tracking and tracing.

4.11.6 Periodic Review

The status of audit observations should be periodically analysed for adherence to the required response timelines.

4.11.7 Reporting

The outcome of the periodic analysis shall be subject to management review and input to a continuous improvement system. The outcome shall also be reported to stakeholders.

4.12 Data Integrity

Data integrity refers to the completeness, consistency, and accuracy of data throughout the data lifecycle. Poor data integrity practices undermine the quality of records and evidence and may ultimately undermine the quality of manufactured products.

Assuring data integrity requires appropriate quality and risk management systems, including adherence to good documentation practices.

The data should comply with ALCOA+ principles defined below:

- **Attributable**: Traceable to a unique individual
- **Legible**: Readable, traceable changes, permanent
- **Contemporaneous**: Recorded at the time the event occurs
- **Original**: First capture of data
- **Accurate**: As intended, unadulterated
- **Complete**: Full information or data set (e.g., audit trail)
- **Consistent**: Chronological, sequential
- **Enduring**: Securely stored for long term use
- **Available**: Accessible during its lifecycle

The ALCOA+ principles shall apply to any system or piece of equipment that is used in the determination of product quality.

Best Practice requires a process to be in place that incorporates the principles of data integrity applicable to data generated by electronic, paper-based and hybrid systems.

The process should ensure all data is documented as intended and compliant with current standards. The effort and resource assigned should commensurate with the risk to product quality.

Requirements for electronic signature and record-keeping are stipulated in 21 CFR part 11 and 21 CFR parts 211, 212.

- ⇨ Source: https://www.gmp-navigator.com/gmp-news/neue-fda-draft-guidance-data-integrity-and-compliance-with-cgmp-veroeffentlicht

4.13 Risk Management

Best Practice requires that packaging suppliers to the pharmaceutical industry, integrate Risk Assessments in their critical processes to identify the extent and effect of potential problems. Risk Assessments should be executed according to the following standard:

- PS9000:2016, section 10.1.1: "Risk Management" and its Annex B: "Guidance on Risk Management".
- PS9000:2016 refers to the following additional standards for suitable Risk Assessment systems:
  - ICH Q9 — Quality Risk Management
  - ISO 31000: 2009 — Risk Management – Principles and Guidelines
  - PQG — Guide to supply chain risk management for the pharmaceutical and medical device industries and their suppliers.

4.14 Qualification / Validation

4.14.1 General

Pharmaceutical companies require manufacturers of printed cartons to carry out qualifications and validations when commissioning printing machines, processing machines, electronic devices and testing equipment.

The manufacturing process for printed cartons is specific. The type of qualification and validation cannot be equated with that of the pharmaceutical industry. This allows printers of cartons for the pharmaceutical industry to have a tailored qualification and validation system.
However, the system shall be based on the following standards:

- GMP Annex 15, "Qualification and Validation"
- PS 9000:2016 section 8.5.1 and Annex C
- 21 CFR Part 11
- GAMP, "Good Automated Manufacturing Practices"

4.14.2 Standard Operating Procedure

Best Practice requires to define the qualification and validation system in a formal Standard Operating Procedure including scope, definitions, responsibilities and process description.

4.14.3 Process Description

The process description in the Standard Operating Procedure shall at least describe:

- Validation Master Plan (VMP) defining the company's approach to validations.
- Description of the different types of validations, such as but not limited to:
  - initial validation
  - concurrent validation
  - retrospective validation
  - like for like situations
- Guidelines on decision making Validation yes or no, and which type of validation to use.
- For each validation project a cross functional validation team shall be put together.
- A risk analysis shall be prepared to determine possible critical process steps and critical parameters. The risk analysis should also determine whether the applicable process poses a risk to the end user.

⇨ For guidance on conducting a risk analysis, see chapter 4 "Quality Systems", section 13 "Risk Management".

- Documentation
  To document qualification and validation activities, standard qualification and validation documents shall be created for each validation project. Such as but not limited to qualification and validation plans, protocols and reports.
- Validation planning
- Validation strategy
  Best Practice requires to include the following steps into the validation system:
  - Design Qualification (DQ)
  - Installation Qualification (IQ)
  - Operational Qualification (OQ)
  - Performance Qualification (PQ)
- Guidelines on re-qualification
  Re-qualification applies in case of:
  - Replacing a quality critical component, excluding like-for-like changes
  - Repairing a quality critical component
  - Changing a quality critical sub component of a qualified process or system
  - Software updates
- Guidelines on re-validation
  Re-validation applies in case changes are made to:
  - Manufacturing location
  - Machine or machine part
  - Material, including the origin of starting materials
  - Critical to quality items in the system
  - GMP relevant items in the system

  Re-validation also applies in case of an increased error occurrence without identifiable root cause. Re-validation does not apply to "like-for-like" changes.
- Change Control
  Best Practice requires to open a formal change control for extensive qualification and validation projects.
  When the Standard Operating Procedure and other qualification and validation documentation offer sufficient detail, smaller projects do not require a formal change control.
- Decommissioning
  Guidelines on decommissioning machines and equipment at the end of their life cycle.

4.15 Vendor Management

Best Practice requires that critical to quality vendors be qualified before use.
The vendor qualification process shall be outlined in a procedure.

Besides purpose, scope, definitions and responsibilities, the Standard Operating Procedure shall include requirements in terms of:

- Vendor selection, including selection criteria for new vendors.
- Contracts, including a Supply Agreement, Confidentiality Agreement and Quality Agreement.
- Audit requirements, such as audit frequency and audit type (on site audit, remote audit, paper audit).
- Vendor performance monitoring.
- Periodic business reviews.
- Vendor status management to assure materials and services are only received by qualified vendors.
- Establishment of an Approved vendor list.
- Vendor disqualification, including criteria for disqualifying vendors and blocking them for purchases.

The vendor management system should prevent purchasing of critical to quality materials and services from vendors that are not qualified.

4.16 Change Management

Pharma customers require documented control of changes which is governed by a procedure.

Changes that require control through the change control system are (and not limited to):

- Facility modifications.
- New equipment or significant changes to existing equipment.
- Sources of critical to quality materials and services.
- Implementation or significant changes to software.
- Production processes.

⇨ The PS9000 standard contains the Best Practice in this regard in its sections:
  - 6.3.1 “Change Control”
  - 8.5.6 “Control of Changes”

4.17 Sampling

The goal of having an effective Sampling Program is to ensure that product produced meets all requirements, both internal and those defined by the customer, protecting both the organisation producing the product and the customer receiving the finished goods.

Hence, as a Best Practice acceptance sampling is to be considered a critical component of the manufacturing process and therefore shall have a clearly defined process that identifies the following:

- Sampling plan is statistically valid and representative of the manufacturing process with oversight assigned to Quality.
- Incorporates customer specific sampling requirements where applicable (i.e., Quality Agreements).
- Defined sampling inspection plans for receipt of materials, production start-up, in-process, final, and formal release of finished product.
- Pulled samples should not be returned to the production area or incorporated into the final product.
- Documented evidence and approval sampling has been performed as defined and product has been accepted.
- Retain samples shall be pulled, separated from the production lot, and stored as defined.
- Appropriate controls shall be in place for product having failed to pass the sampling plan (e.g. segregation activities, labelling requirements, tightened inspection levels).
- Customer (tailgate) samples shall:
  - Be representative of the whole batch with sampling criteria agreed upon with the customer.
  - Be inspected, approved, and released by the organisation's Quality representative.
  - Upon rejection of the samples by the customer, shall follow non-conforming protocols and use tightened sampling criteria appropriate for the issue as required.

⇨ Note: additional Sampling criteria can be found in both ISO2859-1:1999 and PS9000-2016

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