PS 9004

A Guide to the GMP requirements of PS 9000:2001 Pharmaceutical packaging materials

The Institute of Quality Assurance

Pharmaceutical Quality Group

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September 2004

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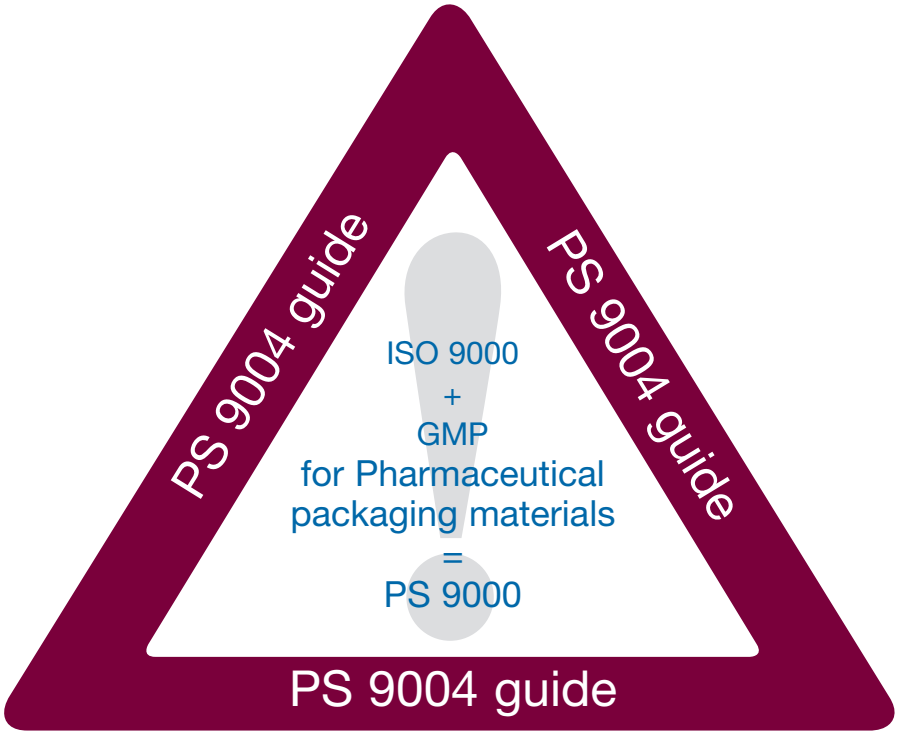
Figure 1. Model of PS 9004: a Guide to the GMP requirements of PS 9000



The symbol  is used in Part 1 to identify risk areas.

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For further information about the Pharmaceutical Quality Group (PQG) and any additional information or updates on PS 9000 or PS 9004 visit the PQG website on: www.pqg.org

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The EU Guide to Good Manufacturing Practice (GMP) emphasizes the need for pharmaceutical manufacturers and assemblers to ensure that the packaging materials that they use are of the appropriate quality. Not only is this in the interests of patient safety, but also in the pharmaceutical industry where the increasing use of automated packaging processes relies heavily on the consistent quality of packaging components.

Each year the Medicines and Healthcare products Regulatory Agency (MHRA) receives and investigates a number of reports of quality defects concerning medicinal products. A significant proportion of these concern packaging errors, some of which are attributable to the use of packaging materials not of the desired quality. The introduction of PS 9000 in 2001 by the Pharmaceutical Quality Group of the Institute of Quality Assurance was a key step in promoting the understanding of GMPs relevant to the suppliers of packaging materials to the pharmaceutical industry. PS 9000 focused on the development and implementation, by suppliers, of a quality management system designed to provide assurance of the quality of their products and to enhance customer satisfaction. Its contribution was welcomed by both industry and the Regulator. PS 9004 is aimed at increasing the awareness of the quality management system requirements embodied in PS 9000. This comprehensive and easy to follow guide explains further the GMP requirements of PS 9000. It adopts a risk assessment approach to the identification and implementation of preventive action and uses case studies to illustrate areas of GMP risk.

The MHRA encourages the introduction of PS 9004 designed to improve product and service quality in the supply of packaging materials for medicinal products, for the benefit of patients and the pharmaceutical industry as a whole.

John Taylor Quality and Systems Manager
Inspection and Enforcement Division, MHRA

What is PS 9004?

This guide aims to assist suppliers of pharmaceutical packaging materials to understand and implement the Quality Management System (QMS) of ISO 9001 and the application standard of PS 9000. It supplements the following documents:

- ISO 9001 which specifies the requirements of the international QMS standard
- ISO 9004 gives guidance on ISO 9001
- PS 9000 is an application standard written by the PQG for suppliers of pharmaceutical packaging materials that integrates ISO 9001 and ISO 9004 together with additional Good Manufacturing Practices (GMP) requirements particular to these suppliers

Companies complying with PS 9000 will comply with ISO 9001 and also the additional GMP requirements endorsed by the highly regulated pharmaceutical industry.

This guide is constructed around the clause structure of PS 9000 (and therefore ISO 9001) to:

- clearly explain the GMP requirements of PS 9000
- list many of the risk areas associated with packaging processes and identify relevant ISO 9001 and PS 9000 clauses
- provide examples of process inputs and process outputs typical of suppliers of pharmaceutical packaging materials, and relate these to the QMS requirements of ISO 9001 and the additional GMP requirements of PS 9000
- give examples of actual case histories of problems arising from the supply of defective pharmaceutical packaging materials and where the consequences would have been avoided by correct application of the GMP requirements of PS 9000. These case histories help to explain the requirements and provide a valuable training resource

How to use this Guide

PS 9004 has been organized in the following way:

- Part 1 consists of a selection of process schematics, illustrating typical operations of a packaging supplier, and giving examples of some of the more significant risks caused by inadequate manufacturing practices
- Part 2 gives guidance on the clauses of PS 9000, by taking the user through each major section and providing examples to illustrate suggested process inputs and outputs
- Annex A gives expanded explanatory notes on several key concepts used in PS 9000
- Annex B gives a listing of other external regulatory references, which are the background to pharmaceutical GMP and which are directly relevant to PS 9000 requirements
- the text is primarily black but blue is used for PS 9000 related GMP text
- red text is used to highlight the 'Risk Areas'

The user can cross refer between the schematics in Part 1 and the process information in Part 2. In addition, the user can move from Part 2 to the additional explanations in the annexes.

The annexes contained within this Guide are a stand-alone explanation of key concepts and external GMP references. The PS 9000 cross-references are for illustrative purposes and are not a definitive list of clauses or references.

The *How to use* section, which follows the contents list, shows the user how to navigate between the different sections of the Guide.

As the range of organizations that may implement PS 9000 is great, both in terms of size and type of business, the guidance given here is illustrative and advisory.

Why was the PS 9004 Guide written?

There are three main reasons:

- to guide professional quality specialists towards the implementation and inspection of a Quality Management System (QMS) in accordance with PS 9000
- to support the training of all the various stakeholders in the PS 9000 process (top management, quality professionals, staff at all levels of packaging

material suppliers and their customers)
- to provide those people who are not quality specialists with a better understanding of the aims, objectives and implementation of PS 9000

How was the PS 9004 Guide written?

A group of experienced quality professionals selected from the packaging supply industry and pharmaceutical customers was recruited by the Pharmaceutical Quality Group Partners Team and given the task of preparing this Guide. Many of the people who contributed to the writing of PS 9000 also participated in the creation of this Guide.

Specific acknowledgements are given for the contributions of the following people:

Roy Evans	PS 9004 Team Leader
David Abraham	Supplier
Ian Harwood	Pharmaceutical
Jill Jenkins	Pharmaceutical
Daniel Peek	Supplier
Richard Rowlett	Supplier
Mike Shorten	Pharmaceutical
Steve Taylor	Pharmaceutical

Additional contributions:

Caroline Fowler	Pharmaceutical
Peter Gough	Pharmaceutical
Ian Holloway	Regulator
Steve Merrit	Pharmaceutical
Ashley McCraight	Consultant
Jeff Monk	Training
Dominic Parry	Training
Steve Pike	Accredited certification
Norman Randall	Consultant
Trevor Stabb	Consultant
Paul Stockbridge	Consultant

QA review:

Tony Harper	Consultant and accredited certification
Afshin Hosseiny	Consultant

QA review (con't):

Jean Lanet	Consultant
Iain Moore	Supplier
Steve Moss	Pharmaceutical
Ashok Chand	Pharmaceutical
John Turner	Consultant

The PQG Partners Team and Steering Committee:

Roy Evans
Tony Harper
Femi Ibironke
Jill Jenkins
Ashley McCraight (PT Chairman)
Steve Moss
Norman Randall (SC Chairman)
Ian Richardson

In addition, the PQG is appreciative of the management of Patheon UK Limited. for the use of their resources and facilities.

Section	Page

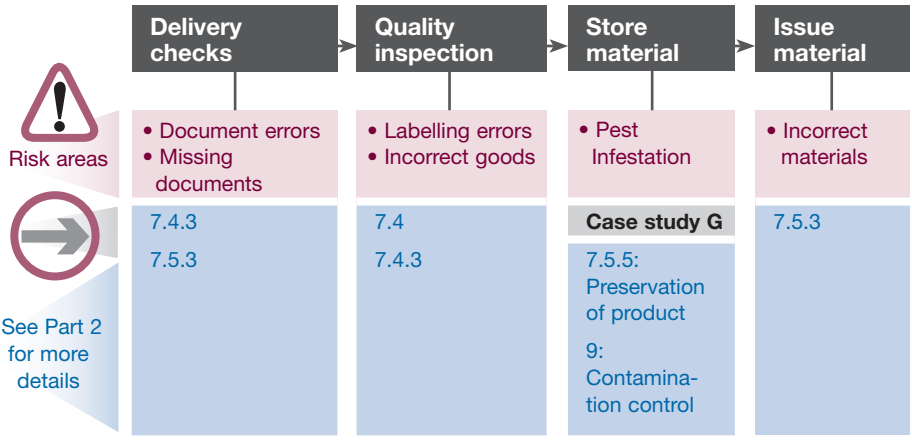
STEP 1

Choose a schematic from the 'Overview of business process' diagram in Part 1 of this guide. (e.g. Schematic 3(a) is illustrative)

STEP 2

From your schematic, choose a particular stage of the process to examine, e.g. Store material (see below).

SCHEMATIC 3 (a) - WAREHOUSE



STEP 3

Consider the Risk Areas shown in red and the real life case study (if shown) - these are detailed at the end of Part 1, following the schematics.

STEP 4

Using the references shown in the schematic, move to the corresponding section in Part 2, entitled 'Guidance on PS 9000 GMP clauses'. This gives reasons for the 'extra' GMPs and shows examples of processes, inputs and outputs.

General synopsis: Clause 9 Contamination control

The capability of facilities and equipment, achieved through their design, location, etc.

Reasons for the 'extra' GMP requirements

The highest priority of the pharmaceutical industry is... etc.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
Specification for design of new facilities, processes, or environment **Specialist support for pest control** Standards for environmental conditions	Processes which identify/control: • operating areas • **pest control** • cleaning procedures	Records of: • processing • cleaning schedules • material disposal • **incidents/audit reports**	Schematic 3(a) Schematic 4(a) Schematic 5 Annex A - all parts

STEP 5

Use the cross references to move back to a relevant process schematic, alternatively refer to Annex A or B for further guidance.

ANNEX A

Additional Explanation of Key Concepts

ANNEX B

Other external GMP references.

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PART 1 - PROCESS SCHEMATICS

PS 9000 GMP references are reproduced in blue
Risk areas are reproduced in red

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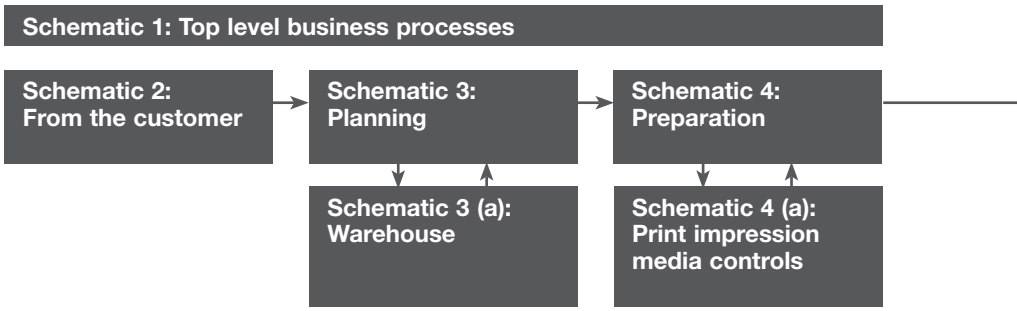
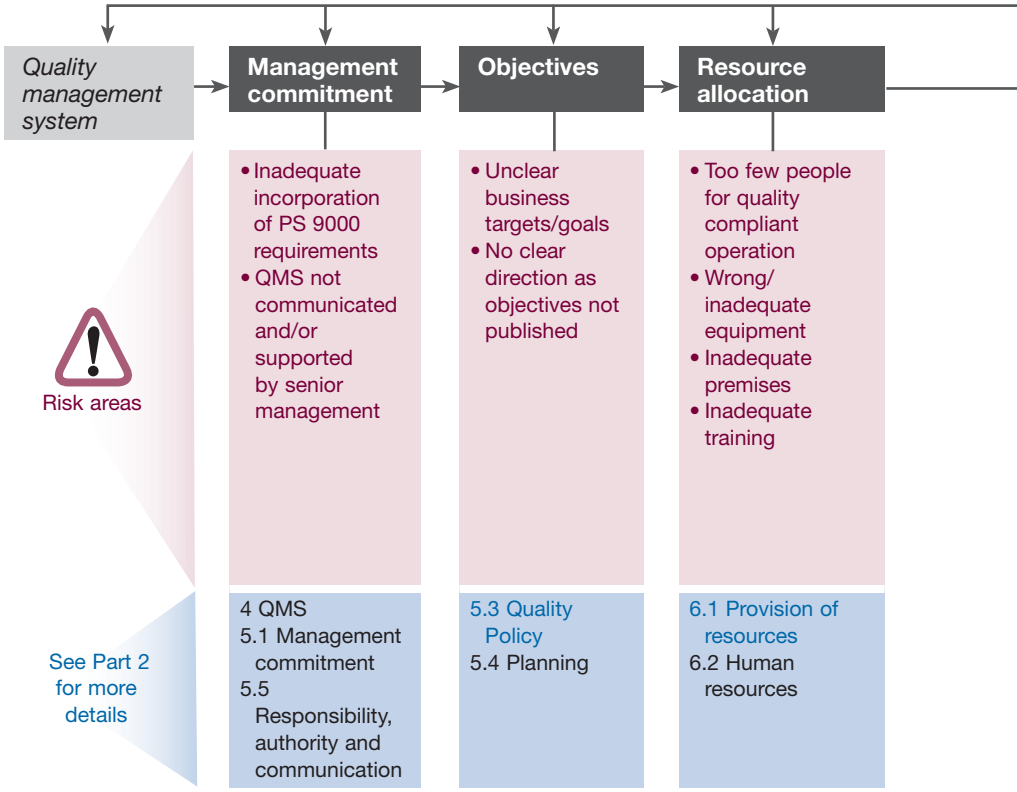
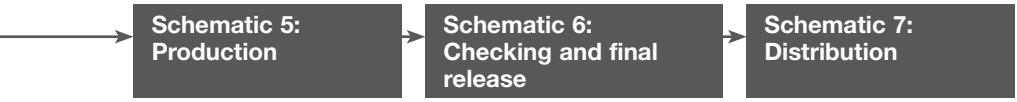
OVERVIEW OF BUSINESS PROCESSES



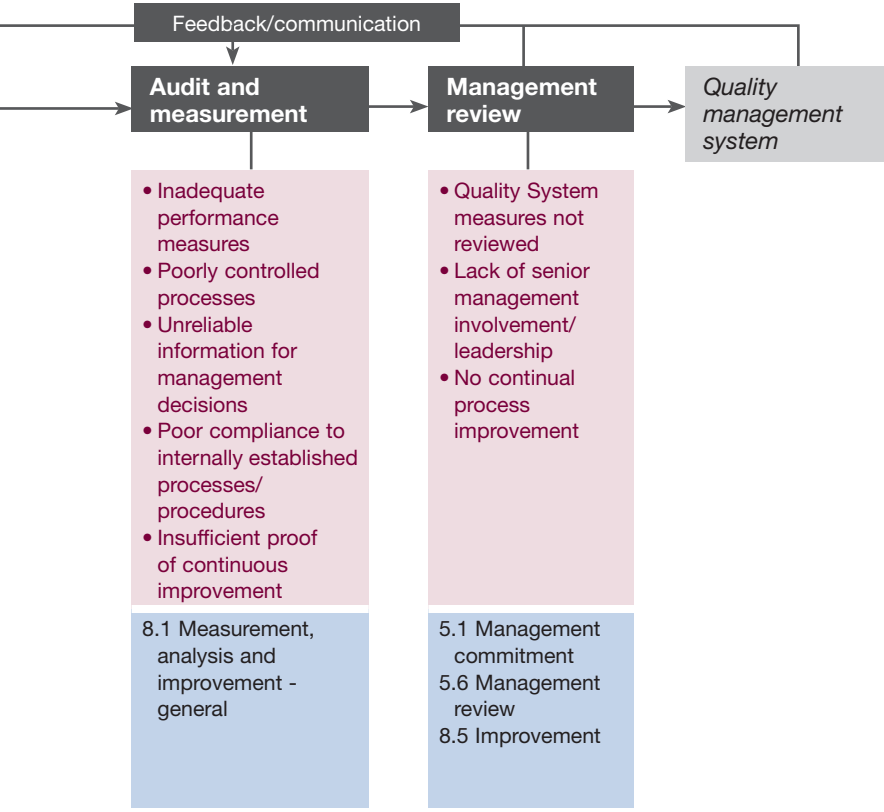
SCHEMATIC 1: TOP LEVEL BUSINESS PROCESSES



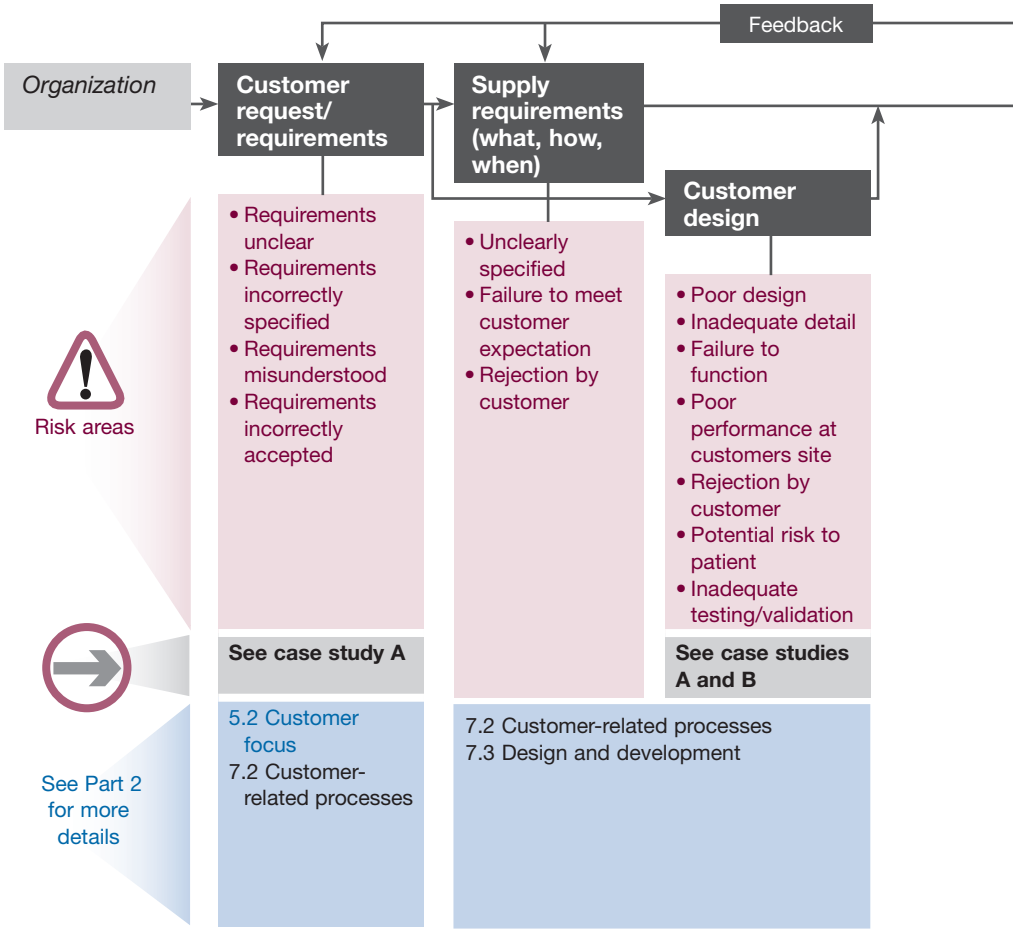
Refer to the hypothetical examples which are located after the schematics.



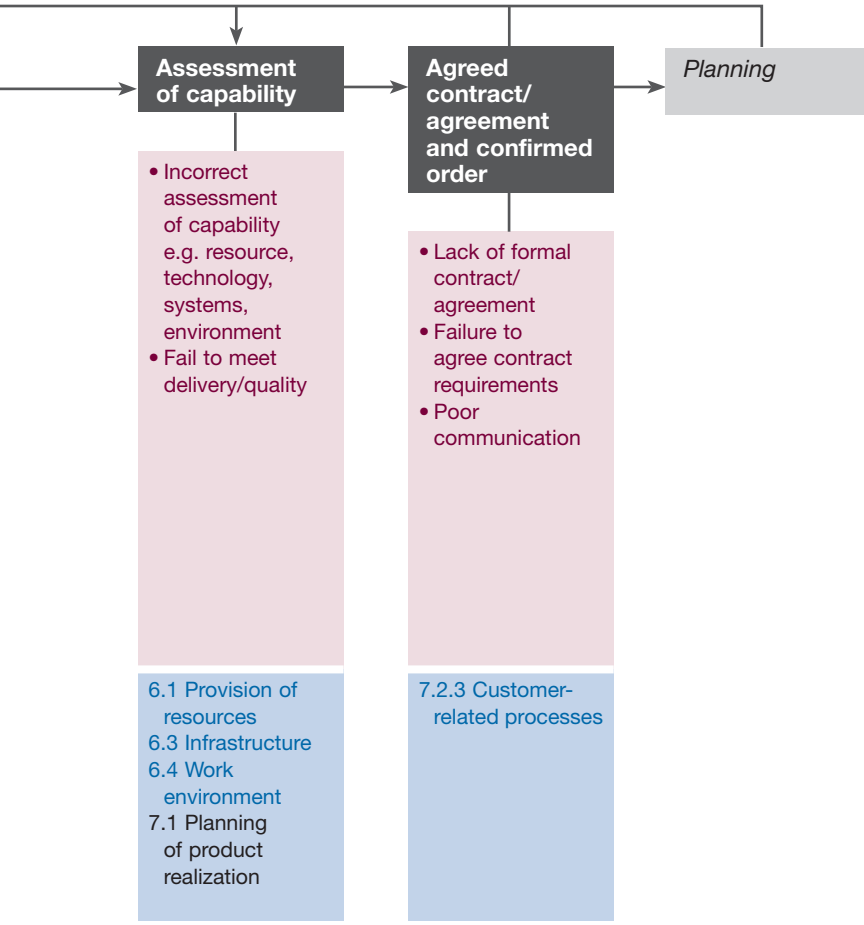
This diagram shows the main business processes from customer requirements through to delivery of final product and provides an index to the schematics



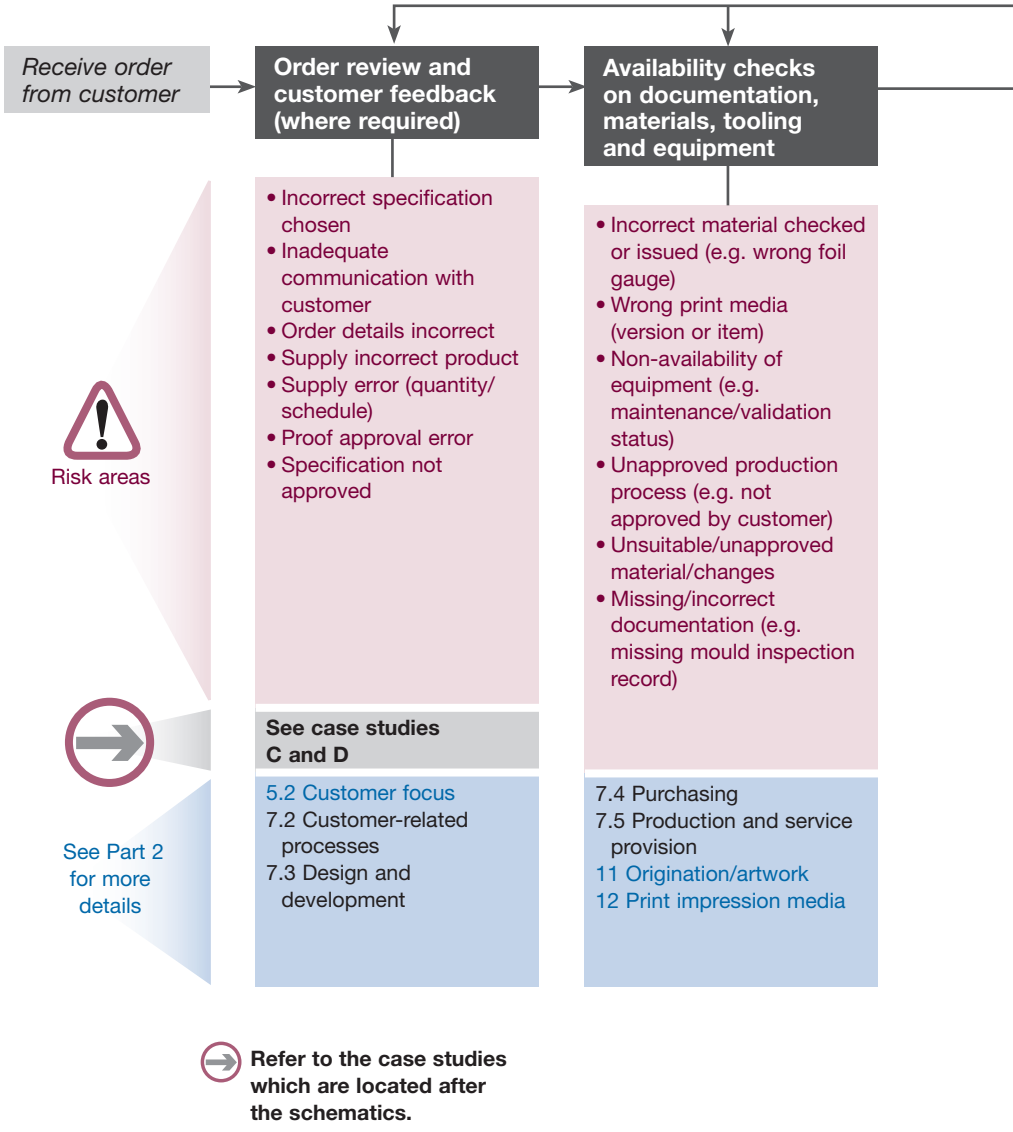
SCHEMATIC 2: FROM THE CUSTOMER



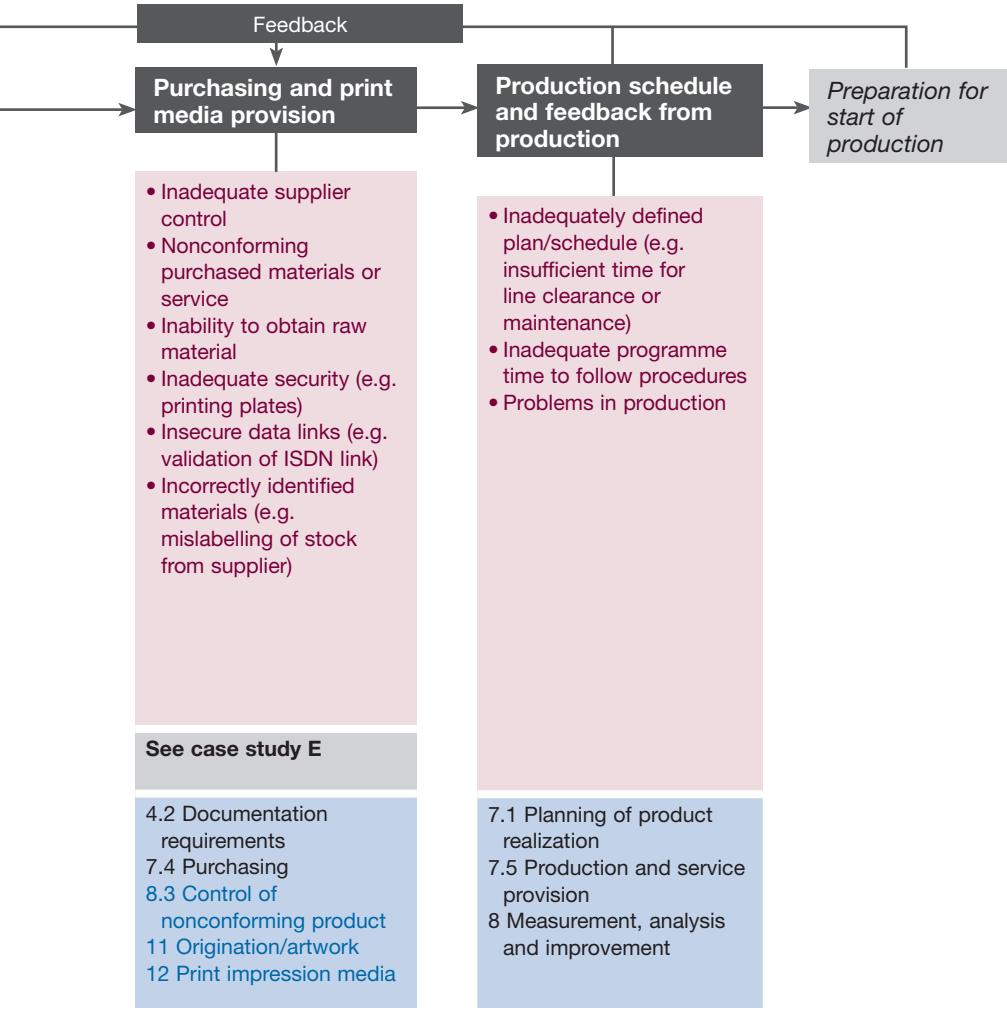
Refer to the case studies which are located after the schematics.


Assessment of capability
Agreed contract/ agreement and confirmed order
Planning
• Incorrect assessment of capability e.g. resource, technology, systems, environment
• Fail to meet delivery/quality
• Lack of formal contract/ agreement
• Failure to agree contract requirements
• Poor communication
6.1 Provision of resources
6.3 Infrastructure
6.4 Work environment
7.1 Planning of product realization
7.2.3 Customer-related processes

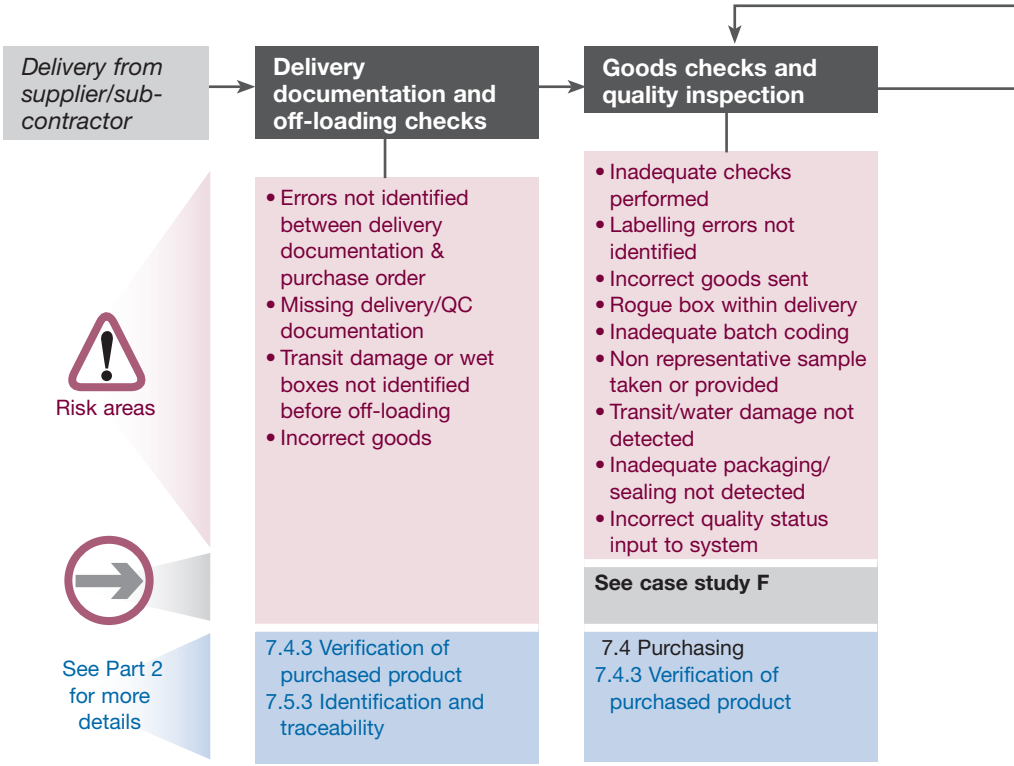
SCHEMATIC 3: PLANNING



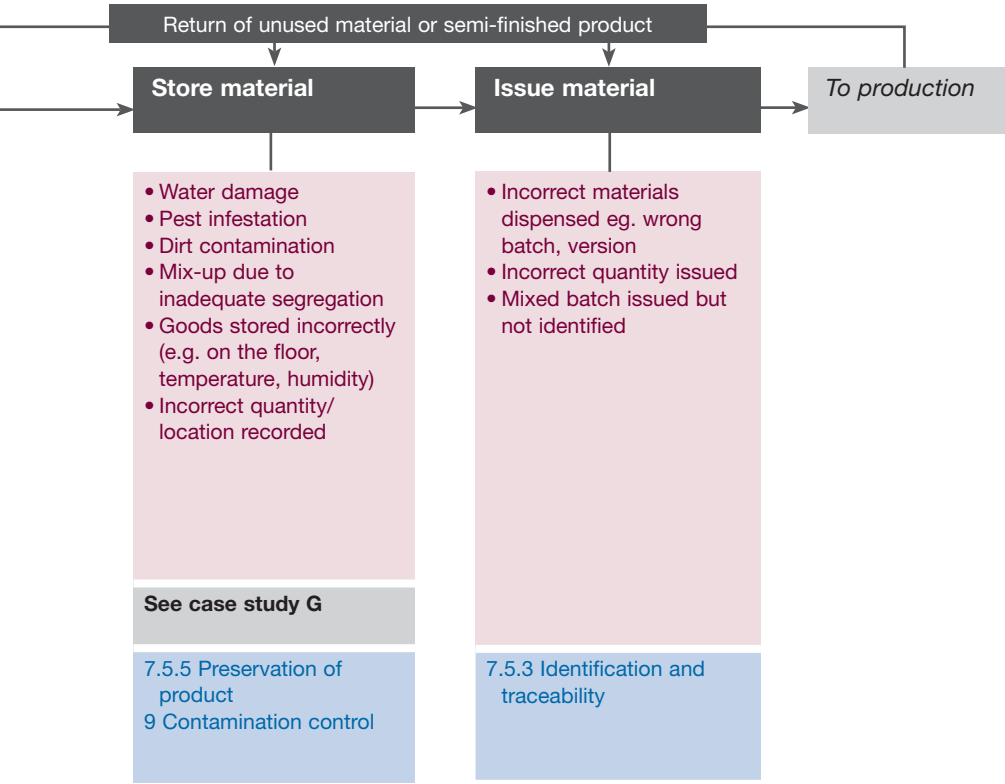
Refer to the case studies which are located after the schematics.


Feedback
Purchasing and print media provision
Production schedule and feedback from production
Preparation for start of production
• Inadequate supplier control
• Nonconforming purchased materials or service
• Inability to obtain raw material
• Inadequate security (e.g. printing plates)
• Insecure data links (e.g. validation of ISDN link)
• Incorrectly identified materials (e.g. mislabelling of stock from supplier)
• Inadequately defined plan/schedule (e.g. insufficient time for line clearance or maintenance)
• Inadequate programme time to follow procedures
• Problems in production
See case study E
4.2 Documentation requirements
7.4 Purchasing
8.3 Control of nonconforming product
11 Origination/artwork
12 Print impression media
7.1 Planning of product realization
7.5 Production and service provision
8 Measurement, analysis and improvement

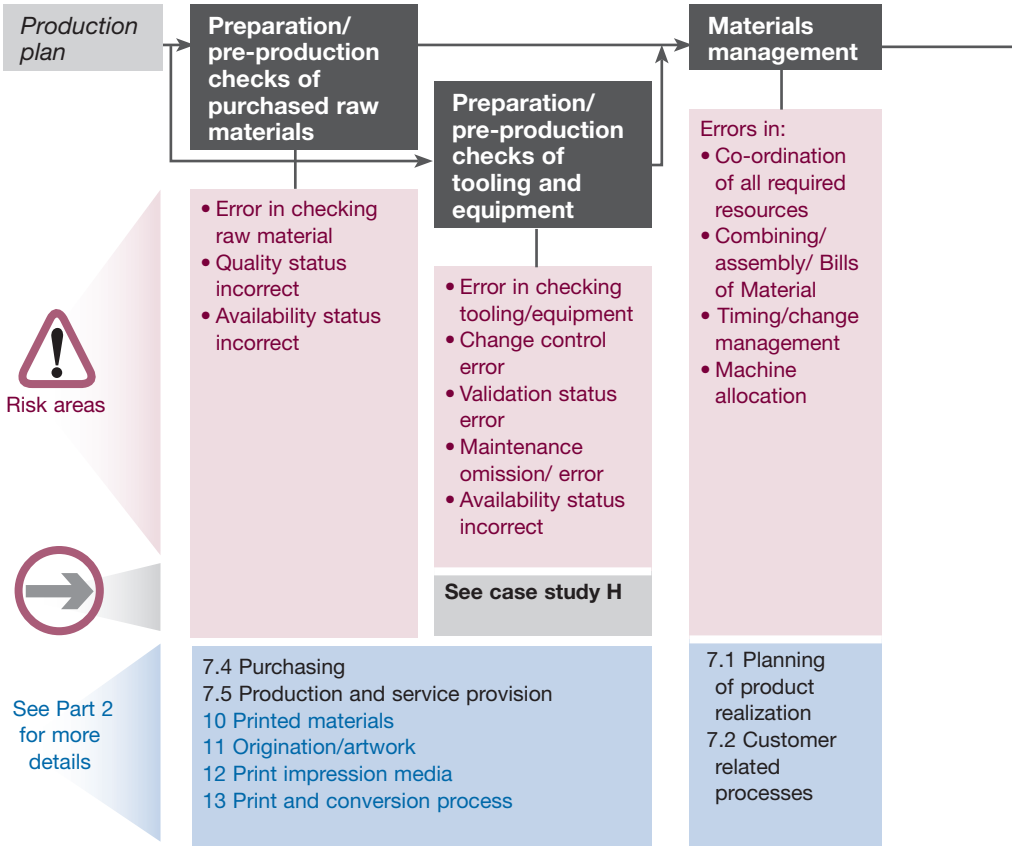
SCHEMATIC 3 (a): WAREHOUSE (purchased materials and in-process)



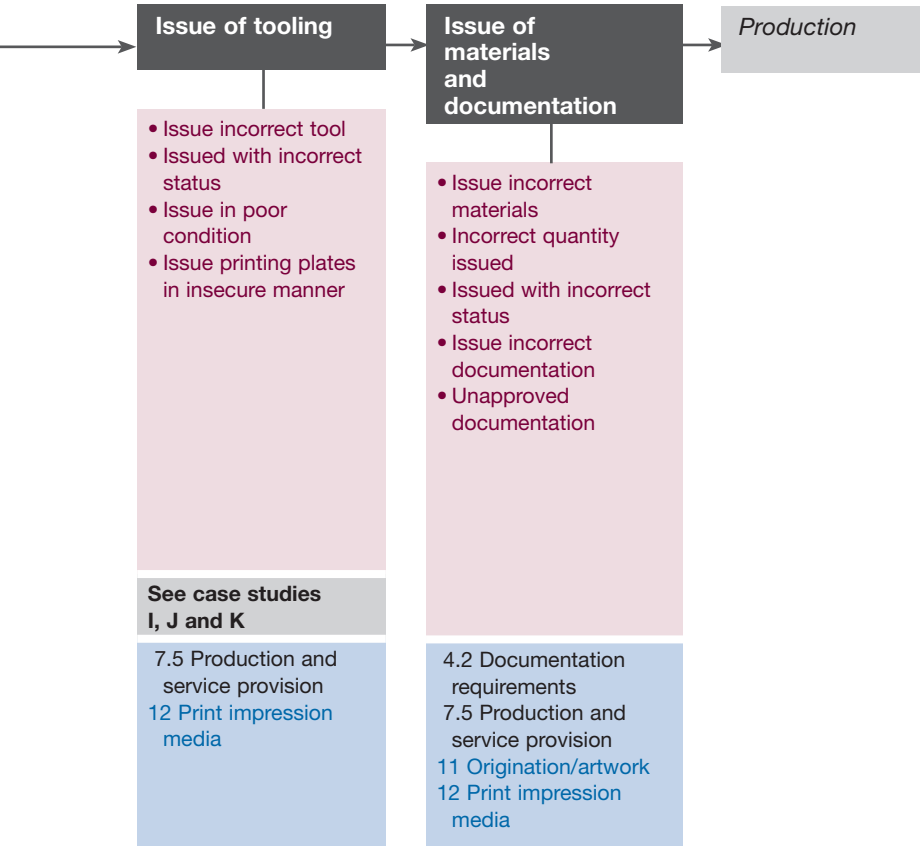
Refer to the case studies which are located after the schematics.


Return of unused material or semi-finished product
Store material
Issue material
To production
• Water damage
• Pest infestation
• Dirt contamination
• Mix-up due to inadequate segregation
• Goods stored incorrectly (e.g. on the floor, temperature, humidity)
• Incorrect quantity/ location recorded
• Incorrect materials dispensed eg. wrong batch, version
• Incorrect quantity issued
• Mixed batch issued but not identified
See case study G
7.5.5 Preservation of product
9 Contamination control
7.5.3 Identification and traceability

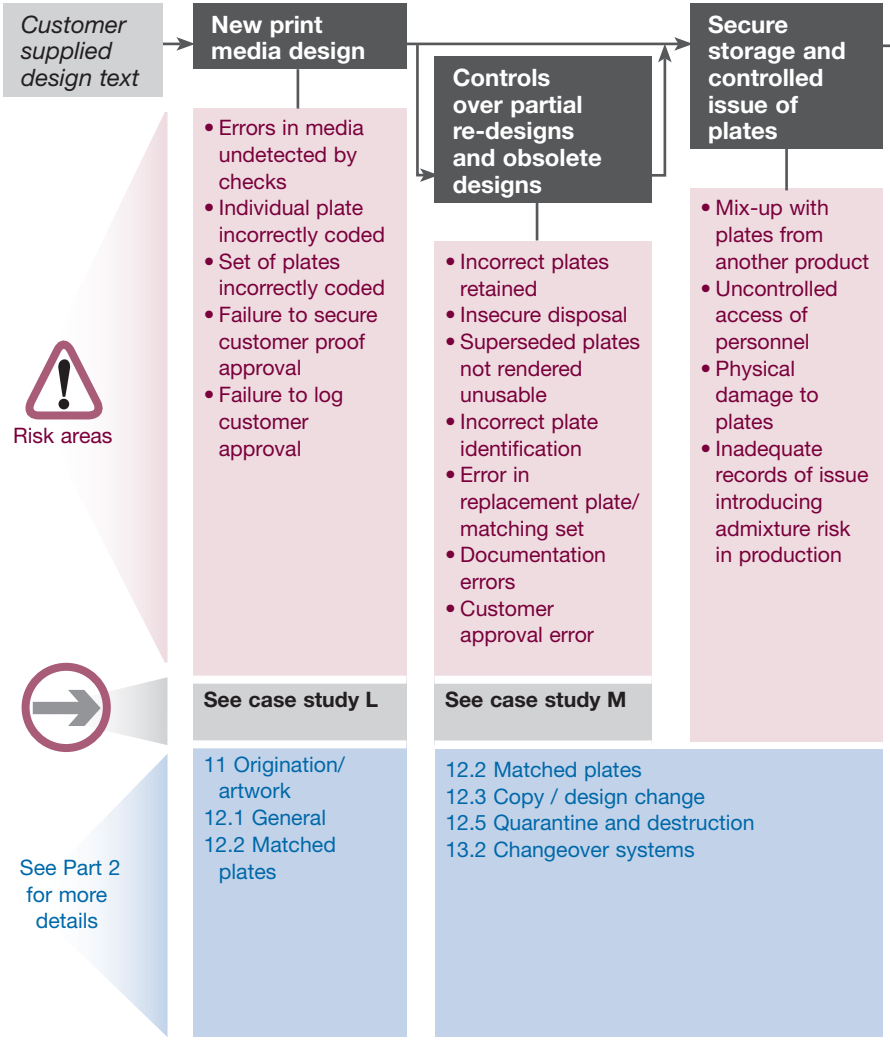
SCHEMATIC 4: PREPARATION



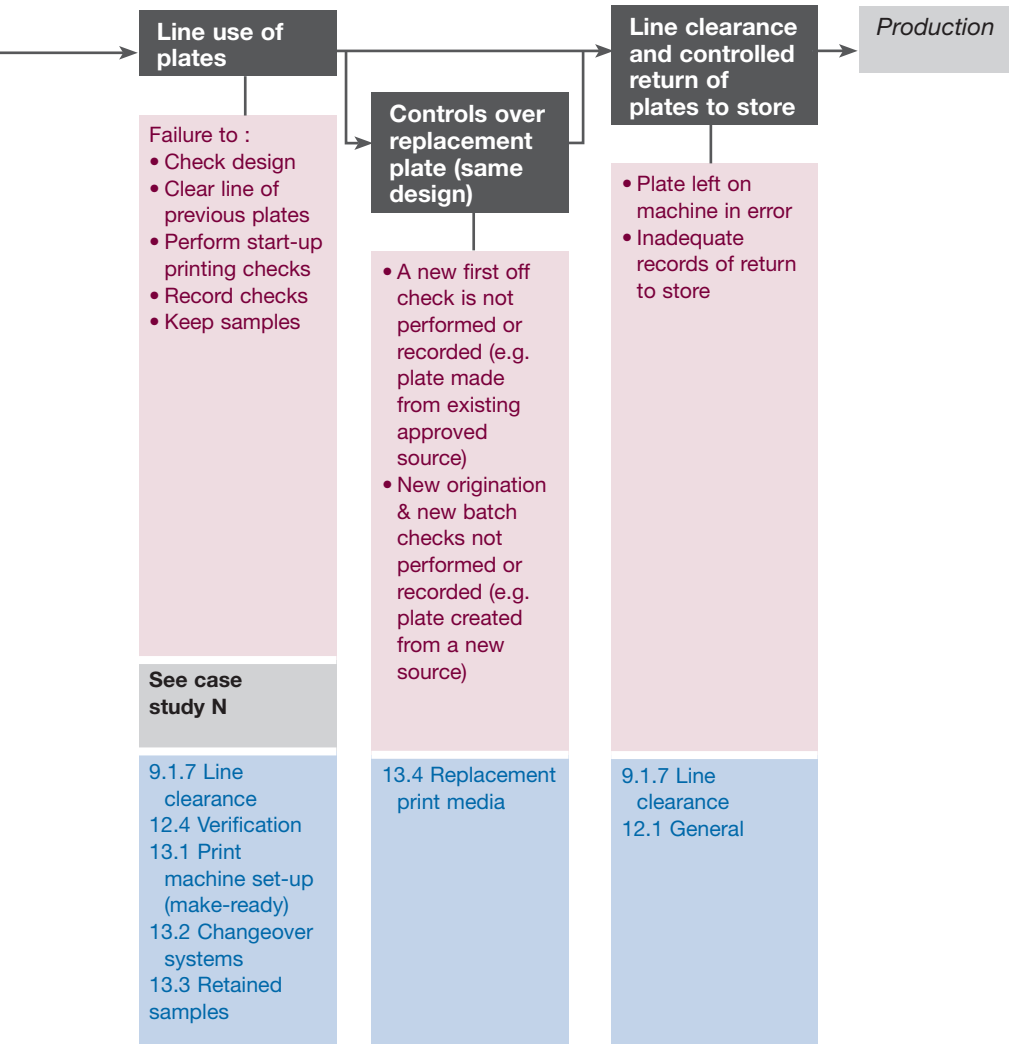
Refer to the case studies which are located after the schematics.


Issue of tooling
Issue of materials and documentation
Production
• Issue incorrect tool
• Issued with incorrect status
• Issue in poor condition
• Issue printing plates in insecure manner
• Issue incorrect materials
• Incorrect quantity issued
• Issued with incorrect status
• Issue incorrect documentation
• Unapproved documentation
See case studies I, J and K
7.5 Production and service provision
12 Print impression media
4.2 Documentation requirements
7.5 Production and service provision
11 Origination/artwork
12 Print impression media

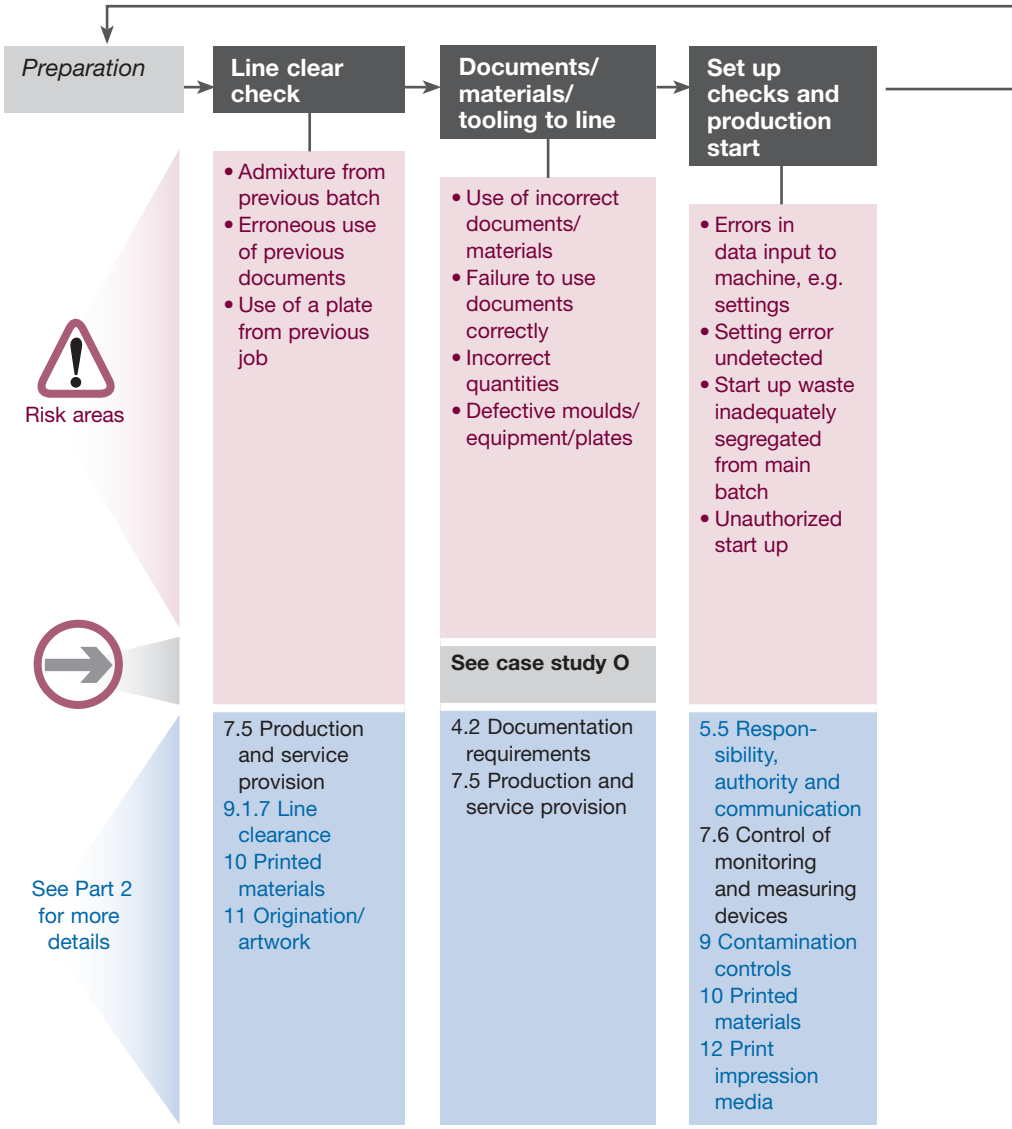
SCHEMATIC 4 (a): PRINT IMPRESSION MEDIA CONTROLS



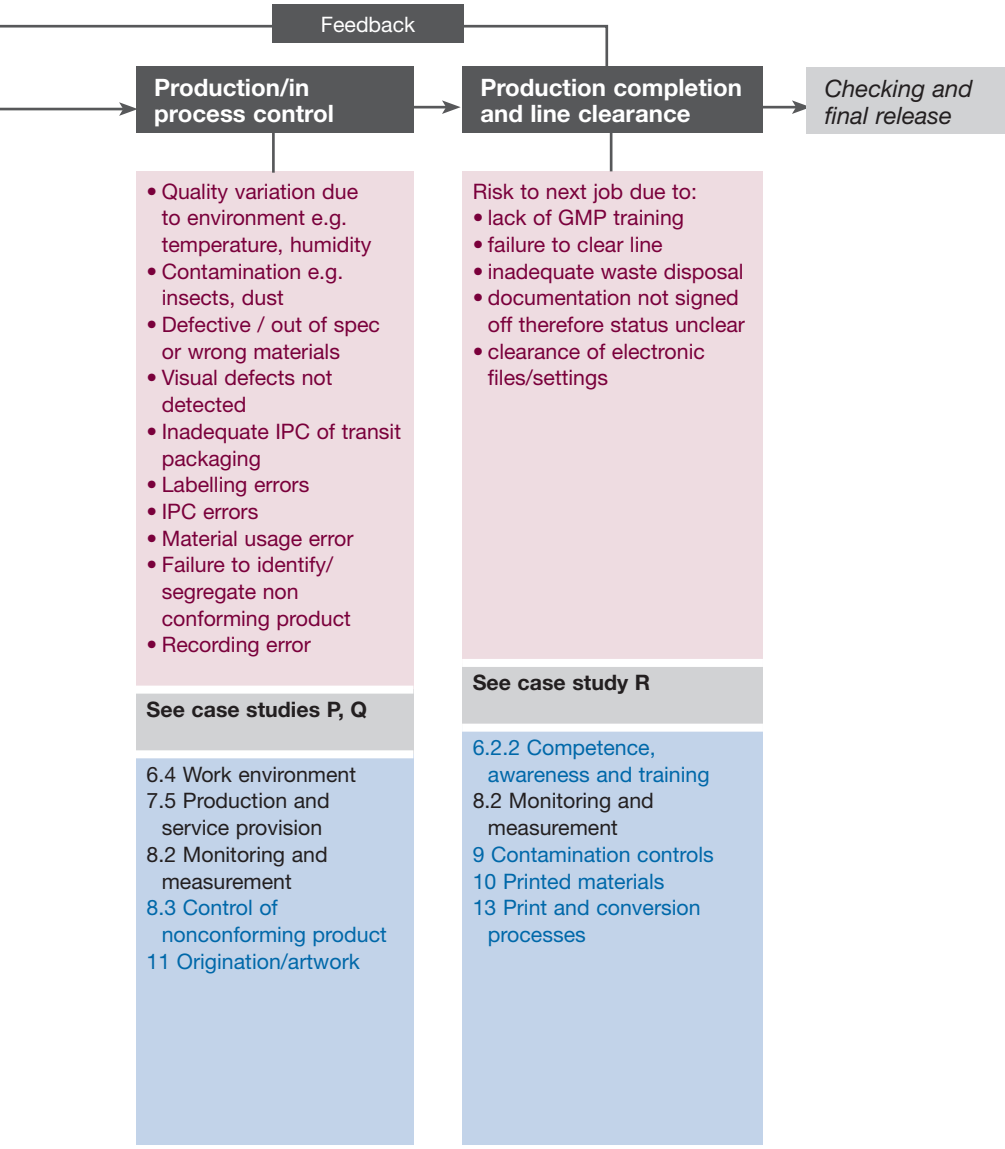
Refer to the case studies which are located after the schematics.


Line use of plates
Failure to :
• Check design
• Clear line of previous plates
• Perform start-up printing checks
• Record checks
• Keep samples
See case study N
9.1.7 Line clearance
12.4 Verification
13.1 Print machine set-up (make-ready)
13.2 Changeover systems
13.3 Retained samples
Controls over replacement plate (same design)
• A new first off check is not performed or recorded (e.g. plate made from existing approved source)
• New origination & new batch checks not performed or recorded (e.g. plate created from a new source)
13.4 Replacement print media
Line clearance and controlled return of plates to store
• Plate left on machine in error
• Inadequate records of return to store
9.1.7 Line clearance
12.1 General
Production

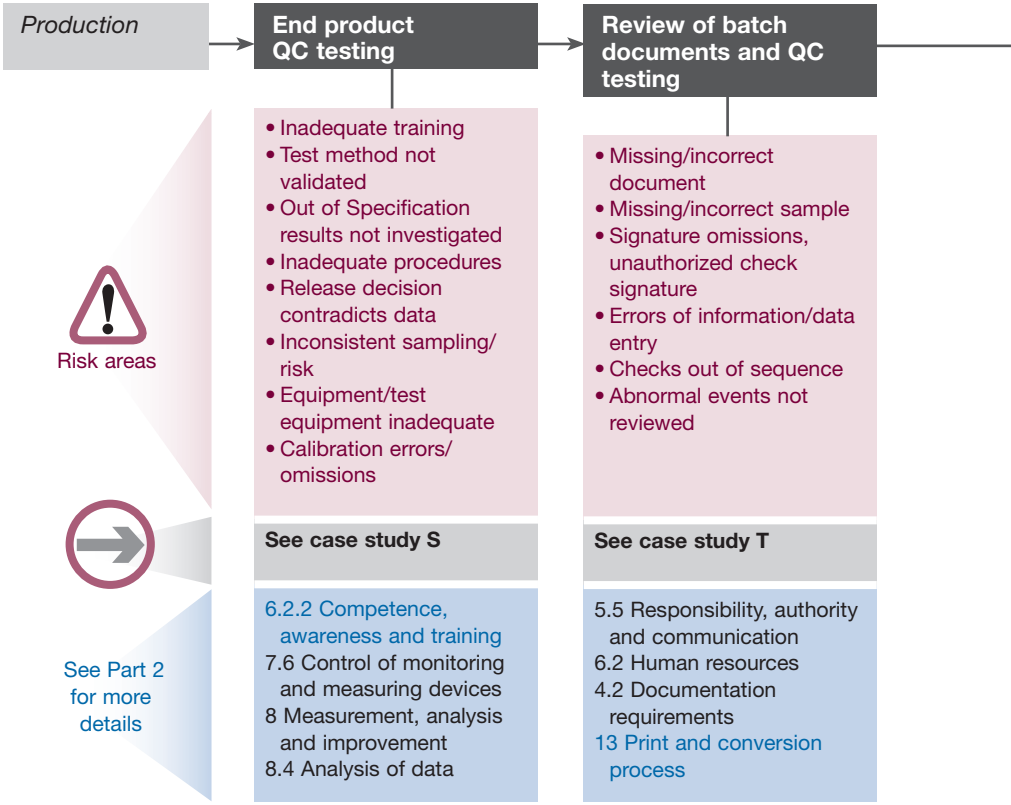
SCHEMATIC 5: PRODUCTION



Refer to the case studies which are located after the schematics.


Feedback
Production/in process control
Production completion and line clearance
Checking and final release
• Quality variation due to environment e.g. temperature, humidity
• Contamination e.g. insects, dust
• Defective / out of spec or wrong materials
• Visual defects not detected
• Inadequate IPC of transit packaging
• Labelling errors
• IPC errors
• Material usage error
• Failure to identify/ segregate non conforming product
• Recording error
See case studies P, Q
6.4 Work environment
7.5 Production and service provision
8.2 Monitoring and measurement
8.3 Control of nonconforming product
11 Origination/artwork
Risk to next job due to:
• lack of GMP training
• failure to clear line
• inadequate waste disposal
• documentation not signed off therefore status unclear
• clearance of electronic files/settings
See case study R
6.2.2 Competence, awareness and training
8.2 Monitoring and measurement
9 Contamination controls
10 Printed materials
13 Print and conversion processes

SCHEMATIC 6: CHECKING AND FINAL RELEASE



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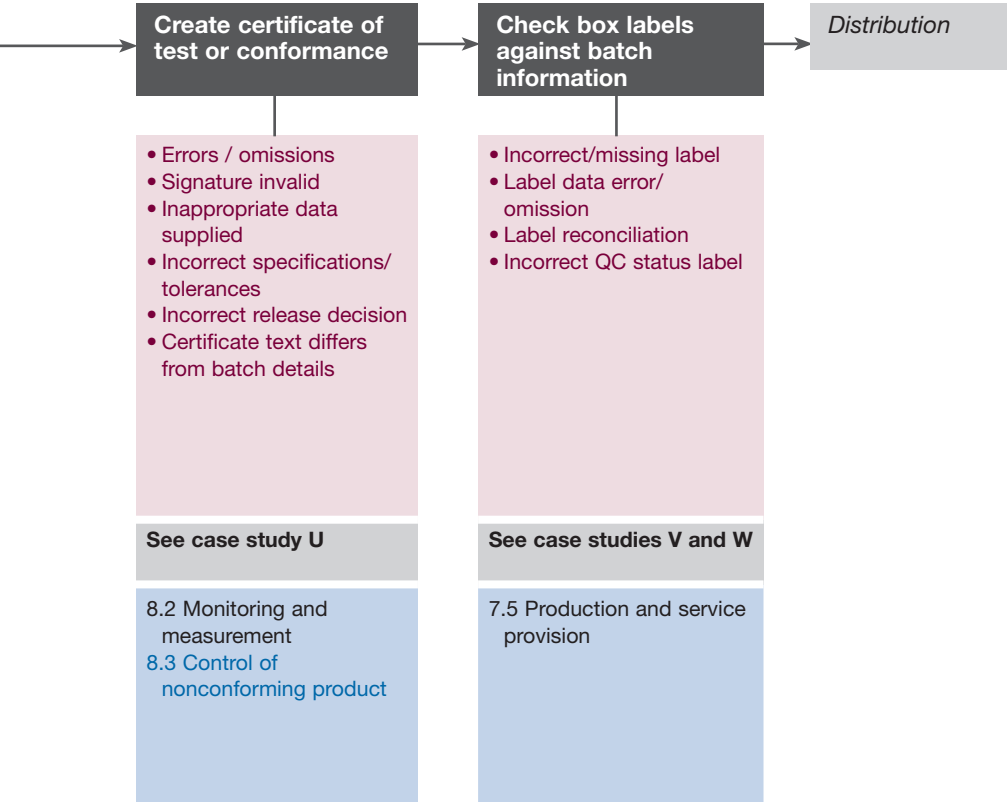
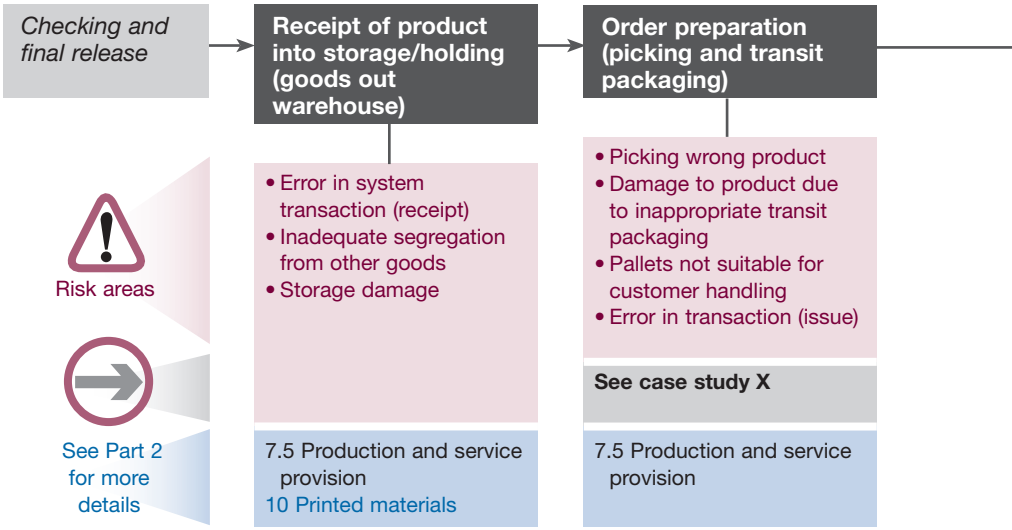
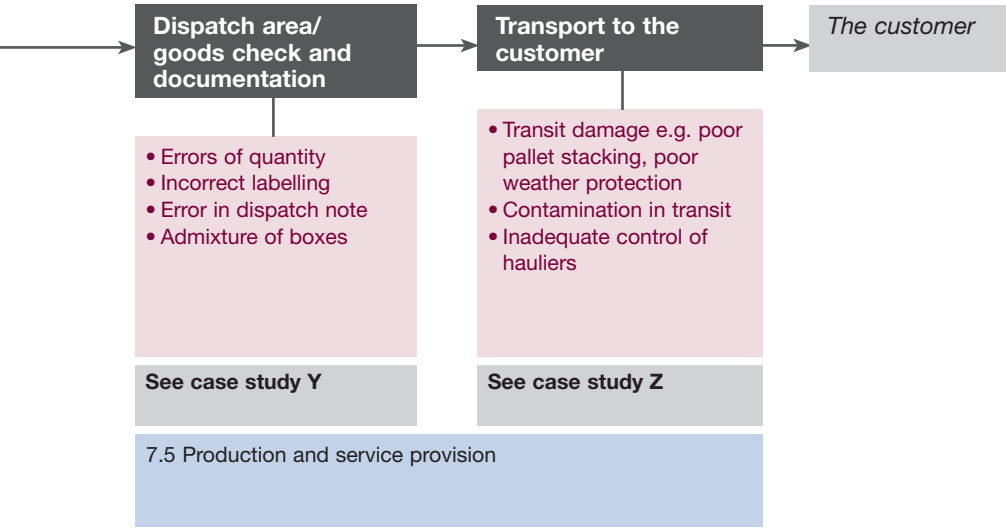

Create certificate of test or conformance
Check box labels against batch information
Distribution
• Errors / omissions
• Signature invalid
• Inappropriate data supplied
• Incorrect specifications/ tolerances
• Incorrect release decision
• Certificate text differs from batch details
• Incorrect/missing label
• Label data error/ omission
• Label reconciliation
• Incorrect QC status label
See case study U
See case studies V and W
8.2 Monitoring and measurement
8.3 Control of nonconforming product
7.5 Production and service provision

SCHEMATIC 7 - DISTRIBUTION



Refer to the case studies which are located after the schematics.


Dispatch area/ goods check and documentation
Transport to the customer
The customer
• Errors of quantity
• Incorrect labelling
• Error in dispatch note
• Admixture of boxes
• Transit damage e.g. poor pallet stacking, poor weather protection
• Contamination in transit
• Inadequate control of hauliers
See case study Y
See case study Z
7.5 Production and service provision

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PART 1 - CASE STUDIES

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Part 1 – Examples and Case studies

These examples and 'real life' case studies should be used with the relevant Schematic, to illustrate specific GMP risk areas and the appropriate QMS processes involved.

HYPOTHETICAL EXAMPLE FOR SCHEMATIC 1 – TOP LEVEL BUSINESS PROCESSES

The senior management of a booklet printing company believes that PS 9000 certification will aid company profitability and smooth throughput because of consistent demand from the pharmaceutical industry, which is not adversely affected by recessions. The company has an enthusiastic Quality Manager who has produced a comprehensive manual with up to date and relevant procedures. However, the Quality Manager is beginning to feel like a 'voice in the wilderness' as there is little evidence that senior management is driving the whole organization to become aligned to the requirements of the standard. The lack of senior management commitment to the continual improvement philosophy and the Good Manufacturing Practices of the pharmaceutical industry means that only superficial actions are taken in areas considered highly visible to visiting auditors. Key individuals are unclear about the standards required of them. The level of customer complaints remains high, some of these complaints being serious mix-ups. Productivity stays unchanged with a high level of wastage. Workforce moral is low and many staff are demotivated.

The company is then purchased by another company that already supplies cartons to the pharmaceutical industry - allowing them to offer a better product range to the customer. The corporate re-organization results in key changes in senior management at the booklet factory. The new managers know their prime objective is to encourage each and every employee to understand the particular needs of their pharmaceutical customers. They understand the value of PS 9000 in a competitive market, but know that the real benefits are much deeper than merely achieving the 'badge'. The Quality Manager begins to feel encouraged and genuinely part of the team. The frequency of management review meetings is increased with the emphasis changed to progressing preventive actions for nonconformities and review-

ing clear measures of performance for key parameters such as complaint rates. The senior management commitment begins to permeate throughout the staff and becomes evident in many areas such as resourcing, training, customer service, and improved product quality. The board of directors soon recognises that the PS 9000 implementation process is enabling them to profitably expand their business, improve relationships with their customers, whilst still significantly reducing their cost of quality.

CASE STUDIES FOR SCHEMATIC 2 – FROM THE CUSTOMER

A Focus - Customer request/requirements

Bar coded product labels could not be read by customer's electronic readers due to shading of background colour, caused by inadequate testing and validation. The packing orders at the pharmaceutical company were delayed which threatened the availability of the medicinal products to the end customers. The labels had to be destroyed, incurring the direct expense of replacement. The product was redesigned with solid background, and all graphics designers were made aware of the issue and to consider the possible need for trials on change of design or introduction of a new design.

B Focus – Customer design

A market need for a needle protection mechanism was specified, but translation of this into a final design was lengthy and complicated. The component did not perform reliably due to limited experimental validation. The problems were addressed through increased communication with the supplier to make the design more robust, involving revalidation and testing. This extended work caused a delay in providing the improved safety product to the patient. An organizational review followed to ensure that in future, adequate resource is devoted at the design and testing stages of product development.

CASE STUDIES FOR SCHEMATIC 3 – PLANNING

C Focus – Order review and customer feedback

The wrong material was ordered by the supplier's UK sales office from their own factory. Normally, orders were placed for 40 micron PVDC coated PVC

(for tablet blister packing), but on this occasion a new order for 60 micron coated film was incorrectly notified by the sales office to the factory in Germany as 40 micron; the incorrect material was delivered and used causing a regulatory noncompliance and potentially inadequately protecting the tablets from moisture. Significant work was necessary by the pharmaceutical company to assess stability data to determine the acceptability of the packed tablet batches. The root cause was established through customer audit of the ordering system at the sales office. An independent check of order details was implemented to prevent repetition.

D Focus – Order review and customer feedback

The printer's proof was incorrectly read by the supplier as 'approved' when it was actually 'rejected'; also the wrong file was used to make replacement printing plates. Cartons for a heart condition medicinal product were printed and used showing on one end flap 14 tablets instead of 28. The consequence of this was that stock had to be recalled from the distribution centres to enable a rework. This delayed the critical medicinal product reaching the market. Working together, customer and organization, the complete sequence of events was reconstructed. In addition to awareness training, the rules regarding issuing artworks and file management between organization and platemaker were made more robust.

E Focus – Purchasing and print media provision

Leaflets with a different paper weight were supplied, due to problems with availability of normal paper. This caused insertion difficulties on the pharmaceutical packing line, high wastage of components and loss of some pharmaceutical product. The supplier was advised of the existing change control clause in the quality agreement/contract and procedures were revised. The supplier managed to obtain further supplies of normal paper.

CASE STUDIES FOR SCHEMATIC 3 (a) – WAREHOUSE (PURCHASED MATERIALS & IN-PROCESS)

F Focus – Goods checks and quality inspection

Self-adhesive labels were failing to stick to glass vials at the customer's premises because a different adhesive had been used. This had been caused by the supplier switching their source of unprinted label material.

The raw material was thought to be of equivalent quality and no extra quality checks were performed at goods-inwards. The change was introduced without informing the customer therefore no formal change control or a risk assessment could be performed. The problem caused chaos on the customer's packing line and it was not certain how well the labels were affixed to 'apparently' satisfactory packed vials. The label printing company pursued the quality issue with its supplier and proper trials of alternatives were subsequently conducted with the pharmaceutical company. In addition, revisions were made to the change control system.

G Focus – Store material

Two dead mice were found inside the pallet wrapping of a consignment of plastic bottles to be used for an antiseptic liquid product. This caused major disruption to the output of the pharmaceutical filling plant. All the stock of bottles had to be manually inspected for contamination. It was necessary to audit the supplier and its remote warehouse. Immediate action involved the relocation of bottle storage back into the main factory. The root cause was inadequate warehouse pest controls at the supplier's remote warehouse. It prompted an extensive programme of work to improve the standards at the site. The product was a low margin item for the pharmaceutical company and it has since been sold off to another company. Although many other factors were involved, this episode only added to the reasons to sell this part of the business.

CASE STUDIES FOR SCHEMATIC 4 – PREPARATION

H Focus – Preparation/pre-production checks of tooling and equipment

Mould tool used to produce parts for a syringe was used in production when the validation documentation had not been fully approved and signed off. This contributed to high variability in functional performance of the assembled syringe with some batches of parts rejected, and it necessitated ongoing improvement work. It also delayed the launch of the pharmaceutical product which in this case was a life saving cancer product. The operational procedures were revised and the operators were retrained.

I Focus – Issue of tooling

Syringe labels were printed correctly, but were cut with corners of the wrong profile/shape due to the issue of an incorrect cutter to the press. The labels were rejected by the pharmaceutical company at the expense of the printers. The time needed to replace the labels meant rescheduling of packing was necessary at the pharmaceutical company. The cutter identification process was reviewed & storage standards were improved.

J Focus – Issue of tooling

Cartons were produced with a varnish free area in the wrong position due to the issue of an incorrect varnish plate. The purpose of a varnish free area is to ensure the printing of variable data (e.g. lot & expiry) is clear and permanent. This error was identified at the pharmaceutical company. The risk existed that variable data applied by the pharmaceutical company could be easily smudged or erased when in the market and this would clearly be a critical problem. The supplier reviewed the varnish plate issuing process and made improvements to the system which linked varnish plate usage to print plate usage.

K Focus – Issue of tooling

Mould tool for a syringe plunger rod was issued to production despite being overdue for refurbishment. This resulted in minor plastic 'flash' being present on the mouldings. If this problem became more serious then loose particles of plastic could break off and contaminate the pharmaceutical syringe pack. The supplier applied for a concession from the customer and this was granted for a limited period because of the extent of the problem. The case highlighted the need for proper planned preventive maintenance and sufficient resources allocated to facilitate it.

CASE STUDIES FOR SCHEMATIC 4 (a) – PRINT IMPRESSION MEDIA CONTROLS

L Focus – New print media design

Artwork supplier made a "cut & paste" error which resulted in cards being part printed with Polish text in the main body of Portuguese text. The cards were for an anti-cancer injection. Fortunately the error was noticed during in-process checks of printing. The error had the potential to become

a product recall if it had reached the end user. An extensive review of the artwork supplier's procedures was completed and a further proof-reading check was introduced.

M Focus – Controls over partial redesigns & obsolete designs

The printed foil for tablet blister strips (used to treat a heart condition) was incorrectly printed with two different identifying codes on the foil (different by one digit). The error occurred during the 'step and repeat' process to generate a single replacement cylinder. The error was only found on inspection at the pharmaceutical company. In this case, no packed stock was lost, but the error could have been more serious. The supplier took the issue up with its cylinder manufacturer and reviewed its inspection procedure for first off sample inspection following cylinder replacement.

N Focus – Line use of plates

A printing plate was left on the leaflet press by the operator after leaving the area to retrieve a spare part. Upon return the operator continued printing, but against the job documentation for the next job. The item was visually very similar and all subsequent checks by operators and QC failed to spot the admixture that had been created. The problem was found on goods inwards checks by the customer, and resulted in a detailed audit of procedures by the customer. Line clearance checks were reviewed, procedures around bar code scanning at the suppliers were enhanced and refresher training was delivered.

CASE STUDIES FOR SCHEMATIC 5 – PRODUCTION

O Focus – Documents/materials/tooling to line

During the folding stage of leaflet production two orders were mixed up. Job A was folded, scanned, labelled and released against Job B documentation, and Job B documentation was folded, scanned, labelled and released against Job A documentation. The mixed-up orders were then delivered to the pharmaceutical company where the error was discovered. The potential for incorrect leaflets to be packed into pharmaceutical packs was increased. The supplier's investigation identified the root cause as human failure to follow established procedures. In addition the codes for the bar code scanner are now input from an independent source (a PS 9000:2001 requirement).

P Focus – Production/in-process control

A delivery of poorly printed foil, used for tablet blister strips, was caused by inadequate 'flagging' of defective material during printing. The 'flagged' material is removed during later stages of slitting and rewinding. The defective material was detected on the customer's packing line and lead to the scrapping of some packed pharmaceutical product. The supplier's printers and the operators responsible for removal of the 'flagged' material were given refresher training to ensure all defective material is removed, up to and around the 'flagged' point in the reel.

Q Focus – Production/in-process control

Plastic tablet bottles were manufactured with a wall thickness that was below specification. This was caused by poor appreciation of the customer's requirements, inadequate in-process monitoring and an inability to segregate product that was out of specification. Packed pharmaceutical product had to be quarantined until all aspects of the problem had been assessed by the pharmaceutical company's QA Department. The issue was resolved through improved specification regarding the criticality of certain dimensions, increased in-process measuring regime and enhanced segregation procedures.

R Focus – Production completion & line clearance

On a reel of label/leaflet combinations, six 'rogue' components (of similar appearance) were found at intermittent points in the reel, by the pharmaceutical customer. This was despite a scanning operation being in place at the supplier. The root cause was human error involving inadequate line clearance and replacing incorrect labels back onto the web during rewinding/scanning. Although the rule existed which forbade this practice, the operator had recently been transferred from a department supplying non-pharmaceutical customers where this rule was not in place. The supplier commenced a fundamental review of procedures and operator retraining.

CASE STUDIES FOR SCHEMATIC 6 – CHECKING & FINAL RELEASE

S Focus – End product QC testing

An out of specification result on a test machine record was transcribed incorrectly as satisfactory on the summary sheet, causing an incorrect

release decision of a batch of syringes. Although, in this case no harm was caused, it highlighted a risk area, should the error have occurred on another safety related function of the syringe. Refresher training was delivered to the operator concerned.

T Focus – Review of Batch documents & QC testing

Carton barcode scanner was switched off during the night shift without QA authorization and not noticed upon review of documentation. This meant that the product had been made without the safeguards required by, and contractually agreed with the customer. The product was therefore inadequately checked for the absence of rogue components. The affected order was rejected and scrapped. A detailed audit was performed by the pharmaceutical company and numerous significant procedural enhancements were made.

U Focus – Create Certificate of Test or Conformance

Irradiated syringes were released for use despite radiation dose figures being omitted from the certificate of test. In this case the dosage was actually satisfactory, however the omission / error had the potential to threaten the sterility of the syringes thus endangering the patient, and to compromise the pharmaceutical sterile filling facility. The certificates are now double checked before release from the irradiation contractor.

V Focus – Check box labels against batch information

A box of shampoo closures was delivered amongst a consignment of tablet bottle closures, caused by box labelling error & poor segregation practices. This resulted in admixture on the filling line at the pharmaceutical company, line downtime, and some lost product. The supplier had been audited on numerous occasions but lack of commitment to eliminate such problems ultimately lead to a change of supplier for the component.

W Focus – Check box labels against batch information

A keying-in error of leaflet product identity code to outer box label printer caused rejection upon delivery to customer. Apart from the disruption caused by the rejection, there was a risk that the material could have been received into stock as a different item, i.e. admixture. The preventive action eventually implemented was to link the box label printer to the mainframe

computer thus removing the necessity to manually key the data into a standalone label printer.

CASE STUDIES FOR SCHEMATIC 7 – DISTRIBUTION

X Focus – Order preparation (picking & transit packaging)

An admixture of boxes of labels was found on receipt by the customer caused by a picking error made due to poor warehouse lighting and lack of a double check. In another incident an admixture of batch of cartons occurred, caused by a picking error due to poor batch segregation in the warehouse. Both batch defectives were found during the customer's receipt checking, but they caused disruption to the product scheduling programmes because of the need to return the material to the supplier for sorting/replacement. The corrective and preventive actions, in both cases, involved a fundamental review of the conditions (and checks made) in the warehouse and implementation of improved lighting and segregation measures.

Y Focus – Despatch area/goods check & documentation

Despatch note details accompanying the delivery differed from physical quantity delivered. This resulted in delays in product release and scheduling disruption while the supplier was contacted. The supplier's despatch checking procedures were reviewed, no fundamental weaknesses were found. In this case, a one-off error had occurred and the issue was discussed with the individual concerned.

Z Focus – Transport to the customer

Goods were damaged in transit due to movement of the load and inadequate control while the vehicle was being loaded. In another incident, goods were damaged by water penetration due to a poorly closed and maintained "curtain" of a flexible sided vehicle. Both examples resulted in the need for product inspection at the customer, and the return of damaged material to the supplier leaving too few components to meet requirements. In the first case, the checks made on loading were increased and in the second example the company decided it was feasible to switch to hard sided vehicles to eliminate the risk of water penetration.

Using the Case Studies - Guidance for Trainers

Introduction

The case studies that have been described here can be used as valuable aides to training programmes, for use either by a supplier or a pharmaceutical company. It is recommended that you select one or more of the case studies that are appropriate to your business and design an activity that will encourage your trainees to discuss the particular subject you would like them to understand. An example of a training exercise protocol is provided below based on a case study selected from Schematic No. 3. Developing a short set of questions similar to those illustrated below should help improve understanding. It will probably be beneficial if such Q & A sets were developed jointly after discussion between pharmaceutical customers and their suppliers.

It will certainly be helpful to provide explanations and visual aides relevant to the case study. For example in the example illustrated below it would be helpful if:

i) For a laminate that you use or manufacture explain which illness(es) the tablets, that are packed within it, are used to treat.
ii) A copy of an analogous page of a Product Authorisation (Licence) was shown and the legal basis of such licences explained.
iii) The function of PVDC in the laminate was explained.

Training Exercise

Case study No. C

Title: Mix-up in the weight of PVDC on a PVC based blister film

In this case study, the wrong material was ordered from the factory. Nomally, orders were placed for 40 micron PVDC coated PVC (for tablet blister packing) - and etc.

Training objectives

Discuss the case study in groups and decide your answers to the following questions:

Q 1. Which requirement(s) of PS 9000 do you consider had not been effectively implemented?

State the clause numbers and your reasons.

Q 2. Why do you think that the thickness of the PVDC could affect the stability of the tablets that were to be packed in the laminate?

Q 3. If this mistake had not been detected what do you think the implications might have been to:

i) The manufacturer of the laminate film?

ii) The pharmaceutical customer?

PS 9004

A Guide to the GMP requirements
of PS 9000:2001 Pharmaceutical packaging materials

PART 2 - GUIDANCE ON PS 9000 GMP CLAUSES

PS 9000 GMP related text is reproduced in blue

General synopsis - Clause 4 Quality management system

A QMS provides a basis for continuous improvement of the organization's effectiveness and efficiency, whilst still considering the various needs of all stakeholders (e.g. customers, suppliers, investors, employees).

Clause 4.1 General requirements

Detailed consideration is required of the needs of stakeholders, the processes to meet those needs and to measure performance.

There are no 'extra' PS 9000 GMPs within this clause. There are important GMP principles in this area, but they are adequately expressed in ISO 9001 and ISO 9004.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Identified processes that meet organization strategic objectives • Customer requirements • Regulatory requirements	Processes which: • define, implement and maintain QMS processes (including management and operational activities) • determine personnel required to carry out processes and training needs • provide premises and equipment for the processes • define and implement controls to measure performance of QMS processes including outsourcing	• Written procedures essential to Quality System • Organization structure that supports QMS • Adequate premises and equipment • Data from processes and measurement systems	Schematic 1

Clause 4.2 Documentation requirements

Documentation is a fundamental part of the QMS that defines what the organization does, provides traceability and evidence of its activities.

Reasons for the 'extra' GMP requirements (refer to PS 9000 clauses 4.2.2; 4.2.3; 4.2.4)

Pharmaceutical companies have, on occasions, experienced problems in the retrieval of accurate historical data from suppliers and these have been attributed to inadequate data system validation and data controls. The process references above are part of a system of data traceability that can provide a complete history of the component's manufacture. This can be vitally important if there is a problem in the use of the pharmaceutical product in the marketplace.

The pharmaceutical company has a regulatory obligation to retain production and packing data for one year beyond the shelf-life of the product. There is therefore a corresponding responsibility (see Annex B) upon the component supplier to establish and maintain accurate and secure data control and retention systems.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Documents that need to be controlled • Standards and regulatory requirements • Customer requirements (specified and unspecified) • Responsibilities for documents (e.g. authors, approvers, etc.) • Process maps	Processes which: • control the document and data management for any media type to cover life-cycle • ensure the security of electronic documents is equal to that of paper documents • provide audit trail for electronic documents and data • control backup and recovery of data • control validation of hardware/software used for document and data management • control archiving/retention of documents and data • define the extent to which PS 9000 applies within the QMS	• Quality manual • Procedures that support the document and data management system • Clear accountabilities and responsibilities Records of: • documentation changes • training • validation	Schematic 3 Schematic 4 Schematic 5 Schematic 6 Annex B

General Synopsis - Clause 5 Management responsibility

Management's responsibility to ensure an effective QMS which recognises the needs of the organization, customers and other key stakeholders.

Clause 5.1 Management commitment

Top management defines the organization's strategy and is responsible for demonstrating commitment to the QMS. Continual improvement of the system and its processes are necessary to ensure customer and regulatory needs are fully satisfied.

There are no 'extra' PS 9000 GMP's within this clause. There are important GMP principles in this area, but they are adequately expressed in ISO 9001 and ISO 9004.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Company strategy/ purpose • Adequate resources to meet requirements	Processes which: • establish quality policy • establish quality objectives • require a Management Review as a means of continual improvement • ensures the communication with staff to help them understand and contribute to QMS implementation (e.g. continuous improvement objectives, customer satisfaction targets, etc.)	• Evidence of staff understanding and commitment • Customer satisfaction measures Clearly documented: • quality policy • quality objectives • improvement plans	Schematic 1

Clause 5.2 Customer focus

A key requirement to provide suitable premises, people, and processes, in order to enhance customer satisfaction.

Reasons for the 'extra' GMP requirements

Pharmaceutical Industry experience shows that from the product development stage onwards, compliant pharmaceutical quality requires facilities and staff to be 'fit for purpose', i.e. 'suitable facilities and competent staff', and that this GMP requirement is equally applicable to the supplier of pharmaceutical packaging components.

Product security and the avoidance of cross contamination underpins all pharmaceutical quality, since these are basic issues that can lead to people taking the wrong medicine, damaging the pharmaceutical company's business, and public confidence in it. (See also Annex A, 'Counterfeit' that covers in detail the needs for controls in areas involving disposal of artwork, process defectives and waste materials, etc.).

Beginning with its regulatory inspectors, the whole pharmaceutical industry is compliance driven, using audits as a measure that GMP practices, as part of a quality system, are in place. Central to this audit focus, is the 'Rules and Guidance for Pharmaceutical Manufacturers and Distributors'. Chapter 9, Internal audits, requires self inspection by the pharmaceutical manufacturer and Annex 8.5, requires that sampling plans for the assessment of packaging material deliveries should, through audits, take into account knowledge of the supplier's quality assurance system.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Customer input/ requirements	Processes which: • consider customer requirements in order to deliver a securely manufactured product to specification • permit customer audits • ensure secure disposal of all print related material	• Suitable facilities • Evidence of GMP training and task competency • Improvement plans from customer audits • Physical control and records of secure disposal of specified materials	Schematic 2 Schematic 3 Annex A Annex B

Clause 5.3 Quality policy

The quality policy is a top-level document, key to communicating and leading continuous improvement to satisfy the needs of the organization, customers and other stakeholders.

Reasons for the 'extra' GMP requirements

All ISO 9001 certificated companies are required to have a 'quality policy'. The avoidance of contamination and maintaining a controlled environment in order to ensure product security and integrity is of such importance to the pharmaceutical industry that these two requirements have to be included in the supplier's quality policy.

While PS 9000:2001 is primarily for suppliers of pharmaceutical packaging materials, some organizations supply different industry sectors (e.g. food, agrochemical, cosmetics). Therefore, for the purposes of clarity, the extent to which this application standard is employed within the organization needs to be documented.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Organization strategy/ purpose • Customer needs including product security requirements and prevention of cross-contamination • Extent to which PS 9000 is used within the organization	Processes which: • define quality policy • review policy to ensure it meets user needs • review quality objectives • communicate quality policy, including contamination control, to internal staff and external people, as appropriate	• Up-to-date quality policy Records of: • awareness/ communication activities • product security and environment controls • implementation	Schematic 1

Clause 5.4 Planning

Strategic business planning is essential to ensure that the organization moves forwards in a way that satisfies the needs of all stakeholders. This section covers the formal planning processes needed to realise organizational strategy through generation of objectives within the quality management system.

There are no 'extra' PS 9000 GMPs within this clause. There are important GMP principles in this area, but they are adequately expressed in ISO 9001 and ISO 9004.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Short and long term organization strategy/ goals • Regulatory requirements • Needs of the organization and markets • Management review findings • Current product and process performance • Resource information • Results from self-assessments and other audits • Industry information/ benchmarking	Processes which: • plan the implementation, and continual improvement of the QMS • provide a framework for the setting of measurable quality objectives, which support the quality policy and strategic goals	• Performance measurement data Defined and documented: • skills and knowledge • responsibilities and authority for implementation of improvement plans Quality objectives: • at organizational levels (e.g. managers, supervisors, operatives) • for functional areas (e.g. production, administration)	Schematic 1

Clause 5.5 Responsibility, authority and communication

All staff should know *what* their responsibilities are and to *whom* they are responsible. Authority needs to be pre-defined, documented and well communicated to ensure activities take place in a controlled manner.

Reasons for the 'extra' GMP requirements (refer to PS 9000 clause 5.5.3 Internal communication)

Staff in all organizations work better when they are kept informed, are appropriately trained and have relevant agreed procedures. A communication process needs to be in place to ensure that staff are customer focussed, motivated and where applicable, are aware of the regulatory, legal, and GMP needs of the pharmaceutical industry that may affect them.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Existing roles and responsibility data • Resource information • Personnel data (qualifications, experience, etc.) • Industry information/ benchmarking	Processes which: • clarify responsibilities and authorities for job elements relating to quality (e.g. state who is allowed to release products for despatch) • appoint a management representative to oversee the QMS (e.g. the QA Manager) • establish internal communication (e.g. monthly team briefings, etc.) Processes to communicate: • responsibilities and authorities for quality (e.g. post organization charts, give people their key responsibilities to read and approve) • quality throughout the organization – all staff should be included, from the most senior manager to the most junior support personnel • the GMP and regulatory requirements to all appropriate staff	• Evidence of communication Responsibilities and authorities which are: • defined and documented • clearly communicated throughout the organization	Schematic 1 Schematic 5 Schematic 6

Clause 5.6 Management review

Senior management must periodically review the QMS to ensure it remains effective and to assess improvement opportunities. This should be done in the context of improving the performance of the whole organization.

There are no 'extra' PS 9000 GMPs within this clause. There are important GMP principles in this area, but they are adequately expressed in ISO 9001 and ISO 9004.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Quality policy and objectives • Quality audit results • Product quality information and conformity data • Opportunities to improve • Feedback from customers • Process performance information • Corrective and preventive actions • Changes that might affect the QMS • Previous QMS reviews	Processes which: • review and evaluate the performance of the QMS • assess whether the QMS requires improvement • evaluate ***beyond*** the QMS itself, to that of the whole organization – its activities, performance and efficiency	• Reviewed quality policy and objectives • Information for strategic/ organizational decision-making Actions to: • communicate findings of review • improve the QMS • improve processes • improve products • address resource needs	Schematic 1

General Synopsis - Clause 6 Resource management

The provision of all resources, including people, infrastructure, work environment and information, needed for operation and improvement of the quality system to assure compliance with the requirements of customers.

Clause 6.1 Provision of resources

It is important to have processes, which determine and provide the resources needed by the organization.

Reasons for the 'extra' GMP requirements

Gaining certification to PS 9000 requires a full and thorough determination of resource requirements. This will enable the implementation of a QMS that satisfies the expectations of the pharmaceutical customer, with the benefits of continuous improvement and customer audit successes.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• QMS process requirements • Process information, data and requirements (people, premises, equipment, etc.) • Current organization people, premises, equipment • PS 9000 specific additional requirements	Processes which: • identify and appoint sufficient personnel • provide resources needed to improve customer satisfaction • provide enough resources to fulfil the requirements of PS 9000	• Defined organization structure and personnel and responsibilities • Adequate personnel to enable improvement programmes and focus on customer requirements • Quantified assessment of resource needs • Authorisation to procure resource	Schematic 1 Schematic 2

Clause 6.2 Human resources

Determine, provide and develop people to support the organization's quality policy and objectives

Reasons for the 'extra' GMP requirements (refer to PS 9000 clause 6.2.2 Competence, awareness and training)

GMP is fundamental to effective control of product quality and requires that GMP training be provided on an ongoing basis. Pharmaceutical customers look for evidence of this at their suppliers.

Cross contamination in packaging can lead to the patient being given the wrong medication with fatal consequences. When items are not manufactured using controlled systems the chance of a mix-up or print error is significantly greater, and the risk cannot be accepted by the pharmaceutical industry.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Identified business processes • Available people to carry out processes • Required competencies/level of training for QMS processes • Recruitment requirements: education, training, skills and experience	Processes which: • identify training and awareness needs (gap analysis) • deliver training and awareness programs • evaluate effectiveness of training and awareness • ensure training covers GMP, the risk and danger of cross-contamination and the importance of following procedures • ensure periodic refresher training is provided	• Defined and documented GMP training schedule Records of: • training • personnel information • curricula vitarum (CVs) • individual development plans	Schematic 1 Schematic 6

Clause 6.3 Infrastructure

Appropriate equipment, premises, services and environment are fundamental requirements of GMP.

Reasons for the 'extra' GMP requirements

Packaging defects, including mislabelling/mix-ups, are the major cause of approximately 25% of defective medicines and batch recalls (see Annex B 3). It must be emphasized that the causes of this problem are not solely attributable to the packaging supply industry since all parts of the supply chain and manufacturing process can be implicated. This also includes the distribution from the supplier to the customer, during use in the customer's processes and also the final market distribution.

Whilst the product should be designed to minimise/avoid contributing to the risk, the infrastructure of manufacturing and support processes at the supplier must also be designed, maintained and operated in compliance with the principles of GMP to assure product security.

It is because of the continuing high proportion of market recalls that are caused by defective packaging that pharmaceutical supplier audits will always assess how the infrastructure may influence product contamination.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Business process requirements for premises, equipment, utilities and other services including hardware and software • Maintenance manuals and schedules • Regulatory requirements	Processes which: • identify, provide and maintain premises, equipment, utilities and other services including hardware and software and transport • ensure that GMP requirements are incorporated to avoid product contamination	• Adequate premises, facilities, equipment and services • Internal reviews and customer feedback • Records of ongoing maintenance and review • Action plans (short and long term) • Cross-contamination avoidance	Schematic 2 Annex A: Segregation controls

Clause 6.4 Work environment

The work environment is critical to ensuring not only product conformity, but also the ability and desire of people to perform effectively.

Reasons for the 'extra' GMP requirements

Preventing contamination of medicinal products may require that the components be manufactured under particular standards of cleanliness, which could ultimately involve cleanrooms (i.e. controlled environments). These enable the pharmaceutical product and patient to be protected. This may apply even when the components undergo a cleaning process at the pharmaceutical manufacturer's site.

For some product contact components, microbial contamination levels (the bioburden) need to be kept at the lowest levels possible. This still applies even when the pharmaceutical processing involves a sterilization operation.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Categories/standards for environmental conditions • Product/manufacturing processes • Customer requirements • Information from ongoing environmental monitoring • People needs/ consideration • Regulatory requirements	Processes which: • identify necessary work environment • identify factors needed to ensure products meet requirements • manage and maintain work environment including cleaning, validation and processes • incorporate appropriate 'cleanroom' conditions for the type of product being made	• Appropriate environment for product being made • Records of environmental monitoring, validation and cleaning	Schematic 2 Schematic 5 Annex A: Risk assessment

General Synopsis - Clause 7 Product realization

Making product involves many interrelated processes, the inputs and outputs of which should be analysed and managed.

Clause 7.1 Planning of product realization

Management should plan the processes needed for product realization.

There are no 'extra' PS 9000 GMPs within this clause. There are important GMP principles in this area but they are adequately expressed in ISO 9001 and ISO 9004.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Quality requirements for the product • Product specifications • Customer requirements • Product requirements – validation, monitoring, test criteria. • Resource requirements specific to the product	Processes which: • plan the production processes • plan the support processes • manage changes • control process/product validation	• Quality plan • Clearly identified processes • An operating plan to manage processes • Identified resource requirements to support the operation and monitoring of processes • Change procedure and records • Validation records	Schematic 2 Schematic 3 Schematic 4 Annex A: Change control Validation (and Qualification)

Clause 7.2 Customer related processes

The organization should have effective processes for communicating with its customers and other interested parties.

Reasons for the 'extra' GMP requirements (refer to PS 9000 clause 7.2.3 Customer communication)

The pharmaceutical industry is heavily regulated by regulatory authorities, throughout the world. Companies are required to obtain a marketing authorization (MA)/ Product Licence (PL) to place a medicinal product on the market. The application for an MA/PL must be supported by extensive data including information on the packaging materials to be used. Companies are not at liberty to make any changes to the product, its components or its method of production without approval from the regulatory authority. The licensing of pharmaceutical products requires that the pharmaceutical companies inform government regulators of virtually all changes. They are not at liberty to change any registered product details without going through an extensive and lengthy submission process.

One particular reason for this communication process is that changes can require trial work (e.g. stability trial) at the pharmaceutical company or other actions, such as machine alterations, with implications for design and planning. In order to give due consideration to each proposed change, there should be a clear agreement between the pharmaceutical customer and organization of what communication is required for various types of change.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Customer stated requirements • External market data • Statutory and regulatory requirements	Processes which: • enable communication with customers (about product information, sales enquiries, complaints, etc.) • review the customer's order, product requirements before products are supplied (e.g. contract review) • require change control measures to be in place to record and monitor changes to processes • review related information – market research, competitor analysis, statutory requirements • specifically identify those types of changes which require prior approval by, or notification to the customer	• Defined product requirements • Documentation denoting customer approval • Effective data exchange covering products, amendments, feedback and complaints • Possible inputs to management planning process (e.g. resource/ machinery implications) Records of: • customer communication (e.g. product specifications, order confirmations, complaint investigations, etc.) • order/product review	Schematic 2 Schematic 3 Schematic 4 Annex A: Change control

Clause 7.3 Design and development

Planning and controlling design and development activities are fundamental to making product that fully meets the requirements of customers.

Reasons for the 'extra' GMP requirements (refer to PS 9000 clauses 7.3.1, 7.3.2, 7.3.5, 7.3.6 and 7.3.7)

The organization often has specialist knowledge regarding product design that can assist in evaluating risks to the end user or patient. This would normally form part of customer/organization communication at the product development stage. Technical data from the design and development stages of a component may be required as part of the pharmaceutical company's submission to regulatory authorities when applying for permission to market a medicinal product. This is mandatory for a component that will be in physical contact with the medicinal product, as the composition of the component material can influence the medicinal product's composition and stability and the safety of the patient.

The availability of validation documents at this stage gives recorded assurance that the design produced has been thoroughly tested and is suitable for long-term production. This, in conjunction with the testing and approval of samples by the customer, enables the design to progress into production in a formal controlled manner.

Similar controls are expected when design and development activities are involved in making modifications to the product or production methods. It is mandatory that the details of the medicinal product lodged with regulatory authorities are accurate and maintained ('The Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2002,' Article 5 European Commission Directives 2003/94/EC and 91/412/EEC).

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
Internal inputs, e.g. • competence requirements for people performing design and development • records and data on existing processes and products • outputs from other processes External inputs, e.g. • customer/marketplace needs • user input to achieve robust design and development • statutory requirements • international standards • industry codes of practice • other requirements for safe operation, handling, storage • environmental/disposal constraints for the products or processes	Processes which: • control planning the design and development of products • control product design and development • control production process design and development • evaluate potential risks of the product design to customer and ultimately the patient • provide technical/material data to the pharmaceutical customer and/or medicinal regulatory authorities and to notify of any changes arising from the supply chain • cover testing, retaining and gaining customer approval of samples resulting from new product designs • produce and provide validation documentation to the customer • control modified or refurbished equipment and tooling and product	• Reports of validation/tests • Information for other functions (e.g. purchasing) • Data to enable verification of design and development process outputs to the process inputs • Evidence of customer approval of changes Identification of: • review, verification and validation appropriate to each design and development stage • responsibilities for design and development Documented: • change control • risk assessments • specifications for product, process, material, testing, safety characteristics • training requirements and records	Schematic 2 Schematic 3 Annex A: Change control Risk assessment Validation (and Qualification)

Clause 7.4 Purchasing

Management has a responsibility to define and implement effective purchasing processes to ensure purchased materials meet stated requirements.

Reasons for the 'extra' GMP processes (refer to PS 9000 clauses 7.4.1 and 7.4.3)

The pharmaceutical company needs to know where all parts of a manufacturing process are performed. These details, including sub-contracted elements, may be 'registered' as part of the marketing authorisation, and thus need customer approval. The pharmaceutical company must be satisfied that there are no other risks to product security or quality involved with subcontracted parts of the manufacturing process. Product quality can also be affected by many contracted out services (e.g. cleaning, maintenance, calibration), and evidence of good management and control of these is expected.

Quarantine of purchased product until approved for use eliminates the risk of using unapproved or unsuitable material.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Product specifications • Contracts, warranties, prices • Logistic requirements • Product identification and traceability • Supplier performance data – quality, price, delivery, response • Audits of suppliers • Commercial dependability of suppliers • Supplier's capabilities • Certification	• Purchasing process that satisfies the organization's needs whilst considering costs and other appropriate performance measures Processes which: • control suppliers • enable verification of purchased products Processes which: • gain customer approval of subcontracted parts of the manufacturing process • control contracted out services that can affect product quality • quarantine purchased product until approved for use	• Co-ordinated purchasing information, e.g. requirements for approval of product, supplier's procedures, processes and equipment, other personnel or quality systems requirements Records of: • inspection checks made on incoming items • the release (for acceptable items) or rejection (for unacceptable items) of purchased goods Evidence of: • a supplier approval scheme in place (e.g. an approved supplier list and audit reports) • the monitoring of subcontractors	Schematic 3 Schematic 3 (a) Schematic 4 Annex A: Change control

Clause 7.5 Production and service provision

Production (or service provision) where key elements are the control and validation of production conditions, and traceability of materials and equipment used.

Reasons for the 'extra' GMP requirements (refer to PS 9000 clauses 7.5.2, 7.5.3, 7.5.4 and 7.5.5)

The special needs of pharmaceutical packaging mean that certain processes are critical to product quality, safety, and function. These 'critical' processes require validation to be certain that they function reliably and consistently. It is important that validation is performed as necessary during development and on start-up in production and also performed when there are changes to production processes.

Identification and traceability is essential to enable a reconstruction of events when investigating a quality problem. To be able to investigate any problem with a medicine in the marketplace, the pharmaceutical company is obliged to retain records for (at least) a year beyond the life of the medicines it is making. There is a corresponding responsibility on the part of the component suppliers to be able to support any such investigation through its retained records of manufacture e.g. traceability of materials, equipment and personnel involved in the components manufacture (see Annex A).

The pharmaceutical company places trust in its suppliers to protect its property. The main consideration is protection from theft and subsequent fraudulent use, unauthorized supply and use in counterfeit medicines. This particularly applies to artwork or data in electronic form due to its ease of transmission.

Following manufacture under controlled conditions, the continuing protection of the product is important to prevent damage and contamination.

Accurate identification of the final product is vital in order to minimise risk of admixture both within the organization and during receipt at the pharmaceutical company. This is always important, but particularly so where there are direct 'supply to line' arrangements, with minimal goods-inwards checking in place at the pharmaceutical site.

Process Inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Raw material batch records • Specifications – product, materials • Manufacturing method/process instructions • Provision of suitable resources – machinery, people • Training of process operators • Environmental instructions • Packing instructions • Validation plans	Processes which: • ensure production/service provision activity is under controlled conditions, i.e. suitable equipment with appropriate monitoring and controls • ensure validation of processes where the resulting output cannot be checked by subsequent measurement • ensure continual improvement of realization processes, e.g. reducing waste, improving methods, preventing problems, improving yield • validate critical processes that could affect product quality including specific examples and revalidation requirements • ensure identification and traceability of materials and equipment used throughout production • protect and care for customer property (e.g. moulds, artwork, electronic data) • protect and clearly identify the final product	• Continual improvement activities Records of: • production (e.g. batch sheets) • process validation/ revalidation • material usage • warehouse and dispatch transactions • product identification	Schematic 3 Schematic 4 Schematic 5 Schematic 6 Schematic 7 Annex A: Counterfeit Admixture Segregation controls Validation (and Qualification)

Clause 7.6 Control of monitoring and measurement devices

Control of such equipment is critical to good control of manufacturing processes.

There are no 'extra' PS 9000 GMPs within this clause. There are important GMP principles in this area but they are adequately expressed in ISO 9001 and ISO 9004.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Outputs from design and development activities - e.g. design tolerances • Product specifications • Customer requirements • Calibration standards	Processes which: • determine the monitoring/measuring and equipment needed • ensure identification and protection of equipment • control calibration • control the monitoring/measuring activities to verify products (and production processes) • control nonconforming equipment/device • control the checks on computer software when used in monitoring and measurement	• List of monitoring/ measuring equipment • Status labelled equipment • Calibration records Procedures for: • monitoring • measuring • calibration	Schematic 5 Schematic 6

General Synopsis - Clause 8 Measurement, analysis and improvement

Measurement information is vital to sound decision making. The organization should monitor its processes, products and all aspects of the QMS in order to provide data for continual improvement in performance.

Clause 8.1 Measurement, analysis and improvement: General

These activities are of such importance that careful planning is needed on how it shall be performed.

There are no 'extra' PS 9000 GMPs within this clause. There are important GMP principles in this area, but they are adequately expressed in ISO 9001 and ISO 9004.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Process analysis work • Company objectives • Customer needs	Processes which: • plan how to monitor/measure processes and products • develop suitable improvement mechanisms • control the implementation of the above	• Formal measurement systems • Statistical techniques • Procedures • Reports	Schematic 3 Schematic 6

Clause 8.2 Monitoring and measurement

Monitoring the satisfaction of customers, other interested parties, monitoring products, processes and systems.

Reasons for the 'extra' GMP requirements (refer to PS 9000 clause 8.2.4 Monitoring and measurement of product)

ISO 9001:2000 requires quality designed and system compliant processes, and complimentary to this in PS 9000 is the need for processes to be operated in a way which maintains product security and avoids contamination (see also 5.2 and 5.3).

Since process assessment is often based upon product samples, these must be representative of the process with the sampling scheme defined. Whilst samples examined on the line are considered secure, a contamination or admixture risk exists if there are inadequate controls on the security handling of samples removed from the production area.

To avoid this risk, PS 9000 specifically requires the secure disposal after examination, of all samples that have been removed from the immediate production area and additionally stipulates they cannot be reincorporated into the product (see also 'Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2002', Chapter 5.54)

It is generally known that processes work better when they have stabilized following start-up and are running continuously. Hence when equipment breaks down or there is an unscheduled interruption that stops the process, quality variability can occur and additional quality monitoring is required on recommencement.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Customer surveys • Focus group data • Feedback on products • Customer requirements/contracts • Market needs • Delivery data • Financial data/costs of nonconformities • Market benchmarking and best practice	Processes that identify (and implement) suitable methods to: • monitor and measure customer satisfaction • monitor and measure the satisfaction of interested parties (other than customers) e.g. employees, investors, suppliers and society • monitor and measure production processes • verify that product is meeting requirements at appropriate stages of production Processes which: • control internal auditing – programme, procedures, auditors • define a statistically valid sampling scheme • prevent samples from being returned to a batch - keep separate then destroy/dispose securely • apply additional monitoring, after a machine breakdown or stoppage	Corrective actions: • when processes fail to achieve planned results • in response to customer information (complaints, surveys etc.) Records of: • product monitoring and measuring activities (e.g. test reports) • audit reports/actions/ follow-up actions Feedback to: • customers • other interested parties	Schematic 5 Schematic 6

Clause 8.3 Control of nonconforming product

It is essential that product not meeting specification be segregated from suitable product until corrected, destroyed, or reclassified.

Reasons for the 'extra' GMP requirements

There is an assumption that all processes work efficiently without problems and that material will be uniform, consistent and fully compliant with the specification. In reality problems can occur resulting in short periods when the process may not be in control and produces nonconforming product. This can result in problems in the market, customer complaints and returned product.

For GMP reasons and good customer relations, the pharmaceutical industry needs to be aware of any quality issues during the manufacture of its packaging materials. The customer should always be notified of nonconforming or associated product, which may have already left the organization, so that the pharmaceutical company can consider any implications to processes, stock or packed product.

Suspect product retained by the supplier or returned from the customer, requires formal GMP controls on its secure storage, handling and remedial rework actions, including a risk assessment to ensure that the reworking process does not introduce further quality problems.

All of these issues require good documentation to provide traceability over time and to reconstruct events if required.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Products not meeting specification • Customer rejects or complaints • Results of inspections or in-process testing activities • Observations by members of staff	Processes which: • review identified nonconforming product and actions to be determined • control the secure physical (or electronic) quarantining of items/data • control rework • re-verify or inspect corrected product (e.g. following rework) • notify customers if problems are found after delivery • identify and control any batches of product that are related to any nonconforming product that has been returned from the customer	• Documented risk assessment for any batches that are reworked to recover stock from a rejected or quarantined batch • Records of customer communications/ notifications • Defined responsibilities/ authorities for dealing with nonconforming product Procedures: • detailing what to do in the event of nonconforming product being detected • for handling rejections and complaints • for handling recovery/ reworks	Schematic 3 Schematic 5 Schematic 6 Annex A: Risk assessment

Clause 8.4 Analysis of data

In addition to monitoring activities, the sensible analysis and interpretation of data is critical to enable good decisions to be taken and business improvements to be made.

There are no 'extra' PS 9000 GMPs within this clause. There are important GMP principles in this area, but they are adequately expressed in ISO 9001 and ISO 9004.

Process inputs	Required processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Outputs from Monitoring and Measurement (8.2) and other processes • Data from relevant sources	Processes which determine the data required, collect and analyse it, to: • evaluate the QMS • monitor and measure its suitability and effectiveness • improve it Processes for: • root cause analysis of problems • analysis of data which uses valid methods and appropriate statistical techniques • decision-making based on results of logical analysis, balanced with experience and knowledge	Trends, information and data about: • customers • suppliers • products • processes • QMS	Schematic 6

Clause 8.5 Improvement

Continual improvement of the QMS is at the heart of the ISO 9001 and PS 9000 philosophy.

There are no 'extra' PS 9000 GMPs within this clause. There are important GMP principles in this area, but they are adequately expressed in ISO 9001 and ISO 9004.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Audit results • Quality data • Quality policy and objectives • Management reviews • Previous corrective and preventive actions • Validation data • Process and product measurements • Data from self assessments • Requirements from customers/interested parties • Financial and service data	Processes to assess ***potential*** nonconformities, study their effects and: • evaluates the need to take preventive action • develops suitable actions to eliminate causes • examines the effectiveness of them Processes to detect ***actual*** nonconformities which: • evaluates the need to take corrective action • develops suitable actions to eliminate causes • examines the effectiveness of them Process that plans for losses sustained by the organization in order to mitigate their potential effects (e.g. fire or weather damage)	• Risk assessment reports • Improvement plans • Procedure for nonconformance management • Preventive and corrective actions taken Records: • of these actions • of the effectiveness of these actions	Schematic 1 Annex A: Risk assessment

General Synopsis - Clause 9 Contamination control

The capability of facilities and equipment, achieved through their design, location, construction, and maintenance, to minimise the risk of process errors and avoid cross-contamination affecting process and product.

Reasons for the 'extra' GMP requirements

The highest quality priority of the pharmaceutical industry is for the component material to meet specifications and meet or exceed defined GMP controls.

Pharmaceutical product safety, efficacy, and stability can all be compromised by chemical contamination of the primary packaging material. Particulate contamination may reduce the visual quality of the product as well as interfere with its function; it can also be a 'carrier medium' for microbial contamination with a potential infection risk to the patient.

GMP controls and procedures provide the safeguards to prevent cross-contamination (admixture). A single 'rogue' component within a batch could create a life-threatening hazard to the patient (see Annex A - Admixture).

Since contamination can take many forms and be introduced anywhere, preventive measures (e.g. good facility design, Standard Operating Procedures, training, area clearance, segregation controls, etc.), must be applied throughout the facility. In addition, similar measures should be included in the design of the process.

PS 9000 specifies GMP requirements across the manufacturing operation as well as the environmental conditions needed for processing packaging materials for use with medicinal products. Three different cleanliness categories are defined dependent upon the material and its application.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Specification for design of new facilities, processes, equipment and environment • Specialist pest and contamination control • Customer requirements • Standards for environmental conditions	Processes which identify/control: • operating areas/activities that contribute to contamination • environmental category appropriate to the product (agree with customer) • handling of material and segregation controls • good practices to avoid contamination during operation, support, and maintenance • pest control • cleaning procedures and checks • training of staff and visitors in contamination avoidance and standards of dress • management and control of waste material • line clearance • change control • environmental monitoring	• Incidents/audit reports • Drawings (e.g. floor plans) • Appropriate environmental category established for product (agreed with customer) Procedures to: • control processes • monitor and control environments Records of: • processing • cleaning schedules • cleaning • training • material disposal	Schematic 3 (a) Schematic 4 (a) Schematic 5 Annex A: all parts

General Synopsis - Clause 10 Printed materials

The application of controls specific to different types of printed materials in order to ensure identity, maximise product security and prevent cross-contamination. It includes the use and verification of various types of security code systems and associated software.

Reasons for the 'extra' GMP requirements

This section intentionally follows the section on Contamination Control because it covers in depth the specific GMP requirements for securely printing components to prevent admixture and cross-contamination.

The risk associated with admixture is that an incorrect printed component, often similar in design to the correct component, will be used to label or contain the pharmaceutical product. This can lead to the patient using the wrong product or using it in an inappropriate manner.

(For more detail refer to Annex A - Additional Explanations of Key Concepts).

There are many stages in the manufacture of printed materials, all of which can benefit from good control procedures. The advantage of security bar codes systems is that automated detection checks can be incorporated into key process stages at the supplier organization and customer.

The pharmaceutical industry believes that, although security bar code systems can approach 100% security confidence, they are not a substitute for other good manufacturing practices.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Product requirements including leaflets, cartons, reel-fed materials, labels and product printing using digital technology • All products made by assembly of sub-components (e.g. label/ leaflet combinations) • Graphic design (e.g. inclusion of security barcode in origination/ artwork) • Machine design/ operational settings • Customer requirements and agreement on quantity tolerances • Specifications for reel-fed materials including splice joins and how reel materials shall be identified • Electronic and/or mechanical machine enhancements (e.g. optical, double sheet detectors) • Packing and storage specifications	Processes which control: • the issue and allocation of security barcodes • the set-up and use of scanners to reject unsuitable material • equipment that can, under certain conditions print with missing colours or text • any overprinting process and its verification • the scanning and off-line verification of barcodes when necessary and challenge of the effectiveness of scanning • the checking of splices in reels • counting/sequential numbering Processes which: • prohibit the replacement of missing labels on a reel • prevent partially printed or blank leaflets • ensure that the line clearance processes include computer artwork file removal (where applicable) • ensure that digital file access is secure, validated and prevents accidental use of incorrect origination/artwork files • ensure secure assembly (e.g. label/ leaflets) with secure production of all sub-components • control validation activities • control packing and storage activities	• Register of security barcodes • Accurate counts detailed on the outer carton labels • Traceability of product (audit trail) • Good packing line performance of components when in use by customer (complaints/ feedback) • Established settings to ensure reproducibility Verified and securely printed product that is: • free from admixture • free from missing print/ errors • accurately counted • correctly assembled (e.g. label/leaflets) Systems proven to be effective, records of: • validation and qualification • verification checks • scanning rejects and review of them • equipment testing	Schematic 4 Schematic 5 Schematic 7 Annex A: Admixture Identification and traceability Line clearance Validation (and Qualification)

General Synopsis – Clause 11 Origination/artwork

The generation of new or amended origination is the start of the manufacturing process for printed items and requires control from concepts to origination and through to final printing. All origination and printed media must be controlled to ensure security and integrity of the final printed product.

Reasons for the 'extra' GMP requirements

Both packaging suppliers and pharmaceutical companies have experience of common problems that occur in the preparation of origination/artwork, which could be avoided by good manufacturing practices.

Origination problems occur in the same way as those for printing of the packaging material and GMP preventive controls to address these, follow the same pattern, (e.g. defined work areas, segregation, line clearance, recorded checks, etc.).

Electronic systems are widely used to produce pharmaceutical origination; it is important that the systems are secure and have controlled access (see PS 9000 4.2.3). Since origination/artwork is comparable to a design process, errors built into the design cannot be removed by later inspection and therefore quality, i.e. GMP, must be built into the creation process. This starts with unique identification of the material and identity checks at all process stages within the organization and during transfer to the customer.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• All origination material • Customer requirements • Customer designs/ specifications • Customer component codes	Processes which: • seek agreement with customer (where required) to sign off a copy of the final proof before production is authorized • require the identification of all origination material (e.g. ensuring that proofs are marked with component numbers and issue dates) • control origination materials and covers storage, issue, return and line clearances • ensure understanding of how codes are used by customers and application of appropriate control measures • require the checking of copy (electronic or hard output) against original specifications and customer approved versions	• A system of control for artwork that prevents the inadvertent use of incorrect items Records of: • approval by customer (e.g. approval of artwork) • in-process checks performed on artworks • line clearances • checks made on in-house produced items against a customer approved master • customer approved masters	Schematic 3 Schematic 4 Schematic 4 (a) Schematic 5 Annex A: Change control Identification and traceability Line clearance

General Synopsis – Clause 12 Print impression media

Life-cycle management of print impression media is essential and should incorporate good communication with the customer to understand the design and application of the product. Key is the traceability from customer design through to delivery of all printed items.

Reasons for the 'extra' GMP requirements

Printing of packaging materials is normally a three-stage process, involving creation of the origination/artwork, production of the print impression media, i.e. 'the plates' and lastly use of the plates to create the text and images on the packaging material.

The GMP requirements for all these stages must therefore be very similar since they have the same objective, i.e. compliance with the customer's specification and avoidance of cross contamination/mix-ups.

Print designs can be very similar and difficult to differentiate, particularly with modern company 'house' designs or for a family range of product presentations. Print impression media must therefore be strictly controlled with unique identification codes, and checks incorporated into all usage, together with secure and controlled disposal of impression media when eventually superseded. For more information see Annex A - Additional Explanations of Key Concepts. Also 'Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2002', Chapter 5.43.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• All printed items • All origination material (e.g. films, electronic files) • Print impression media (e.g. plates, gravures, etc.) • All sets of printing plates • Customer approved design (e.g. customer issued specification, or a customer approved proof) • Design requirements for a multi-plate set (e.g. a two colour design, or a design that, for production reasons. needs to be split across two print stations) • Requirement for a design change • Any revised printed products/designs (e.g. a new customer specification) • All revised or obsolete items	Processes which: • control all media (e.g. identification, checking, issue and return of plates) • ensure that all plates of the set are identified and used • ensure that where one or more plates in a set are common to several items (e.g. a patterned background that is used for a range of label designs), controls exist to ensure that shared and unique parts of a set are used appropriately • check all printed output against approved specifications during set-up, to ensure that the correct item is being made at the correct quality • control change including records of changes or revisions • ensure that identification and authorisation of print media changes is as rigorous as the initial origination • prevent use of print media whilst undergoing or awaiting change • render unusable any print media declared obsolete • ensure that when plates are replaced within a set, adequate controls exist to prevent error • control the quarantine and destruction of plates and other print media (e.g. segregated storage, quarantine labels, etc.) • require a formal approval before the operator is allowed to run the press	• Documentary evidence (e.g. that a full set of matched plates was signed out to the job, or in-process checks that all colours are present in the printed item) Records of: • checks carried out on media • plate issue and return • identity changes and item revisions • approval to run (e.g. a signed pass sheet, first off samples etc.) • revision of items • disposal of obsolete items once revised	Schematic 3 Schematic 4 Schematic 4 (a) Schematic 5 Annex A: Admixture Change control Segregation controls

General Synopsis – Clause 13 Print and conversion processes

This clause covers the GMPs required to ensure adequate control throughout the make-ready and production processes of printed materials

Reasons for the 'extra' GMP requirements

This clause addresses a number of specific aspects of the print process that are associated with known risk areas, i.e. risk of serious print errors and/or cross-contamination.

The details in this section of PS 9000 represent current best practice, routinely seen by pharmaceutical auditors during audits of progressive suppliers who are aware of the GMP needs of the pharmaceutical industry. This means that the most dangerous of practices, for example 'Gang printing', is excluded because of the historical association with mix-ups. While it is accepted that the risk might now be statistically low, it is not zero and the consequences cannot be accepted by the pharmaceutical industry. (For more information see Annex A - Additional Explanations of Key Concepts).

However, in certain situations for example, using printed material to set-up the machine, or where total line clearance may be impractical due to the machine technology, an approach involving a documented assessment of risk with suitable alternative security checks introduced, is allowed.

Process inputs	Processes	Process outputs and evidence	Cross refer to Schematic/Annex
• Customer specification/design requirements • Any special customer agreed requirements • Suitable equipment, materials, trained staff • Braille specifications where required	Processes which: • limit the use of printed material for machine set-up purposes • involve a risk assessment of changeover systems (e.g. where the nature of the machinery does not permit a total line-clearance) • control any samples taken • verify any changes of print media before continuing production, to ensure consistent quality • ensure when new plates are made from a new source file, the subsequent work is treated as a new batch • ensure when new plates are made from a fixed/approved file, the subsequent work must undergo a first off check • ensure any Braille symbols meet specification • control storage to ensure security, integrity and traceability • control the holding of stock (when contractually agreed) • exclude gang printing due to potential for cross-contamination	• Good logical flow of materials and clear segregation Records of: • production controls/ checks • all replacement of plates • samples taken and disposition	Schematic 4 Schematic 4 (a) Schematic 6 Annex A: Admixture Risk assessment Segregation controls

The Institute of Quality Assurance
Pharmaceutical Quality Group

PS 9004

A Guide to the GMP requirements
of PS 9000:2001 Pharmaceutical packaging materials

ANNEX A - ADDITIONAL EXPLANATION OF KEY CONCEPTS

PS 9000 GMP related text is reproduced in blue

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Admixture

Ref:	Definition/References	Explanation
3.1	**PS 9000 Definition** The presence within the batch of one or more items not of the nature of that specified by the product description, i.e. cross contamination. Other terms used include 'mix-up', 'rogue' or 'stranger'	Data supplied by the MHRA on their investigations into defective medicine shows that 12 % involve mislabelling in its widest sense (i.e. the product container is printed, or labelled, cartoned or has a descriptive leaflet which is either incorrect or has text which is not compatible with the use of the product), see Table Annex B3. The source of admixture can originate at the supplier, the pharmaceutical manufacturer and the distribution chain or at the point of dispensing. Some causes might be outside the control of the pharmaceutical manufacturer, e.g. the pharmacist dispensing the product. However the pharmaceutical manufacturer needs to take all possible precautions to prevent mix-up, including: • bar coded items (and detectors) • visual codes • colour/text differentiation • procedural controls at supplier (i.e. the focus of PS 9000) and at the pharmaceutical manufacturer (i.e. GMP) • physical segregation Mislabelling of the medicinal product introduces the risk that the patient will: • use the wrong product • use the product in an inappropriate manner Furthermore, there can be serious damage to market confidence in the company's products or pharmaceutical products in general. Product recalls are very serious, and may cause withdrawal of a critical medicinal product, otherwise urgently needed in the market. However, the risk of causing patient harm cannot be over-emphasised and should never be forgotten. One historically recognised cause of admixtures is via 'gang printed' sources where two or more different designs are printed on the same matrix at the same time. This conflicts with a strict GMP principle, which can
	PS 9000 References	
3.14	Cross-contamination	
6.2.2	Competence, awareness and training	
6.3	Infrastructure	
8.3	Control of non-conforming product	
9.1.7	Line clearance (cross-contamination control)	
9.1.8	Segregation controls (cross-contamination control)	
9.1.11	Personal hygiene and security	
10.1.5	Converter's flap code	
10.2	Reel fed materials (general)	
10.3	Reel fed self-adhesive labels	
13.5	Gang Printing	

Ref:	Definition/References	Explanation
		be paraphrased, as “it is bad practice for a process to deliberately mix product in the expectation that technology or procedures can and will later differentiate and separate them”. In the USA gang printing can be permitted according to 21 CFR 211.122(f) where “the labelling from gang printed sheets is adequately differentiated by size, shape or color”. This contrasts with the view in Europe where it is known that colour differences have proved inadequate to prevent mix-ups and best practice therefore prohibits gang printing. These two approaches might seem contradictory but the requirement detailed in PS 9000 is strictly in keeping with Europe’s view of ‘Risk Assessment’ where the possibility of a critical admixture, even though small, cannot be accepted.

Change control

Ref:	Definition/References	Explanation
3.7	**PS 9000 Definition** A process that ensures changes to materials, methods, equipment and software are properly documented, validated, approved and traceable.	The development of a new component or material is a period of extensive design change, with controls and liaison between customer and supplier. This results in specifications approved by customer and supplier, covering raw materials, sources, processes, and tests. Later in the product life-cycle, variability can occur through uncontrolled changes.
	PS 9000 References	
3.31	Risk Assessment	The following are examples of changes which could affect component dimensions, constituents or other characteristics (e.g. surface finish), creating operational problems for the customer, or incompatibility during the shelf-life of the medicinal product: • refurbishment of injection moulds • use of a different production line • raw materials sourced from a new supplier • reprogramming of equipment controlling computers • replacement equipment To avoid the risk of uncontrolled changes PS 9000 requires the use of a Change Control process which: • documents all planned changes • assesses potential problems (e.g. Risk Assessment) • revalidates where required • includes an independent change review and authorisation • notifies the customer and schedules the introduction of the change • provides traceability on the change • retains a record The bottom line of Change Control is to plan and document change to avoid potential issues that could affect supplier and/or customer. For further information see ‘Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2002’, Section A15.43, A15.44.
4.2.3	Control of documents (electronic)	
7.2.3	Customer communication	
7.3.2	Design and development inputs	
7.3.7	Control of design and development changes	
7.5.2	Validation of processes for production and service provision	
9.1.6(b)	Materials (starting, ancillary and intermediate)	
12.3	Copy/design change	
13.4	Replacement print media	
	PS 9004 References	
Annex A	Risk assessment	
Annex A	Validation	

Ref:	Definition/References	Explanation

Counterfeit

Ref:	Definition/References	Explanation
3.13	**PS 9000 Definition** A copy produced without authority with the intention of deceiving a user as to its true origin	Most people will have heard of counterfeit consumer products, such as watches and perfumes, but may not be aware that in some parts of the world there is a serious problem involving counterfeit medicinal products. The scale of the problem can amount to many billions of dollars, and governments are even sensitive that this practice might eventually pose a serious risk to the normal commercial supply of medicinal products. This is evidenced by the May 2003 FDA directive to pharmaceutical companies supplying the US market, requiring notification within five days of the detection of a counterfeit product. In the UK the practice is rare but not unknown, as "the last example of a counterfeit product entering the legal supply chain was approximately 20 years ago". However data from the World Health Organisation, (WHO), shows that "between 1984 and 1999, there were 771 reports of counterfeit drugs, the majority (78%) of these reports came from developing countries". Similarly "a recent report from Russia showed that 12% of medicines in circulation were counterfeit products and it was as high as 40% in the Ukraine". (Reference 1). To illustrate the risk posed to the patient by counterfeit drugs, it is necessary not only to consider the level of incidents but also the lack of drug efficacy or potential toxicity of these products, e.g. for the years 2000-01, of the cases reported to the WHO, "43% had no active ingredients, while a further 21% had low content, 7% had the wrong ingredient and 24% were of generally poor quality" (Reference 2). It will be easy to understand that while the possible consequences of buying a counterfeit watch are simply disappointment or embarrassment, using a counterfeit drug may carry serious, or even fatal, health risks. Some counterfeit drugs are very crude copies of the original product while others are less so. However the counterfeiter is always keen to
	PS 9000 References	
5.2	Customer focus	
5.3	Quality Policy	
7.4.1	Purchasing process	
9.1.10	Waste material (cross-contamination control)	
11.1	Origination procedures and work areas	
12.1	Print impression media – General	
12.5	Quarantine and destruction	

Ref:	Definition/References	Explanation
		use ‘quality image’ packaging that is as close as possible to the original pharmaceutical packaging because people usually believe what is printed on the carton or label. For obvious reasons there is pressure from enforcement agencies that “the pharmaceutical industry, importers, distributors and consumer organization should adopt a shared responsibility in the fight against counterfeit drugs”. (Reference 2). In some markets “a variety of anti-counterfeiting measures have been put into place by pharmaceutical manufacturers, for example, the use of holograms and other devices on the packaging”. (Reference 1). It is therefore clear why the pharmaceutical industry attaches such importance to basic security of print media at the suppliers, to ensure that: • all print media is securely stored. • there is controlled access to the print media stores • obsolete and no longer required media is made unusable and disposed of securely • all waste and scrap material is stored securely and rendered unusable prior to disposal. (see 21CFR 211.122) By preventing access to legitimate print media, the packaging supplier removes the opportunity for the counterfeiter to use authentic and genuine materials, for the good of the pharmaceutical supplier, customer and product user. Reference 1 British Pharmaceutical Conference, Harrogate, UK, September 2003. Reference 2 International Pharmaceutical Federation Congress, Sydney, Australia, September 2003. Acknowledgement for the above quotations is made to The Pharmaceutical Journal (Volume 271, pages 453-454, 465-466).

Identification and traceability

Ref:	Definition/References	Explanation
	PS 9000 Definition There is no PS 9000 definition for identification	A fundamental requirement when an operational problem occurs at the pharmaceutical manufacturer, (e.g. material usage problem, market complaint, etc.), is an effective QMS, which assists problem resolution. Operational problems can occur for many reasons, but should the problem be related to a supplier's material, then it is essential that the total inter-company record system enables traceability of the material on site from delivery and during manufacture at the supplier organization. Through GMP guidance via the regulatory organizations, e.g. Medicines and Healthcare products Regulatory Agency (MHRA), all pharmaceutical companies are required to use unique and unambiguous lot numbers and material identification codes, since it is the cornerstone of traceability, avoids potential confusion or misunderstanding and allows referral to: • the delivery date and supplier • the quantity received • receipt check results • remaining stock • batch and market usage A requirement for medicinal products is that records are retained for at least one year after the expiry of the batch in which they were used. For this reason, and that packaging materials may not be used immediately, PS 9000 requires suppliers to keep quality records for at least "5 years from the last date of supply of the batch of packaging material". Similarly, to provide complete traceability, supplier's documented quality systems require: • unique material identifications, for raw materials used in the product, as well as for the product itself • records showing batch history (e.g. process dates, quantity made, in-process test results) • change control records • record retention system This system can then allow tracking back to the same quality data as that for the pharmaceutical
3.35	Traceability - The ability to follow data/records logically forwards or backwards within and between organizations, to allow reconstruction of events.	
	PS 9000 References	
3.29	Quality Records	
7.5.3	Identification and traceability	
7.5.5	Preservation of product	
8.3	Control of non-conforming product	
9.1.10	Waste material (cross-contamination control)	
10.1.1	Security barcode systems - General	
10.2	Reel fed materials (General)	
11.1	Origination procedures and work areas	
12.1	Print impression media - General	
12.2	Matched plates	
12.3	Copy/design change	

Ref:	Definition/References	Explanation
13.3 13.7	Retained samples Batched production and stock holding	manufacturer detailed above, e.g. • raw material data, quantity received, receipt test data • supply source details • where else the same batch of raw material may have been used • how it was stored • personnel employed on processing and testing • possible environmental monitoring data, (if relevant) • customer shipment data Whilst the main purposes of an effective identification and traceability system are to control use and to assist in problem analysis, the supplier also possesses the means to operate a continual improvement process, which aids company financial and quality efficiency.

Line clearance

Ref:	Definition/References	Explanation
3.19	**PS 9000 Definition** The assurance that a production facility (line), and its associated working area is completely cleared of all materials, waste, products, samples, documentation, etc. associated with the current production, prior to the introduction of new documentation and materials required for commencement of the next production run.	A fundamental requirement in the practice of avoiding mix-ups is ensuring that only the materials, documents, etc. as required for that product, are on a line or machine, or in a working area at any one time. This material or document has to be that allocated and issued for that particular batch or job. Virtually all investigations following a mix-up, focus on the batch that preceded the incident product, or was being processed or handled in the vicinity, e.g. an adjacent line. The obvious risk of inadequate line clearance is that once a rogue material is introduced into a batch it is virtually impossible to reliably detect and remove in subsequent operations. The only practical quality measure is therefore not detection, but prevention, using procedures, checks, counterchecks and training. The least serious effect of a mix-up is processing difficulties on the pharmaceutical manufacturer's packaging line, e.g. the rogue components are too large or too small to process properly and they block hoppers and feed chutes. However, even this can disrupt a smooth running process and cause product variability. The most serious consequences involve a rogue component or material, which is incorporated into the pharmaceutical manufacturer's product, with potential implications ranging from product instability to patient confusion on usage instructions and market recall. Line clearance is an essential element in product mix-up prevention and needs to focus on: • input materials on the line from the previous batch • samples and waste from the previous batch • documents on the line from the previous batch (e.g. process instructions or test procedures) Line clearance activities need to be documented and cover all areas, not just the machine or line, i.e.
	PS 9000 References	
9.1.7	Line clearance (cross-contamination control)	
10.7	Digital printing	
11.1	Origination procedures and work areas	
13.2	Changeover systems	
	PS 9004 Reference	
Annex A	Admixture	

Ref:	Definition/References	Explanation
		• the whole machine, including hoppers, conveyors, reject stations, etc. • the floor around the line • benches, cupboards, shelves, etc. around the line • pallets, etc. PS 9000 calls for a dual approach to line clearance, i.e. • a recorded line clearance at the end of each production run • an independent recorded check immediately prior to the next run. Similar security precautions are needed when there are temporary line stoppages to ensure that other operations, e.g. maintenance, do not accidentally introduce rogue materials, which, because the process is in the middle of a run, is thought to be secure.

Risk assessment

Ref:	Definition/References	Explanation
3.31	**PS 9000 Definition** A documented assessment of potential failures or faults arising from new or changed processes, materials, equipment or facilities, which could affect product quality, performance or use	Most companies will have experienced the situation where a response to a process problem, or a change, results in a second, sometimes more serious problem. Often, the secondary problem could have been avoided if the change or the original process problem had been given proper consideration and planning. This consideration is known as Risk Assessment, and its application is best explained by two typical examples:
	PS 9000 References (References to risk and/or risk assessment)	**1. Batch Reworking/Sorting**
4.2.3 (d)	Control of documents (electronic)	When tests revealed a 'cosmetic' defect in a printed component, reworking the batch introduced a critical 'rogue' component, due to inadequate rework area cleandown from the previous job.
7.3.1	Design and development planning	The initial defect was minor, but the ultimate consequences of an undetected rogue component reaching the patient could be fatal.
8.3	Control of non-conforming product	A risk assessment of the rework process must cover the areas specified in PS 9000 Clause 8.3. However, the rework/sorting process may introduce other GMP risks related to, e.g. infrastructure, competency, work environment, and so an assessment should consider risks of: • a mix-up with other materials • contamination or damage from further handling • incomplete rework due to poor training • difficulty in detecting the difference between good and bad product • inadequate defect description • poor lighting, poor job separation, poor labelling in inspection area • discontinuous sorting process (over several days or by different staff) • poor separation between sorted/unsorted material • poor labelling of sorted/unsorted product The risk assessment should include complete batch
9.1.1	General	
9.1.2	Facilities design	
9.1.4	Cleaning	
9.1.5	Pest Control	
9.1.10	Waste material (cross-contamination control)	
9.1.11	Personal hygiene and security	
9.2.1 d)	Minimum environmental conditions	
13.2	Changeover systems	

Ref:	Definition/References	Explanation
7.1.3.3 Annex A Annex A	**ISO 9004 Reference** Product and process validation and changes **PS 9004 References** Change control Validation	documentation, i.e. details of the product and problems, lot number and quantity, defects involved, deadline, etc. From this a suitable plan of rework can be generated which includes: • identification and segregation of the batch, (before, during and after sorting) • inspection area cleandown checks • special lighting needs, tools and equipment to assist rework • documentation of the sorting process, the objective and data collection form • training of staff (using a controlled example of the defective to illustrate the problem) • secure area for removed defectives • repackaging (and relabelling) of sorted product • area clean down, on completion and recorded defectives disposal • final process release check (matching that for a new batch) • records (of rework details included in batch file) • process revision (where practical) • notification to customers (where required) • completion reviews It is important that management ensures that the urgency to act quickly to rectify defective product does not compromise documented procedures designed to avoid admixtures or introduce other risks to product quality. **2. Process Change** A refurbished or replacement tool/mould is returned to production use without a “full” examination of its potential effect on the product, resulting in surface finish differences compared with pre-change product. This change affected the customer’s process, e.g. the fit with other components, processing at normal speed. This type of ongoing change or upgrade is not uncommon, and it is known that a similar surface finish problem can be triggered by supplier changes to running speeds, cycling conditions, the

Ref:	Definition/References	Explanation
		software of process controllers, i.e. computers or programmable logic controllers (PLC's). As for the first example, assessment of the change should involve: • documentation details of the change including hardware, software, reasons for change etc. • risk assessment technique to be used, e.g. failure mode and effect analysis (FMEA) • plan of controlled change to include risk assessment of both the supplier's process and customer's process, e.g. i. Implications to the supplier's process: - installation/changeover - process speeds - process conditions - yield wastage - staff retraining - tool identification - specification and procedural revisions ii. Implications to the customer's process: - phase in (old and new requirement) - compatibility (with product, other components) - differences (visual, performance, dimensions) - change schedule (old stock, etc.) - notification (to regulators, market, etc.) - specification (revisions to documents) - machine set-up (changes) Details of the eventual change introduction can include: • management (responsibility for change implementation and customer notification) • documentation (details of the change, reason or purpose e.g. what, how, when, why) • review (past specification, performance characteristics, issues, requirements, change schedule) • reference or involvement of customer • risks (documented, classified, with responses, actions and cures)

Ref:	Definition/References	Explanation

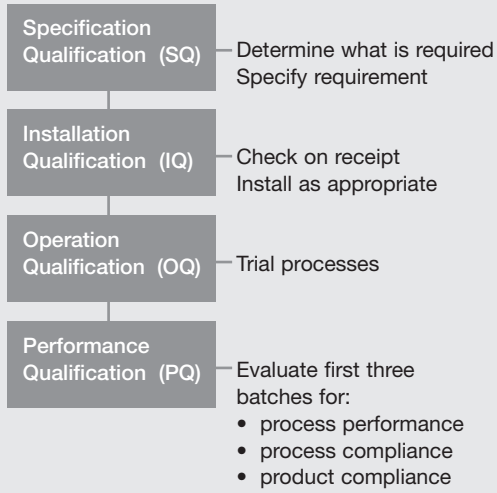
		• compliance of the 'agreed' specification, to meet:
		  - organizational needs
		  - customer's needs
		• change implementation plan
		
		Outputs from the change implementation can include:
		• testing (at customer or supplier)
		• trials and/or revalidation (at customer or supplier, in market)
		• revisions (and additions to requirements)
		• records (of performance, new specification, controls, etc.)
		• modifications (details)
		• phase in (changeover schedules)
		• phase in (controls and schedule to monitor and measure performance compliance)
		• change of identification numbers (reference numbers to control new item)
		• revised specifications (supplier and customer agreed)
		• completion review
		
		For further information see 21CFR 211.115 Reprocessing

Segregation controls

Ref:	Definition/References	Explanation
	PS 9000 Definition Note: There is no definition in PS 9000	To avoid the risk of product cross-contamination, it is essential that, in addition to normal good material handling disciplines, there is adequate process segregation during manufacture.
	PS 9000 References	PS 9000 states, “working areas should be defined and segregated”.
3.37	Working (work) areas	
8.3	Control of nonconforming product	Often in practice, a separation gap between processes of 1 – 2 metres is maintained, with the actual process areas identified by lines marked on the floor. This can be wasteful of space and is often abused when pallet materials straddle the delineating segregation lines.
9.1.2	Facilities Design	
9.1.8	Segregation controls (cross-contamination control)	A more absolute method, routinely used in the pharmaceutical industry, is to use a physical barrier between processes - PS 9000 states: • “Where physical barriers are used to segregate working areas they shall be a minimum of 1.5 metres high and continuous from floor level.” • “Inspection and sorting areas shall be defined and segregated by physical barriers of a minimum of 1.5 metres high and continuous from floor level.”
11.1	Origination procedures and work areas	
13.1	Print machine set up (make-ready).	The purpose behind these requirements is that most working conveyor belts are about 1m high and similarly pallets are stacked to about 1m high, hence, a 1.5 metre barrier effectively prevents items falling over the barrier. Making it continuous from floor level, i.e. sealed to the floor prevents the transfer of items passing under the barrier. Making the barrier solid, with no openings or holes, prevents passage of items through the barrier (if mesh barriers are used, the hole size needs to be sufficiently small to prevent product passing through). These measures have been proven effective in preventing cross transfer i.e. preventing admixture, mix-ups, rogues or strangers. For further information see 21 CFR 211.130(a).

Ref:	Definition/References	Explanation

Validation (and Qualification)

Ref:	Definition/References	Explanation
3.36	**PS 9000 Definition** Documented confirmation that a procedure, process, equipment, material, activity or system, performs as intended and achieves the expected results in accordance with predefined acceptance criteria.	**Qualification** Before implementing a validation program it is necessary to link into the more comprehensive 'qualification system' which is shown in the diagram below: 
	PS 9000 References	
4.2.3	Control of documents (electronic)	
7.3.6	Design and development validation	
7.5.2	Validation of processes for production and service provision	
9.2.3	Enhanced cleanroom conditions	**Validation** Through experience of operational and in-market problems, the pharmaceutical industry has found that validation is the only dependable method to fully understand the process capability and to ensure process control. It should be an essential tool at the supply organization and is a requirement of PS 9000, for reasons detailed below. Inconsistent product quality can often be traced to an inadequately controlled process which has not been validated and where process parameters have not been fully defined. Validation can be viewed as a key part of a defect prevention system and as such requires no justification when management objectives are for an efficient process. However, the sound operational
10.2	Reel fed materials (general)	
10.4	Leaflets	
10.5	Board products (cartons, cards, wallets, catch cards etc.)	
10.6	Combination products	
10.7	Digital printing	

Ref:	Definition/References	Explanation
	PS 9004 References	reasons for validation includes ensuring: • the process is controllable and operates consistently with defined control settings • compliance with the product requirements, i.e. variability only occurs within the agreed specification • compliance with known regulatory requirements, (where applicable) • change is controlled • prevention of problems for the organization and/or customer Validation is not simply for production processes, but is relevant to test equipment used on line or in the laboratory, as well as computer hardware and software. From the above detail it is clear that there is a need for a validation protocol before introducing new equipment. To establish a comprehensive and focused programme, it is beneficial but not essential for the organization to liaise with the pharmaceutical customer. Here there is a wealth of validation experience and the motivation exists to assist suppliers in defect and problem prevention. A general validation procedure is practical and often used, (e.g. an across the process Validation Master Plan or VMP), which can define the broad scope of the validation approach. This can then be customised for any specific item needing assessment. The VMP can cover: **1. The scope** • New process or test equipment that contributes to product quality or process efficiency, e.g. i. a new machine (e.g. an injection blow moulding machine) ii. a new machine tool, (e.g. a 24 impression mould replacing a 16 impression mould) • New process software (e.g. new process software from the existing supplier) • New starting materials, (e.g. replacement equivalent grade from a new supplier) • Others where appropriate
Annex A	Change control	
Annex A	Risk assessment	

Ref:	Definition/References	Explanation
		PS 9000, reference 7.5.2 identifies specific examples where validation and revalidation are required. Similarly, control of change (see Annex A-Change Control), needs to be incorporated within the validation system, when the risk assessment, (see Annex A-Risk Assessment), identifies that change may introduce a significant risk of problems (to organization or customer). The VMP should include changes to, e.g.: • equipment hardware, e.g. i. refurbished moulds or tools ii. full maintenance strip down and rebuild iii. relocation of equipment to a new position • process materials, e.g. i. revised specification material from the existing supplier ii. the same specification material but made through a different process. iii. process materials delivered in a different format, (e.g. quantity, presentation etc.) **2. Responsibilities for, e.g.:** • the validation protocol • the trials • the testing • final acceptance authorisation **3. Equipment parameters, e.g.:** • operating conditions - according to theory or practice • control settings - running speeds/cycle times, e.g. temperature/pressure **4. Product Specification, e.g.:** • confirmation - against existing specification • compliance - against a draft specification • variability - inside or outside specification **5. Trial conditions, e.g.:** • duration • output quantity/units to be produced • environmental controls

Ref:	Definition/References	Explanation
		6. Sample evaluation, e.g.: • Tests, (e.g. visual/measurement/function) • units examined, e.g. from beginning, middle and end of trial) • test comparison with previous data • test location, e.g. on site and/or at customer • numbers retained, e.g. for future reference **7. Documentation responsibilities, e.g.:** • validation protocol preparation • report preparation • report circulation (to customer where appropriate) • report and protocol archiving • revised operating/test procedures (where applicable) **8. Training, e.g.:** • revised training where applicable, (and revised training documentation) **9. Revision authorisation, e.g.:** • to process conditions and settings (organization) • to product specification (organization and customer) • to procedures **10. Validation review, e.g.:** • completion review including any lessons from the validation process The success of an operational validation system can be measured through the lack of problems encountered following the introduction of new hardware /software or after a change. However even where a minor problem might be encountered, the details can be reviewed and the lessons built into the validation practice, as an example of continual improvement.

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ANNEX B - OTHER EXTERNAL GMP REFERENCES

B1. Code of Federal Regulations 21 Part 211
Current Good Manufacturing Practice for Finished Pharmaceuticals

(www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm
(select CFR Part No. 211 and search))

Ref. 21 CFR	Summary	PS 9000 Cross Reference
211.42(a)	Building design to facilitate cleaning and maintenance	9.1 Facilities, equipment and operating conditions 9.1.2 Facilities design
211.42(b)	Adequate building space for orderly placement of equipment and material to prevent mix-ups	9.1.2 Facilities design
211.63	Equipment design to facilitate cleaning and maintenance	9.1.3 Equipment and maintenance
211.67	Equipment cleaning and maintenance	9.1.4 Cleaning
211.68(b)	Electronic equipment change control	4.2.3 Control of documents (Electronic) 4.2.4 Control of records
211.80(b)	Off floor material storage	9.1.2 Facilities design
211.115	Procedures for reprocessing	9.1.10 Waste material (cross-contamination control) 8.3 Control of non-conforming product
211.122(e)	Disposal of obsolete material	9.1.10 Waste material (cross-contamination control) 12.5 Quarantine and destruction
211.122(f)	Use of gang printed materials	13.5 Gang printing
211.130(a)	Prevention of mix-ups and cross-contamination by physical or spatial separation	9.1.2 Facilities design 9.1.8 Segregation controls (cross-contamination control)
211.180	General Requirements (records and reports)	4.2.4 Control of records
211.182	Equipment cleaning and use log	9.1.7 Line clearance (cross-contamination control) 11.1 Origination procedures and work areas
211.204	Returned products	8.3 Control of non-conforming product

B2. Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2002

(http://pharmacos.eudra.org/F2/eudralex/vol-4/home.htm)

EU Guide to Pharmaceutical GMP	Summary	PS 9000 Cross Reference General information
Chapter 3.4	Protection against infestation	9.1.5 Pest control
Chapter 3.8	Avoidance of cross-contamination	9.1 Facilities, equipment and operating conditions 9.1.1 General 9.1.2 Facilities design
Chapter 3.36	Equipment cleaning	9.1.7 Line clearance (cross-contamination control) 9.1.4 Cleaning
Chapter 4.8	Retention of records	4.2.4 Control of records
Chapter 4.22	Sampling procedures and precautions	8.2.4 Monitoring and measurement of product
Chapter 5.22/5.23	Process changes	7.5.2 Validation of processes for production and service provision
Chapter 5.35/5.45	Line clearance checks	9.1.7 Line clearance control (cross-contamination control)
Chapter 5.54	Sample disposal	8.2.4 Monitoring and measurement of product
Chapter 5.43	Obsolete material disposal	9.1.10 Waste control (cross-contamination control)
Chapter 5.44	Physical segregation to minimise risk of cross contamination	9.1.2 Facilities design 9.1.8 Segregation controls (cross-contamination control)
Chapter 5.62	Reprocessing of rejected product	8.3 Control of nonconforming product
Chapter 6.14	Sample retention	8.2.4 Monitoring and measurement of product
Chapter 8	Complaints	8.3 Control of nonconforming product
Annex 8 (3) and (5)	Supplier GMP	5.2 Customer focus
Annex 11 (2)	Computer system validation	4.2.3 Control of documents (electronic) 7.3.6 Design and development validation 7.5.2 Validation of processes for production and service provision

EU Guide to Pharmaceutical GMP	Summary	PS 9000 Cross Reference General information
Annex 15 (43) and (44)	Change control	4.2.3 Control of documents (electronic) 7.2.3 Customer communication 7.3.2 Design and development inputs 7.5.2 Validation of processes for production and service provision
Annex 16 (8)	Finished product batch certification that manufacture and testing are in compliance with the marketing authorisation	7.2 Customer related processes 7.4 Purchasing
Annex 18 (9)	Labelling of active pharmaceutical ingredients	7.4.3 Verification of purchased product 7.5.3 Identification and traceability 7.5.5 Preservation of product

B3. MHRA Defect Investigations

Defect Type	Report Received		
	Year 02/03	Year 01/02	Year 00/01
Noncompliance to product specification (stability)	6	19	16
ADR (adverse drug reaction)	9	16	23
Product mix-up	3	14	18
Noncompliance to product specification (analytical)	11	12	9
Other	77	10	29
Other particulates	15	9	14
Wrong data	0	9	18
Label mix-up	6	8	13
Container	5	7	6
Leaflet Missing/mix-up	12	5	9
Closure Fault	1	4	3
Precipitation	2	4	1
Label details missing	6	4	0
Lack of efficacy	12	4	0
Lack of sterility assurance	5	3	2
Re-labelling error	21	3	5
Glass particulates	6	2	2
Adulteration	1	2	0
Under fill	1	2	5
Wrong data/poor print	3	1	0
Fibre particles	1	1	0
Solubility	0	1	0
Wrong fill	3	0	3
Bacteria contamination	3	0	2
Mould Contamination	1	0	1
Label Missing	2	0	1
Poor Print	0	0	3
Total	**212**	**140**	**183**

This table includes all formal defect investigations carried out by the MHRA, whether they were confirmed as quality defects or not. Some of these investigations resulted in batch recalls.

It does not include all defects reported to the MHRA or all investigations carried out by licence holders and not reported to the MHRA.

Some headings are very similar, and in most cases could be combined, e.g. product mix-up is usually where the wrong tablets are found in a pack.

Acknowledgement to:
The Defective Medicines Report Centre
MHRA
May 2003

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The Institute of Quality Assurance
Pharmaceutical Quality Group

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