DOCUMENTATION

Procedures and records: Receipt

- There should be written procedures and records for the receipt of each delivery of each starting material, (including bulk, intermediate or finished goods), primary, secondary and printed packaging materials.
- There should be written procedures for the internal labeling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

79

DOCUMENTATION

Procedures and records: Receipt

The records of the receipts should include:

(a) The name of the material on the delivery note and the containers;

(b) The “in-house” name and/or code of material (if different from a);

(c) Date of receipt;

(d) Supplier’s name and, manufacturer’s name;

(e) Manufacturer’s batch or reference number;

(f) Total quantity and number of containers received;

(g) The batch number assigned after receipt;

(h) Any relevant comment.

80

الفرق بين الـ primary والـ secondary معروف أخدناه بالصناعيّة

← هسّالو مادة عندي فاتت على المستودع ومادة pass ومادة رُفضت
هل راح يكون الهم نفس الـ label؟
عادة راح يكون عنا شي باللون الأخضر مكتوب عليه "Reject"
شكله بسلايد (89) الـ pass لونه أخضر.. المخزن في المستودع
لونه أبيض.. وهكذا
حتى على الغرفة يلي بيشتغل فيها المصنّع .. مكتوب على البوابة تاعتها
اسم المستحضر، واسم المصنّع واسم الـ batch number..

→ Sampling and Testing. حكينا عنهم كتير.. اقرأوهم.
أي شي حاطة عليه صح أنا تحدث الدكتورة عنه، وتكون شرحته
قبل بشكل مفصّل .. عشان هيك اقرأوهم وأي شي مش واضح
(you can Ask me)

← قبل ما تبلش تصنّع بالـ batch، الغرفة لازم تكون نظيفة من
بروتوكولات معينة .. لو مثلًا صنعت دواء معيّن وثاني يوم بدي
اصنّع دواء ثاني من نفس المكان .. لهيك بيجوا ويعملوا عينات مسح
وبيأكدوا إنه المكان نظيف تمامًا .. إذا نظيف بحل شغلك مش
نظيف.. ارجع نظف لحتى مرّة.

DOCUMENTATION

Procedures and records: Sampling

- There should be written procedures for sampling, which include the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality.

Procedures and records: Testing

- There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

81

DOCUMENTATION

Procedures and records

There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached, where appropriate, for the following examples:

1. Personnel matters including signature lists, training in GMP and technical matters, clothing and hygiene and verification of the effectiveness of training.
2. Validation and qualification of processes, equipment and systems;
3. Equipment assembly and calibration;
4. Technology transfer;
5. Maintenance, cleaning and sanitation;
6. Environmental monitoring;
7. Pest control;

82

DOCUMENTATION

Procedures and records

There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached, where appropriate, for the following examples:

1. Complaints;
2. Recalls;
3. Returns;
4. Change control;
5. Investigations into deviations and non-conformances;
6. Internal quality/GMP compliance audits;
7. Summaries of records where appropriate (e.g. product quality review);
8. Supplier audits.

83

DOCUMENTATION

Procedures and records

- Records should be maintained for the distribution of each batch of a product in order to facilitate recall of any batch, if necessary.
- Logbooks should be kept for major or critical analytical testing, production equipment, and areas where product has been processed.
- They should be used to record in chronological order, as appropriate, any use of the area, equipment/method, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out.

84

بجدين في عنا اشي اسمه اذ Calibrations، أنا مش وزنت مثلاً شيء معين .. بروح أعمل Calibrations .. في عندي شي اسمه Log books

بيكون للـ Calibrations عليه معلومات انه أنا اليوم عملت بتاريخ كذا معايرة .. وبلي عمل هالشي فلان .. فبكون كل شي مسجل فيه.

أيضًا الآلات لازم تتركب بشكل صحيح، بيعايروها تحت إنه مثلًا تنحل هاد العدد من الحبّات.

PRODUCTION

- Production should be performed and supervised by competent people.
- All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.
- All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed data.

85

PRODUCTION

- Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department.
- Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.
- Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

86

PRODUCTION

- All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.
- Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.
- Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or crosscontamination.
- At every stage of processing, products and materials should be protected from microbial and other contamination.

87

PRODUCTION

- When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitizing materials.
- At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.

88

PRODUCTION

- Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format.
- It is often helpful in addition to the wording on the labels to use colors to indicate status (for example, quarantined, accepted, rejected, clean,…).
- Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

89

PRODUCTION

- Any deviation from instructions or procedures should be avoided as far as possible.
- If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate.
- Access to production premises should be restricted to authorized personnel.
- Normally, the production of non-medicinal products should be avoided in areas and with the equipment destined for the production of medicinal products.

90

PRODUCTION

Prevention of Cross-contamination in Production

Cross-contamination should be avoided by appropriate technical or organizational measures, for example:

(a) production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;

(b) providing appropriate air-locks and air extraction;

(c) minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

(d) keeping protective clothing inside areas where products with special risk of cross-contamination are processed;

(e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of crosscontamination;

(f) using "closed systems" of production;

(g) testing for residues and use of cleaning status labels on equipment.

91

شابتر لحاله.

PRODUCTION

Validation

- Validation studies should be conducted in accordance with defined procedures. Results and conclusions should be recorded.
- When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing.
- The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.
- Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process should be validated.
- Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results.

92

PRODUCTION

Starting Materials

- The purchase of starting materials should involve staff who have a particular and thorough knowledge of the suppliers.
- Starting materials should only be purchased from approved suppliers named in the relevant specification and, where possible, directly from the producer.
- For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels.
- If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.

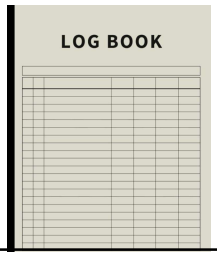
93

PRODUCTION

Starting Materials

Labels should bear at least the following information:

1. the designated name of the product and the internal code reference where applicable;
2. a batch number given at receipt;
3. where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);
4. where appropriate, an expiry date or a date beyond which retesting is necessary.



94

PRODUCTION

Starting Materials

- There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material.
- Only starting materials which have been released by the QC Department and which are within their shelf life should be used.
- Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.
- Each dispensed material and its weight or volume should be independently checked and the check recorded.

95

PRODUCTION

Processing Operations: intermediate and bulk products

- Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.
- Intermediate and bulk products should be kept under appropriate conditions.
- Critical processes should be validated.
- Any necessary in-process controls and environmental controls should be carried out and recorded.
- Any significant deviation from the expected yield should be recorded and investigated.

96

PRODUCTION

Packaging Materials

- Attention similar to that given to starting materials.
- Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorized access.
- Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups.
- Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

97

PRODUCTION

Packaging Operations

- Particular attention should be given to minimising the risk of:
  - cross-contamination
  - mix-ups
  - substitutions
- Different products should not be packaged in close proximity unless there is physical segregation

98

* packging Materials

← علبة كلنا عارفينها .. مثلاً دواء الحكة لما يصنعوه عندهم على أكثر من غرفة .. غرفة تلزق عليه الـ Label وغرفة تحط المعلقة فيها .. إلخ وكان في علبة cut والـ loose كان إلها غرف خاصة.

→ Outdated or absolete ⇐

هو الشي يلي توقف العمل فيه .. مثلاً كان شعار الشركة لونه أحمر غيرته وصار لونه أخضر

الـ box يلي لونه أبيض .. ممكن يتحول للون أصفر مع التخزين لازم ينكب

→ packging Operations

⇐ أكثر الأشياء يلي تعمل خطورة ممكن تصير خلال عملية الـ packging هما هدول الثلاث ← cross-con -

packging هو إنك تعمل ← mix-ups -

two product لـ .. substitutions → إنه يجيبوا

مع بعض ويخربطوا بعلبة يلي لازم نعبيها بس ١٤ حبة

يروحوا يجيبوا وحدة تعبي 28 حبة مثلاً.

(تبديل)

PRODUCTION

Packaging Operations

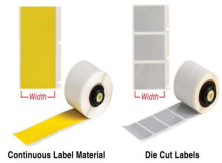
- Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation.
- The line-clearance should be performed according to an appropriate check-list.
- The name and batch number of the product being handled should be displayed at each packaging station or line.
- All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.

99

PRODUCTION

Packaging Operations

- Containers for filling should be clean before filling
- Normally, filling and sealing should be followed as quickly as possible by labelling.



- If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.
- Special care should be taken when using cut-labels and when over-printing is carried out off-line.
- Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.
- Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.
- Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing

100

PRODUCTION

Packaging Operations

On-line control of the product during packaging should include at least checking the following:

(a) general appearance of the packages;

(b) whether the packages are complete;

(c) whether the correct products and packaging materials are used;

(d) whether any over-printing is correct;

(e) correct functioning of line monitors.

➢Samples taken away from the packaging line should not be returned.

101

PRODUCTION

Packaging Operations

- Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorised personnel.
- Detailed record should be kept of this operation.
- Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.
- Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded.
- A documented procedure should be followed if uncoded printed materials are returned to stock.

102

- شو الأشياء يلي تفحصها لل Packging .. كم حبة فيه .. هل الكرتونة تاعتي مطحوجة مثلًا .. هل في معلقة هل في الأشياء الموجودة أو المفروض تكون موجودة حسب ال List تاعتي .. وهادهو ال Check-list وما في شي مطبوع مرتين مثلًا ..

مثلًا مرّة زمان لما اجوا يشيكوا على الدواء FDA لـ .. حاولوا يفتحوا الدواء ما رضي يفتح .. هاد خطأ كبير .. فسحبوا الدواء من السوق.

PRODUCTION

Finished Products

- Finished products should be held in quarantine until their final release under conditions established by the manufacturer.
- After release, finished products should be stored as usable stock under conditions established by the manufacturer.

103

PRODUCTION

Rejected, Recovered and Returned Materials

- Rejected materials and products should be clearly marked as such and stored separately in restricted areas.
- They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed.
- Whatever action is taken should be approved and recorded by authorised personnel.
- The reprocessing of rejected products should be exceptional and is only permitted:
  - if the quality of the final product is not affected,
  - if the specifications are met
  - if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved.
- Record should be kept of the reprocessing.

104

PRODUCTION

Rejected, Recovered and Returned Materials

- The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.
- Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for re-sale, re-labelling or recovery in a subsequent batch only after they have been critically assessed by the Quality Control Department in accordance with a written procedure.

105

QUALITY CONTROL

GMP for QC is concerned with the following aspects:

- sampling,
- specifications
- testing
- organisation,
- documentation
- release procedures

The main aims of GMP for QC is to:

- ensure that the necessary and relevant tests are carried out,
- and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory

106

QUALITY CONTROL

- Each holder of a manufacturing authorisation should have a Quality Control Department.
- This department should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal.
- Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.
- Quality Control personnel should have access to production areas for sampling and investigation as appropriate

107

QUALITY CONTROL

Documentation

The following details should be readily available to the Quality Control Department:

- specifications;
- sampling procedures;
- testing procedures and records (including analytical worksheets and/or laboratory notebooks);
- analytical reports and/or certificates;
- data from environmental monitoring, where required;
- validation records of test methods, where applicable;
- procedures for and records of the calibration of instruments and maintenance of equipment

108

QUALITY CONTROL

Documentation

❑The following details should be readily available to the Quality Control Department:

- specifications;
- sampling procedures;
- testing procedures and records (including analytical worksheets and/or laboratory notebooks);
- analytical reports and/or certificates;
- data from environmental monitoring, where required;
- validation records of test methods, where applicable;
- procedures for and records of the calibration of instruments and maintenance of equipment

❑For some kinds of data (e.g. analytical tests results, yields, environmental controls) it is recommended that records are kept in a manner permitting **trend evaluation**.

109

QUALITY CONTROL

Sampling

The sample taking should be done in accordance with approved written procedures that describe:

- the method of sampling;
- the equipment to be used;
- the amount of the sample to be taken;
- instructions for any required sub-division of the sample;
- the type and condition of the sample container to be used;
- the identification of containers sampled;
- any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
- the storage conditions;
- instructions for the cleaning and storage of sampling equipment.

110

QUALITY CONTROL

Sampling

- Reference samples should be representative of the batch of materials or products from which they are taken.
- Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process).
- Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn

111

QUALITY CONTROL

Testing

- Analytical methods should be validated.
- All testing operations described in the marketing authorization should be carried out according to the approved methods.
- The results obtained should be recorded and checked to make sure that they are consistent with each other.
- Any calculations should be critically examined.

112

QUALITY CONTROL

Testing

The tests performed should be recorded and the records should include at least the following data:

(a) name of the material or product and, where applicable, dosage form;

(b) batch number and, where appropriate, the manufacturer and/or supplier;

(c) references to the relevant specifications and testing procedures;

(d) test results, including observations and calculations, and reference to any certificates of analysis;

(e) dates of testing;

(f) initials of the persons who performed the testing;

(g) initials of the persons who verified the testing and the calculations, where appropriate;

(h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

113

QUALITY CONTROL

Testing

- All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by Quality Control and the results recorded.
- Laboratory reagents intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them.
- The expiry date of unstable reagents and culture media should be indicated on the label, together with specific storage conditions.
- In addition, for volumetric solutions, the last date of standardisation and the last current factor should be indicated.

114

QUALITY CONTROL

Testing

- Animals used for testing components, materials or products, should, where appropriate, be quarantined before use.
- They should be maintained and controlled in a manner that assures their suitability for the intended use.
- They should be identified, and adequate records should be maintained, showing the history of their use.

115

QUALITY CONTROL

On-going stability program

- After marketing, the stability of the medicinal product should be monitored according to a continuous appropriate program that will permit the detection of any stability issue (e.g. changes in levels of impurities or dissolution profile).
- The purpose of the on-going stability program is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions.

116

QUALITY CONTROL

On-going stability program

- Stability studies on reconstituted product are performed during product development and need not be monitored on an on-going basis.
- The equipment used for the on-going stability program (stability chambers among others) should be qualified and maintained.

- The on-going stability program should be described in a written protocol.

117

QUALITY CONTROL

On-going stability program

The protocol should include the following parameters:

- number of batch(es) per strength and different batch sizes, if applicable;
- relevant physical, chemical, microbiological and biological test methods;
- acceptance criteria;
- reference to test methods;
- description of the container closure system(s);
- testing intervals (time points);
- description of the conditions of storage (standardized ICH conditions for long term testing, consistent with the product labelling, should be used);
- other applicable parameters specific to the medicinal product..

118

QUALITY CONTROL

On-going stability program

- The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis.
- Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability program (unless none are produced during that year).
- An on-going stability study should be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing or recovery operation should also be considered for inclusion.

119

QUALITY CONTROL

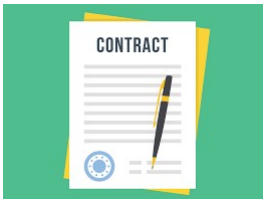
On-going stability program

- Results of on-going stability studies should be made available to key personnel and, in particular, to the Qualified Person(s).
- Out of specification or significant atypical trends should be investigated.
- Any confirmed out of specification result, or significant negative trend, should be reported to the relevant competent authorities.

120

OUTSOURCED ACTIVITIES

- Any activity covered by the GMP Guide that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality.
- There must be a written Contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party.



121

COMPLAINTS AND PRODUCT RECALL

Complaints

- A person should be designated responsible for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him.
- If this person is not the Qualified Person, the latter should be made aware of any complaint, investigation or recall.
- There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

122

COMPLAINTS AND PRODUCT RECALL

Complaints

- Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated.
- All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.
- If a product defect is discovered or suspected in a batch, consideration should be given to checking other batches in order to determine whether they are also affected.
- Complaints records should be reviewed regularly.

123

COMPLAINTS AND PRODUCT RECALL

Complaints

- Special attention should be given to establishing whether a complaint was caused because of counterfeiting.
- The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, detection of counterfeiting or any other serious quality problems with a product.

- **Follow until resolution**

124

SELF INSPECTION

- Self inspections should be conducted in order to monitor the implementation and compliance with GMP principles and to propose necessary corrective measures.
- Personnel matters, premises, equipment, documentation, production, quality control, distribution of the medicinal products, arrangements for dealing with complaints and recalls, and self inspection, should be examined at intervals following a pre-arranged program in order to verify their conformity with the principles of Quality Assurance.

125

SELF INSPECTION

- Self inspections should be conducted in an independent and detailed way by designated competent person(s) from the company.
- Independent audits by external experts may also be useful.
- All self inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures.
- Statements on the actions subsequently taken should also be recorded.

126

Glossary

BATCH (OR LOT)

- A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.

BATCH NUMBER (OR LOT NUMBER)

- A distinctive combination of numbers and/or letters which specifically identifies a batch

127

Glossary

BULK PRODUCT

- Any product which has completed all processing stages up to, but not including, final packaging.

FINISHED PRODUCT

- A medicinal product which has undergone all stages of production, including packaging in its final container.

INTERMEDIATE PRODUCT

- Partly processed material which must undergo further manufacturing steps before it becomes a bulk product.

128

Glossary

CLEAN AREA

- An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

CONTAINED AREA

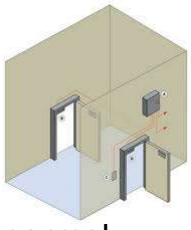
- An area constructed and operated in such a manner (and equipped with appropriate air handling and filtration) so as to prevent contamination of the external environment by biological agents from within the area.

129

Glossary

AIR-LOCK

- An enclosed space with two or more doors, and which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the air-flow between those rooms when they need to be entered. An air-lock is designed for and used by either people or goods.



RECONCILIATION

- A comparison, making due allowance for normal variation, between the amount of product or materials theoretically and actually produced or used.

130

Glossary

CALIBRATION

- The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

CROSS-CONTAMINATION

- Contamination of a material or of a product with another material or product.

131

Glossary

STARTING MATERIAL

- Any substance used in the production of a medicinal product, but excluding packaging materials.

PACKAGING MATERIAL

- Any material employed in the packaging of a medicinal product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

132

Glossary

QUARANTINE

- The status of starting or packaging materials, intermediate, bulk or finished products isolated physically or by other effective means whilst awaiting a decision on their release or refusal.

REPROCESSING

- The reworking of all or part of a batch of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations.

133