The IPEC Good Distribution Practices Guide

FOR PHARMACEUTICAL EXCIPIENTS

2006

IPEC Good Distribution Practices Guide for Pharmaceutical Excipients

This document has been written to provide guidance for those companies involved in the supply chain of pharmaceutical excipients. Examples based on practical experience are provided to facilitate the application of GDP. However, alternative approaches may be acceptable.

This guide provides additional explanatory notes to:

***"GOOD TRADE AND DISTRIBUTION PRACTICES FOR PHARMACEUTICAL STARTING MATERIALS"* [1]**

World Health Organization, WHO Technical Report Series, No. 917, 2003

The explanatory notes in this guide are the views of The International Pharmaceutical Excipients Council (IPEC) and not necessarily those of WHO.

World Health Organization:
"We are pleased to see that IPEC is using the recommendations from WHO's technical report on Good Trade and Distribution Practices for Pharmaceutical Starting Materials. We hope that this will help to make those recommendations more widely known and allow for their intended implementation. We look forward to our continued collaboration aiming at providing quality medicines to patients."

(Dr. Lembit Rägo, Dr. Sabine Kopp; December 2005)

Table of contents Pages

I. Introductory Note

The International Pharmaceutical Excipients Council (IPEC) first published a *GMP Audit Guideline for Distributors of Bulk Pharmaceutical Excipients* in 2000. This Guideline was designed as a tool to assist in evaluating the practices and quality systems of distributors who store excipients in their warehouses and those who both repackage and store excipients. During 2001, and again in 2006, IPEC revised its GMP Guidelines for manufacturers of excipients and decided to publish a complementary document for distributors of excipients.

In the meantime WHO published its guideline on *Good Trade and Distribution Practice for Pharmaceutical Starting Materials (GTDP)* [1] the scope of which extends to active pharmaceutical ingredients and excipients. As a result, IPEC is publishing its *Good Distribution Practices Guide for Pharmaceutical Excipients* based on the WHO GTDP guideline [1] as an explanatory document.

The WHO GTDP document provides the general principles of good practices in the pharmaceutical starting materials supply chain. This IPEC document should provide the practical approach with examples that provide guidance on the application of WHO GTDP principles. In addition, extracts have been taken from IPEC PQG GMP Guide 2006 [2] to clarify certain requirements and maintain consistency.
For the purpose of this guide “distributors” includes those parties involved in trade and distribution, (re)processors, (re)packagers, transport and warehousing companies, forwarding agents, brokers, traders, and suppliers other than the original manufacturer.

II. Scope

This document is based on the WHO *Good Trade and Distribution Practice for Pharmaceutical Starting Materials (GTDP)* guideline [1], and therefore it follows the same structure.

It applies to steps in the distribution/supply chain starting from the point at which an excipient is transferred outside the control of the original manufacturer's material management system. Some sections and/or sub-sections in this document may not apply to all involved parties. This document is meant to provide guidance in the application of the GTDP; however, alternative approaches may be acceptable.
To help the user to identify the sections applicable to the activities, see table 1 - *Matrix of Applicability* and table 2 - *Applicability for supply chain activities*.
The matrix differentiates between activities involving warehousing and distribution from those involving further processing such as distributor bulk storage, repackaging, sampling, or labelling activities with excipients, reflecting different levels of control. For definitions, please refer to Annex A.
Further processing activities, such as blending, mixing, milling, micronization or any other physical manipulation of pharmaceutical excipients, should also refer to relevant aspects of the IPEC PQG GMP Guide 2006 [2].
In addition to this text *Introductory Note, Scope, General Considerations* and the *Glossary* of WHO GTDP guideline [1] should be referenced.

III. Pharmaceutical Grade Excipients

Parties involved in the supply chain should be aware that an excipient can only be pharmaceutical grade when it is in compliance with pharmacopoeial specification and/or appropriate regulatory requirements (if existing for the specific excipient) and is manufactured, repackaged, and handled in accordance with excipient GMPs (e.g. IPEC PQG GMP [2], WHO Excipient GMP [6]). Upgrading technical or industrial grade material to pharmaceutical grade quality only on the basis of analytical results found in conformance with the requirements of a pharmacopoeial monograph is an unacceptable practice.

IV. Acknowledgements

The International Pharmaceutical Excipients Council (IPEC) prepared this document. IPEC is an international industry association with a distinguished worldwide membership of chemical, pharmaceutical and food firms that develop, manufacture, distribute, sell and use pharmaceutical excipients. IPEC was formed in 1991 to address prevalent industry concerns related to the harmonization of international excipient standards, the introduction of useful new excipients to the marketplace, and the development of good manufacturing practices for excipients. IPEC is an umbrella

organization comprised of three regional pharmaceutical excipient industry associations in the United States, Europe, and Japan. The objective of the three organizations, which are known respectively as IPEC Americas, IPEC-Europe and JPEC, is to promote the safety and efficacy of finished dosage forms worldwide.

IPEC would like to acknowledge the World Health Organisation (WHO) for their extensive efforts in developing the guidelines *"GOOD TRADE AND DISTRIBUTION PRACTICES FOR PHARMACEUTICAL STARTING MATERIALS"* [1], which are valued by IPEC as a significant step forward in the development of tools for the improvement of safety and quality of starting materials and finished pharmaceuticals.

This document is the result of significant collaboration between IPEC-Europe and IPEC-Americas. IPEC greatly appreciates the many hours of hard work by the following individuals devoted to developing this guide and the generous support provided by their employers:

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Table 1: Matrix of Applicability

	Warehousing / Distribution (packed excipients)			Additional Processing Activities				
Activity: / **Section:**	Transportation of packed excipients	Warehousing (storage of packed excipients)	Broking, Trading, Reselling packed excipients	Repackaging, Processing	Sampling, Testing and Re-testing	Relabelling	Bulk handling, bulk storage	Transportation of bulk excipients
1. Quality Management	X+	X	X+	X	X	X	X	X+
2. Organization and Personnel	X+	X+	X+	X	X	X	X	X
3. Premises		X+		X	X	X	X	
4. Warehousing and Storage		X+		X		X+	X	
5. Equipment				X	X+		X	X
6. Documentation	X+	X+	X+	X	X+	X	X+	X+
7. Repackaging and Relabelling				X	X+	X+	X+	
8. Complaints	X	X	X	X	X+	X	X	X
9. Recalls*			X+	X		X	X	
10. Returned goods		X		X		X	X	
11. Handling of non-conforming materials		X+		X		X	X	
12. Dispatch and Transport	X+							X
13. Contract activities	X	X	X	X	X	X	X	X

X = applicable + = only partly applicable

* In the USA the term recall has specific regulatory implications that do not directly apply to excipients; therefore the term *retrieval* is typically used in the USA.

Table 2: Applicability for Supply Chain Activities

A supply chain participant, who exclusively carries out a specific activity, should apply the sections of the document mentioned under an activity. If a company carries out different activities all sections mentioned under all conducted activities should be applied.

1. Activities including direct contact with excipients

1.1 Repackaging, Processing

Applicable sections:
1., 2., 3., 4., 5., 6., 7., 8., 9., 10., 11., 13.

1.2 Sampling, Testing, Re-testing

Applicable sections:
1., 2., 3., 5. (except 5.2 and 5.6); 6. (except 6.7, 6.8), 7. (except 7.1, 7.2, 7.3, 7.4, 7.6, 7.7, 7.8, 7.9, 7.10, 7.11, 7.15), 8. (except 8.4 and 8.5), 13.

1.3 Relabelling

Applicable sections:
1., 2., 3., 4 (except 4.9), , 6., 7. (except 7.13. and 7.14), 8., 9., 10., 11., 13.

1.4 Bulk handling and bulk storage

Applicable sections:
1., 2., 3., 4., 5., 6. (except 6.8), 7. (except 7.5, 7.6, 7.9, 7.10), 8., 9., 10., 11., 13.

1.5 Transportation of bulk excipients

Applicable sections:
1. (except 1.7), 2., 5., 6. (except 6.3, 6.4, 6.7, 6.8, 6.9), 8., 12., 13.

2. Activities including non-direct contact with excipients (handling of packaged excipients)

2.1 Transportation of packed excipients

Applicable sections:
1. (except 1.7), 2. (except 2.6), 6. (except 6.3, 6.4, 6.7, 6.8, 6.9), 8., 12. (except 12.4 and 12.7), 13.

2.2 Warehousing (storage of packed excipients)

Applicable sections :
1., 2. (except 2.6), 3. (except 3.5), 4. (except 4.9), 6. (except 6.3, 6.4, 6.7, 6.8), 8., 10., 11. (except 11.2 and 11.4), 13.

2.3 Broking, Trading, Reselling originally packed excipients

Applicable sections:
1. (except 1.7), 2. (except 2.5 and 2.6), 6. (except 6.1, 6.7, 6.8), 8., 9. (except 9.4), 13.

	Good trade and distribution practices for pharmaceutical starting materials (GTDP), **WHO Technical Report Series, No. 917, 2003**	***IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006***
1.	**Quality Management**	
1.1	Within an organization quality assurance serves as a management tool. In contractual situations quality assurance also serves to generate confidence in the supplier. There should be a documented quality policy describing the overall intentions and direction of the supplier regarding quality, as formally expressed and authorized by management.	Parties involved in the excipient supply chain should establish a Quality Management System to manage the quality of their products and services, in order to maintain the original quality of the excipients. This is important when opening the original manufacturer sealed containers, performing: bulk handling, sampling, testing, processing (physical and chemical manipulation), repackaging, or relabelling activities. As an essential prerequisite for any Quality Management System, the top management should elaborate a corporate quality philosophy (Quality Policy).
1.2	Quality management should include: • an appropriate infrastructure or "quality system", encompassing the organizational structure, procedures, processes, and resources; • systematic actions necessary to ensure adequate confidence that a material (or service) and relevant documentation will satisfy given requirements for quality. The totality of these actions is termed (quality assurance); and • a clear procedure for approving suppliers of pharmaceutical starting materials and services (for details see GMP).	A system should be in place to control documents and data that relate to the requirements of the applicable Quality System. It is suggested to prepare a Quality Manual stating the corporate Quality Policy and describing the Quality Management System. This Quality Manual is the documented basis for the Quality System. It describes the commitment of the participant involved in the excipient distribution chain to the appropriate quality standards mentioned in this document. The Quality Manual should include at a minimum the following elements: - scope of the Quality Management System, - organisational structure, - written procedures, processes and resources or reference to them, and - a description of the sequence and interaction between the procedures and departmental functions. The Quality Management System should also include a procedure to verify that any supplier of excipients, packaging materials or services has the capability to consistently meet previously agreed requirements. This may include periodic audits of the vendor's manufacturing facility if deemed necessary.
1.3	The system should cover quality assurance principles.	*See 1.2*
1.4	All parties involved in the manufacture and supply chain must share responsibility for the quality and safety of the materials and products to ensure that they are fit for their intended use.	Parties involved should share responsibility for assuring that the excipient provided by the distributor conforms to the mutually agreed specification requirements of the pharmaceutical manufacturer and/or is suitable for the intended use of the excipient.
1.5	The responsibilities placed on any one individual should not be so extensive as to present any risk to quality. In the event of a supplier having a limited number of	There should be an adequate number of qualified personnel available either in-house or contractors to carry out all operations in compliance with this guide

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	staff, some duties may be delegated or contracted out to designated persons who are appropriately qualified. There should, however, be no gaps or unexplained overlaps related to the application of GTDP	(*refer to 2.2.*)
1.6	Where electronic commerce (e-commerce) is used defined procedures and adequate systems should be in place to ensure traceability and confidence in the quality of the material.	*See 6.10.*
1.7	Authorized release procedures should be in place to ensure that material of an appropriate quality is sourced from approved suppliers and released for its intended purpose.	If an excipient is provided only in originally sealed containers from the manufacturer, no additional testing and batch release are required. Inspection of the integrity of the packaging (including labelling) and seals should be carried out. A copy of the manufacturer's quality documents (such as COA or COC) should be provided for each delivery.
1.8	Inspection and certification of compliance with a quality system (such as applicable International Standards Organization (ISO) series and hazard analysis and critical control point (HACCP)) by external bodies is recommended. However, this should not be seen as a substitute for the implementation of these guidelines or for conforming with pharmaceutical GMP requirements, as applicable.	ISO or HACCP certification is not a mandatory requirement for excipient manufacturers and other companies involved in the supply chain. These standards should provide assurance that the excipient was produced and handled in conformance with an appropriate quality management system (IPEC PQG GMP Guide [2] is recommended).
1.9	A system should be in place for the performance of regular internal audits with the aim of continuous improvement. The findings of the audit and any corrective actions taken should be documented and brought to the attention of the responsible management.	Internal audits should be carried out at a frequency based on the status and importance of the Quality Management System activity. Audits and follow up actions should be carried out in accordance with documented procedures. Audit results should be documented and discussed with management personnel having responsibility in the area audited. Furthermore, corrective action and preventive action should be undertaken on the non-conformities found.
2	**Organization and Personnel**	
2.1	There should be an adequate organizational structure and sufficient personnel should be employed to carry out all the tasks for which the supplier is responsible.	*Self explanatory*
2.2	Individual responsibilities should be clearly defined, understood by the individuals concerned and recorded in writing (as job descriptions or in a contract). Certain activities, such as supervision over performance of activities in accordance with local legislation, may require special attention. Personnel should be suitably qualified and authorized to undertake their duties and responsibilities.	Personnel performing work affecting the excipient quality, including third parties, should have an adequate combination of training, education, and experience to carry out that work. Levels of authorization should be clearly defined in job descriptions. Records should be maintained listing the name, address, and qualifications of any contracted service provider and the type of service they provide.
2.3	All personnel should be aware of the principles of GTDP.	Awareness of the principles includes this IPEC GDP Guide.

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2.4	Personnel should receive initial and continuing training relevant to their tasks. All personnel should be motivated to support the establishment and maintenance of quality standards.	Quality standards applied should be part of a regular training program provided by qualified individuals and the training should be documented. The extent of training should be dependent upon the company's activities. All personnel should receive initial and regular follow-up training according to the potential impact of the activities on the excipient.
2.5	Personnel dealing with hazardous materials (such as highly active, toxic, infectious or sensitising materials) should be given specific training and should be provided with the necessary protective equipment.	*Self explanatory*
2.6	Personnel who may be exposed to materials from open containers should maintain good hygiene, have no open wounds and be equipped with an appropriate protective outfit, such as gloves, masks and goggles.	To protect excipients from contamination by personnel activities such as handling of unpacked excipient while performing operations like excipient sampling, bulk handling and repackaging personnel should: - wear clean protective apparel such as head, face, hand, and arm coverings, as necessary; - remove or cover jewellery and other loose items; - store and consume food, drink, tobacco products and similar items only in certain designated areas; - receive an adequate and continued personal hygiene training to practice good sanitation and health habits; - be instructed to report to supervisory personnel any health conditions that may have an adverse effect on excipients.
3	**Premises**	
3.1	Premises must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, mix-ups, build-up of dust or dirt and, in general, any adverse effect on the quality of materials.	Extract from IPEC PQG GMP Guide 2006 [2], chapter 6.3.1: (For the word "manufacturing" read "handling".) <u>*Buildings and Facilities*</u> *The prevention of contamination should be considered in the design of the manufacturing processes and facilities, particularly where the excipient is exposed. Buildings and facilities used in the production, processing, packaging, testing, or storage of an excipient should be maintained in a good state of repair and should be of suitable size, construction, and location to facilitate cleaning, maintenance, and correct operation, appropriate to the type of processing.* *Manufacturing processes associated with the production of highly sensitizing or toxic products (e.g. herbicides, pesticides etc.) should be located in dedicated*

	Good trade and distribution practices for pharmaceutical starting materials (GTDP), **WHO Technical Report Series, No. 917, 2003**	***IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006***
		facilities or equipment separate from that used for excipient manufacture. If this is not possible, then appropriate measures (e.g. cleaning, inactivation) should be implemented to avoid cross-contamination and the effectiveness of these measures should be demonstrated. *There should be adequate facilities for the testing of raw materials, packaging components, intermediates, and finished excipients.*
3.2	Measures should be in place to prevent unauthorized persons from entering the premises.	*Self explanatory*
3.3	Premises should be designed and equipped so as to afford maximum protection against the entry of insects, rodents or other animals.	Extract from IPEC PQG GMP Guide 2006 [2], chapter 6.4.4: *<u>Pest Control</u>* *Buildings should be free from infestation by rodents, birds, insects, and other vermin. Some raw materials, particularly botanicals, may contain some unavoidable contamination, such as rodent or other animal filth or infestation. The manufacturer should have sufficient control methods to prevent the increase of such contamination or infestation in holding areas or its spread to other areas of the plant.*
3.4	Suitable supporting facilities and utilities (such as air control, lighting and ventilation) should be in place and appropriate to the activities performed.	*Self explanatory*
3.5	There should normally be a separate sampling area for pharmaceutical starting materials in a controlled environment. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination. Adequate cleaning procedures should be in place for the sampling areas.	*Self explanatory*
4	**Warehousing and Storage**	
	GSP is applicable in all circumstances in which and all areas where materials are stored.	GSP – Good Storage Practice [3]
4.1	There should be authorized procedures describing the activities relating to the receipt, storage and distribution of materials.	Written procedures should describe receipt of the excipient, its storage and further dispatch. Some considerations (that may not be applicable in all situations) are: - Receipt: visual inspection of the container (packaged or bulk) integrity, confirmation of material identity from the label against documentation, evidence of infestation; - Storage: cleanliness of excipient storage area, accuracy of the inventory

	Good trade and distribution practices for pharmaceutical starting materials (GTDP), **WHO Technical Report Series, No. 917, 2003**	*IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006*
		locator system; - Dispatch: truck cleanliness, tracking records, verification of correct material by matching excipient label against dispatch documentation, cleanliness of containers, and transport equipment.
4.2	Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials.	Excipients should be stored in a manner to protect their quality as well as their packaging and labelling. The facility should be organized in a manner to facilitate selection of designated materials. Excipients should be stored in conformance with safety requirements.
4.3	Receipt and dispatch bays should be equipped with the means to protect materials from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned before storage if necessary.	Protection from adverse environmental conditions should be considered as a minimum requirement (e.g. roof or shelter) but specified storage conditions should be met when required.
4.4	Segregated areas should be provided for the storage of rejected, recalled and returned material, including those with damaged packaging.	*See 4.2*
4.5	Segregated areas and materials should be appropriately identified.	Segregation can be achieved through physical or computer control with appropriate systems in place.
4.6	The required storage conditions as specified for the product should be maintained within acceptable limits. The storage areas should be kept clean and dry.	*see 4.2*
4.7	Where special storage conditions are required (e.g. particular requirements for temperature or humidity) these should be provided, monitored and recorded.	An assessment should be conducted to confirm that designated conditions could be met. Records should demonstrate on-going conformance to specified conditions. In such cases recorders should be installed. Separate air-conditioned areas should be considered where necessary.
4.8	Highly active materials, narcotics, other dangerous drugs and substances presenting special risks of abuse, fire or explosion should be stored in safe, dedicated and secure areas. In addition international conventions and national legislation may apply.	*Self explanatory*
4.9	Special attention should be given to the design, use, cleaning and maintenance of all equipment for bulk handling and storage, such as tanks and silos.	*See 5.1*
4.10	Spillages should be cleaned as soon as possible to prevent possible cross-contamination and hazard.	*Self explanatory*
4.11	Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, closed containers in enclosed areas, taking into account the relevant national legislation.	*See sections 4.2, 4.4, 4.5 and 4.8.*
4.12	A system should be in place to ensure that those materials due to expire first are sold or distributed first (Earliest Expiry/First Out (EEFO)). Where no expiry	*Self explanatory*

	Good trade and distribution practices for pharmaceutical starting materials (GTDP), **WHO Technical Report Series, No. 917, 2003**	***IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006***
	dates are specified for the materials, the First In/First Out (FIFO) principle should be applied.	
4.13	Storage areas should be clean and free from accumulated waste and from vermin. A written sanitation programme should be available, indicating the frequency of cleaning and the methods to be used to clean the premises and storage areas. There should also be a written programme for pest control.	There should be records to show when inspections were made including observations of the findings for vermin and all pest control activities. Materials used for control of vermin should not adversely affect the Excipient (see also 3.3).
5	**Equipment**	
5.1	Equipment must be located, designed, constructed, adapted, used and maintained to suit the operations to be carried out. Defective equipment should not be used, and should either be removed or labelled as defective. Equipment should be disposed of in such a way as to prevent any misuse.	Extract from IPEC PQG GMP Guide 2006 [2], chapter 6.3.2: *<u>Equipment</u>* *Equipment used in the production, processing, packaging, testing, or storage of an excipient should be maintained in a good state of repair and should be of suitable size, construction, and location to facilitate cleaning, maintenance, and correct operation, depending on the type of processing (e.g. batch vs. continuous).* *Equipment should be commissioned before use to ensure that it is functioning as intended.* *Where equipment is located outdoors there should be suitable control to minimise the risk to excipient quality from the environment (e.g. processing within a closed system).* *<u>Equipment Construction</u>* *Process equipment should be constructed so that contact surfaces will not be reactive, additive, or absorptive and thus not alter the quality of the excipient. Substances required for operation, such as lubricants or coolants, should preferably not come into contact with raw materials, packaging materials, intermediates, or finished excipients. Where contact is possible, substances suitable for use in food applications should be utilised.* *Equipment should be designed to minimize the possibility of contamination caused by direct operator contact in such activities as the unloading of centrifuge bags, use of transfer hoses (particularly those used to transfer powders), and the operation of drying equipment and pumps. The sanitary design of transfer and processing equipment should be evaluated. Equipment with moving parts should be assessed in regard to the integrity of seals and packing materials to control the risk of contamination.*

	***Good trade and distribution practices for pharmaceutical starting materials (GTDP)*, WHO Technical Report Series, No. 917, 2003**	***IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006***
		Equipment Maintenance *Documented procedures should be established and followed for maintenance of critical equipment used in the production, processing, packaging, testing, or holding of the excipient. There should be records of quality critical equipment use and maintenance. These records can be in the form of a log, computer database, or other appropriate documentation.*
5.2	The layout, design and use of equipment must aim to minimize the risk of errors and to permit effective cleaning and maintenance to avoid cross-contamination, build-up of dust or dirt and any adverse effect on the quality of materials.	*Self explanatory*
5.3	Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.	*Self explanatory*
5.4	All services, piping and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases, liquids and other materials.	*Self explanatory*
5.5	Balances and other measuring equipment of an appropriate range and precision should be available and should be calibrated on a scheduled basis.	There should be procedures in place for calibration and means to verify calibration status. Calibration records should be maintained.
5.6	Procedures should be in place for the operation and maintenance of equipment. Lubricants and other materials used on surfaces that come into direct contact with the materials should be of the appropriate grade, e.g. food-grade oil.	*See 5.1.*
5.7	Washing and cleaning equipment should be chosen and used such that it cannot be a source of contamination.	*Self explanatory*
5.8	Dedicated equipment should be used where possible when handling and/or processing pharmaceutical starting materials. Where non-dedicated equipment is used cleaning validation should be performed.	When non-dedicated equipment coming in direct contact with the product is used for excipient handling (e.g. storage tanks, bulk trucks, pipes and hoses, repackaging equipment etc.; *see also 7.7*), appropriate cleaning procedures and effective cleaning schedules should be maintained and recorded. Multi-purpose equipment should only be used again after verification of the cleaning efficiency. Cleaning efficiency should be verified by e.g.: – testing the final rinse after cleaning for residues of the previous product or, – checking the equipment after cleaning for residues of the previous product or alternatively, – by testing each batch for residues of the previous product handled with the same equipment in order to avoid contamination and carry-over of previously processed products.

	Good trade and distribution practices for pharmaceutical starting materials (GTDP), **WHO Technical Report Series, No. 917, 2003**	***IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006***
6	**Documentation**	
6.1	Documents, in particular instructions and procedures relating to any activity that might have an impact on the quality of materials, should be designed, completed, reviewed and distributed with care. Documents should be completed, approved, signed and dated by appropriate authorized persons and should not be changed without authorization.	*Self explanatory*
6.2	Documents should have unambiguous contents: their title, nature and purpose should be clearly stated. They should be laid out in an orderly manner and be easy to check.	A revision history of documents should be readily available.
6.3	Original Certificates of Analysis (COAs) should accompany materials supplied by manufacturers to suppliers. COAs issued by the manufacturer should indicate which results were obtained by testing the original material and which results came from skip lot testing. The use of the Model COA as adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations is recommended [5].	A distributor should not change the original title and data of the COA or other quality documents. Whenever possible, the original manufacturer's documentation should be used, or transcription of data should be verified. The original manufacturing site should be identified by name or unique identifier on the COA or any other document agreed upon with the customer. Additional data resulting from analyses conducted by the distributor should be provided with clear indication of the source of data. Quality documents should allow traceability back to the manufacturer, along with a contact reference. If any lot mixing is carried out, COAs from manufacturers are no longer valid and the distributor should perform analyses in its own laboratory or at a named and qualified contract laboratory. Otherwise the distributor can supply a certificate of compliance (COC), provided that all other repackaging and storage activities are carried out according to these guidelines.
6.4	Before any material is sold or distributed, the supplier should ensure that the COAs and results are available and that the results are within the required specifications. Alternatively the customer should be informed without delay of the results as soon as these become available. For each shipment the COA should be forwarded to the pharmaceutical product manufacturer.	*Self explanatory*
6.5	The original manufacturer and intermediaries handling the material should always be traceable and the information available to authorities and end-users, downstream and upstream.	*Self explanatory*
6.6	Mechanisms should exist to allow for transfer of information, including the transfer of quality or regulatory information between a manufacturer and a customer, and of information to the regulatory authority upon request.	*Self explanatory*
6.7	Labels applied to containers should be clear, unambiguous, permanently fixed	*Self explanatory*

	Good trade and distribution practices for pharmaceutical starting materials (GTDP), **WHO Technical Report Series, No. 917, 2003**	*IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006*
	and in the company's agreed format. The information on the label should be indelible.	
6.8	Each container should be identified by labelling bearing at least the following information: – the name of the pharmaceutical starting material, including grade and reference to pharmacopoeias, where relevant; – if applicable, with the International Nonproprietary Names (INNs); – the amount (weight or volume); – the batch number assigned by the original manufacturer or the batch number assigned by the repacker, if the material has been repacked and relabelled; – the retest date or expiry date (where applicable); – any special storage conditions; – handling precautions, where necessary; – identification of the original manufacturing site; and – name and contact details of the supplier.	Label generating systems and procedures should be controlled and documented. Appropriate verification and records should be maintained. If agreed upon with the pharmaceutical customer information about the original manufacturing site may also be provided in other ways or on other documents.
6.9	Relevant storage, handling and safety data sheets should be available.	*Self explanatory*
6.10	Records must be kept and must be readily available upon request in accordance with GSP [3].	The security and methods of archiving and retrieval of such records should be considered.
7	**Repackaging and relabelling**	
7.1	Operations, such as combining into a homogeneous batch, repackaging and/or relabelling, are manufacturing processes and their performance should therefore follow GMP.	Processes where excipients are exposed to the environment such as transferring excipient from one container to another, e.g. from bulk equipment to storage tanks/silos or from storage tanks/silos into containers, are critical for product quality. Under these conditions excipients may be contaminated with other products, lubricants, cleaners or any other foreign matters. To minimize these risks IPEC PQG GMP principles should be applied.
7.2	Special attention should be given to the following points: ♦ prevention of contamination, cross-contamination and mix-ups;	Special attention should be given to the following points: ♦ Contamination, cross-contamination and mix-ups should be avoided by using suitable equipment and cleaning procedures according to the recommendations of chapter 5 of this document and with adequate labeling. Environmental conditions and repackaging procedures should be designed to avoid contamination and cross-contamination during repackaging and relabelling operations. Filtered air in the repackaging area should be

	Good trade and distribution practices for pharmaceutical starting materials (GTDP), **WHO Technical Report Series, No. 917, 2003**	*IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006*
		considered where necessary for the product. Protective clothing for the operators should be clearly defined.
	♦ security of stocks of labels, line clearance checks, on-line inspections, destruction of excess batch-printed labels;	♦ Labels should be printed with a controlled system ensuring that all necessary information is correct *(see 6.8).* Sufficient crosschecks should be installed to ensure proper data transfer. A procedure should be installed to avoid mis-labeling. Therefore printing and usage of labels should be a restricted process. All labelling operations (e.g. generating, printing, storage, usage, destruction) should always be recorded. Labelled containers should be inspected and surplus labels should be destroyed to avoid any misuse. If labels will not be printed just-in–time, security stock should be controlled and limited access should be defined.
	♦ good sanitation and hygiene practices;	♦ Repackaging and relabelling processes should be carried out in an environment clean enough to avoid contamination. It should be clearly defined where and how an excipient will be repackaged and relabelled. Personnel involved in repackaging processes should wear clean protective apparel such as head, face, hand, and arm coverings, if necessary and practice appropriate personnel hygiene (e.g. hand disinfection, following health requirements, health monitoring, covering exposed jewellery). Personnel should be trained on special hygiene requirements. Training should be recorded. Repackaging areas should be regularly cleaned and sanitized.
	♦ maintaining batch integrity (normally mixing of different batches of the same solid material should not be done);	♦ Where new batch numbers are assigned, traceability to original batch numbers should be ensured by proper documentation. Assigning one batch number to containers of different batches complying with the same specification is an unacceptable practice (*see also 7.3 and 7.4*).
	♦ as part of batch records all labels that were removed from the original container during operations, and a sample of the new label, should be kept;	♦ *Self explanatory*
	♦ if more than one batch of label is used in one operation, samples of each batch should be kept; and	♦ *Self explanatory*

	Good trade and distribution practices for pharmaceutical starting materials (GTDP), **WHO Technical Report Series, No. 917, 2003**	***IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006***
	♦ maintaining product identity and integrity.	♦ All repackaging and relabelling processes should be designed and carried out to avoid commingling and carry-over and to ensure full traceability of the excipients back to the original manufacturer and traceability downstream to the final customer. Every step should be sufficiently recorded by responsible personnel. Name of operator, date and time of every step should also be recorded. This should also be ensured if computerized systems are used. All repackaging and relabelling requirements should be defined in written procedures.
7.3	When different batches of a material from the same original manufacturing site are received by a distributor and combined into a homogenous batch, the conformity of each batch with its specification should be confirmed before it is added.	Blending of batches or lots of excipients that individually do not conform to specifications, with other lots that do conform (in an attempt to salvage, or hide adulterated material) is not an acceptable practice. A batch can only be homogenous when conforming material is thoroughly mixed. Mixing to form a homogeneous batch is a manufacturing step and should be defined in a written procedure. Mixing should always be controlled and homogeneity should be verified and documented.
7.4	Only materials from the same manufacturing site received by a distributor and conforming to the same specifications can be mixed. If different batches of the same material are mixed to form a homogeneous batch it should be defined as a new batch, tested and supplied with a batch certificate of analysis. In such cases the customer should be informed that the material supplied is a mixture of manufacturers' batches. The supplied material must have a certificate of conformity to a specification at date of supply.	*See also 7.1* The blending process should be verified to ensure that it will not impact the quality of the excipient. The blended excipient should be tested to ensure conformance to the specification and to provide data for the Certificate of Analysis (COA). A Certificate of Conformity (COC) may be appropriate under certain circumstances with appropriate controls in place.
7.5	In all cases the original COA of the original manufacturer should be provided. If retesting is done, both the original and the new COA should be provided. The batch referred to on the new COA should be traceable to the original COA.	Quality documents accompanying deliveries should be subject to an agreement between distributor and final customer. In case of retesting, analytical methods of the original manufacturer and/or pharmacopoeia methods should be applied. Where other methods are applied, these should be agreed upon between both parties.
7.6	Repackaging of materials should be carried out with primary packaging materials for which the quality and suitability have been established to be equal to or better than those of the original container. The approval of the supplier is necessary for the packaging material used for the repackaging.	Primary packaging material specifications should be established and a written procedure should clearly define primary packaging materials for each individual excipient based upon the excipients stability. If the same type of packaging material is used for repackaging then it should be equivalent to that used by the original manufacturer. In such cases the re-packager and distributor may rely on the manufacturer's stability evaluation and

	Good trade and distribution practices for pharmaceutical starting materials (GTDP), **WHO Technical Report Series, No. 917, 2003**	*IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006*
		assign the same shelf life for the excipient. When primary packaging material differs from the original manufacturer's primary packaging material or if the head space increases significantly, an evaluation of the container and its closure system should demonstrate that it is adequate to protect the excipient from deterioration and contamination beyond its established specification for the shelf life (re-test or expiration period) defined by the excipient manufacturer. Otherwise the shelf life defined by the manufacturer cannot be transferred to the repackaged material. The need for stability studies should be confirmed. Storage and handling procedures should be installed which protect containers and closures and minimise the risk of contamination, damage or deterioration, and which will avoid mix-ups (e.g. between containers that have different specifications but are similar in appearance).
7.7	The re-use of containers should be discouraged unless they have been cleaned using a validated procedure. Recycled containers should not be used unless there is evidence that the quality of the material packed will not be adversely affected.	Returned containers may have unknown residues from other than the intended use. Therefore, use of new containers is recommended for excipients. However, if containers are reused, a procedure should demonstrate a rationale for cleaning procedures for specific excipients and their different types of container *(see also 5.8).* There should be an agreement defining the specific conditions (e.g. handling, sealing, cleaning) of reuse between distributor and customer. If returnable excipient containers are reused, all previous labelling should be removed or defaced.
7.8	Materials should be repackaged only if efficient environmental control exists to ensure that there is no possibility of contamination, cross-contamination, degradation, physicochemical changes and/or mix-ups. The quality of air supplied to the area should be suitable for the activities performed, e.g. efficient filtration.	Environmental controls should ensure that temperature, humidity and cleanliness of air and equipment are appropriate to avoid any contamination or deterioration of the excipient. It is recommended to define the necessary environmental conditions for the repackaging of each excipient. Environmental control is a specialist subject and experts should be consulted. (*see also section 2.6).*
7.9	Suitable procedures should be followed to ensure proper label control.	Procedures should be implemented to ensure that the correct quantity of labels are printed and issued and that labels contain the necessary information. The procedure should also define that labels are reconciled and any excess labels immediately destroyed or returned to controlled storage and appropriately recorded. Repackaging and relabelling facilities should be inspected immediately prior to use, ensuring that all materials that are not required for the next repackaging operation have been removed.
7.10	Containers of repackaged material and relabelled containers should bear both the	If agreed upon with the pharmaceutical customer, information about the original

	Good trade and distribution practices for pharmaceutical starting materials (GTDP), **WHO Technical Report Series, No. 917, 2003**	*IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006*
	name of the original manufacturing site and the name of the distributor/repacker.	manufacturing site may also be provided in other ways or on other documents.
7.11	Procedures should be in place to ensure maintenance of the identity and quality of the material by appropriate means, both before and after repackaging operations.	These procedures should include documented traceability downstream and up-stream.
7.12	Batch release procedures should be in place in accordance with GMP.	Appropriate testing of repackaged materials should be performed to demonstrate consistency of excipient quality. Testing of the complete specification is not necessary in such cases but some defined key quality parameters, which may be affected by the repackaging process, should be tested. Until these tests have been performed, the repackaged materials should be kept under quarantine and identified as such. The materials should comply with the defined specifications before they can be released for distribution. Excipient testing and release should be performed by the Quality Unit and conform to written specifications and analytical test methods. There should be a procedure to ensure that test data are recorded and evaluated prior to release of the repackaged or transferred excipient.
7.13	Only official pharmacopoeial methods or validated analytical test methods should be used for the analysis.	For control of key parameters during repackaging and or full retesting of excipients, official pharmacopoeia methods or methods validated against the pharmacopoeia methods should be used. Otherwise the original manufacturer's analytical methods are recommended. The methods used should be listed on the Certificate of Analysis accompanying the excipient or made available to the customer by other documents. These documents should also reference any contract laboratory that is used to perform analyses. The Certificate of Analysis should identify which tests have been performed on the individual batch and which tests have been performed via skip lot testing.
7.14	Samples of APIs and excipients of appropriate quantities should be kept for at least 1 year after the expiry or retest date, or for 1 year after distribution is complete.	If excipients are repackaged, processed or packaged from bulk, retained samples representative of the excipient batch should be kept for one year after the expiration or re-evaluation date or for one year after distribution is complete. The sample size should be the amount required to perform two complete analyses. Storage conditions of the samples should avoid any contamination and deterioration.
7.15	The repacker and relabeller should ensure that the stability of the material is not adversely affected by the repackaging or relabelling. Stability studies to justify assigned expiry or retest dates should be conducted if the pharmaceutical starting material is repackaged in a container different from that used by the original	Stability and expiration dating of excipients are primarily the responsibility of the excipient manufacturer. If an excipient is transferred to another container or repackaged by the distributor, stability and shelf life (retest or expiry period) considerations have

	Good trade and distribution practices for pharmaceutical starting materials (GTDP), **WHO Technical Report Series, No. 917, 2003**	***IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006***
	manufacturer. It is recognized that some excipients may not need additional stability studies.	to be taken into account. The type of container, primary packaging materials and storage conditions used by the repackaging site has to be taken into account when shelf life (retest or expiry period) is defined for excipients. The recommended expiration date provided by the original manufacturer should not be extended without demonstrating stability to justify an extended shelf life (retest or expiry period). In such a case the type of container and storage conditions should be clearly defined. If the need for special storage conditions exists (e.g. protection from light, heat, etc.), such restrictions should be indicated on the labelling.
8	**Complaints**	
8.1	All complaints and other information concerning potentially defective materials must be carefully reviewed according to written procedures that describe the action to be taken, and including the criteria on which a decision to recall a product should be based.	Customer complaints and information about possible defects should be systematically documented and investigated, based on a written procedure with assigned responsibilities.
8.2	Any complaint concerning a material defect should be recorded and thoroughly investigated to identify the origin or reason for the complaint (e.g. the repackaging procedure, the original manufacturing process, etc.).	Investigations should be formally conducted and written up in a timely manner to establish if the complaint is justified, to identify root cause(s), to define any initial and/or follow up action(s), and the method of communication, e.g. to the customer, original manufacturer, authorities etc. Complaint records should be retained and regularly evaluated for trends, frequency and criticality in order to identify possible additional needs for corrective or preventive actions.
8.3	If a defect in a pharmaceutical starting material is discovered or suspected, consideration should be given as to whether other batches should be checked.	Investigations should identify whether the reported defect is limited to a single batch of material, or if other batches need to be considered as part of the investigation. Any additional batches implicated should be identified and labelled (e.g. “under quarantine”) accordingly.
8.4	Where necessary, appropriate follow-up action, possibly including a recall, should be taken after investigation and evaluation of the complaint.	For product recalls see section 9. .
8.5	The manufacturer and customers should be informed if action is needed following possible faulty manufacturing, packaging, deterioration, or any other serious quality problems with a pharmaceutical starting material.	Confirmed serious problems related to product quality should be communicated upstream to the manufacturer and also downstream to the customer(s) in case they may have received material with the same batch number.

	Good trade and distribution practices for pharmaceutical starting materials (GTDP), **WHO Technical Report Series, No. 917, 2003**	***IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006***
9	**Recalls**	In the USA the term recall has specific regulatory implications that do not directly apply to excipients; therefore the term retrieval is typically used in the USA.
9.1	There should be a system for recalling promptly and effectively from the market, materials known or suspected to be defective.	Functions involved in the supply chain should implement written procedures to manage excipient recall (retrieval) promptly and effectively. The procedure should: – describe how the process of recall (retrieval) should be managed, based on the risk involved, – describe a decision making process with defined responsibilities, – define the functions involved in the process (e.g. Quality Assurance, sales, logistics, competent authorities etc.) – define the communication process and documentation, and – define the steps needed to retrieve the material.
9.2	The original manufacturer should be informed in the event of a recall.	*Self explanatory*
9.3	There should be established written procedures for the organization of any recall activity; these should be regularly checked and updated.	*Self explanatory*
9.4	All recalled materials should be stored in a secure, segregated area while their fate is decided.	*Self explanatory*
9.5	In the event of serious or potentially life-threatening situations all customers and competent authorities in all countries to which a given material may have been distributed should be promptly informed of any intention to recall the material.	*See section 9.1*
9.6	All records should be readily available to the designated person(s) responsible for recalls. These records should contain sufficient information on materials supplied to customers (including exported materials).	*See section 9.1*
9.7	The effectiveness of the arrangements for recalls should be evaluated at regular intervals.	*Self explanatory*
10	**Returned goods**	
10.1	Goods returned to the supplier should be appropriately identified and handled in accordance with a procedure addressing at least the keeping of the material in quarantine in a dedicated area, and its assessment and disposition by a designated person. Where any doubt arises over the quality of the materials, they should not be considered suitable for reissue or reuse.	Returned excipients should be identified as such and held pending resolution. Procedures for holding, labelling, testing, and any processing of the returned excipient should be in accordance with written procedures. Records of returned products should be maintained and should include the name of the excipient and the lot number (or batch number), reason for the return, quantity returned, date of disposition, and ultimate fate of the returned excipient.

	Good trade and distribution practices for pharmaceutical starting materials (GTDP), **WHO Technical Report Series, No. 917, 2003**	***IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006***
11	**Handling of non-conforming materials**	
11.1	Non-conforming materials should be handled in accordance with a procedure that will prevent their introduction or reintroduction into the market. Records covering all activities, including destruction, disposal, return and reclassification, should be maintained.	*Self explanatory*
11.2	An investigation should be performed to establish whether any other batches are also affected. Corrective measures should be taken where necessary.	The investigation should be documented as well as actions taken to prevent recurrence of the problem.
11.3	The disposition of the material, including downgrading to other suitable purposes should be documented.	*Self explanatory*
11.4	Non-conforming materials should never be blended with materials that do comply with specifications.	*Self explanatory*
12	**Dispatch and Transport**	
12.1	Materials should be transported in a manner that will ensure the maintenance of controlled conditions where applicable (e.g. temperature, protection from the environment). The transport process should not adversely affect the materials.	Transport conditions and the equipment to be used should be defined according to the characteristics of the products. Any special transport conditions should be monitored and recorded.
12.2	Requirements for special transport and/or storage conditions should be stated on the label. If the pharmaceutical starting material is intended to be transferred outside the control of the manufacturer's materials management system, the name and address of the manufacturer, quality of contents, special transport conditions and any special legal requirements should also be included on the label.	Documents accompanying a delivery should also list any special requirements for storage and transportation. If agreed upon with the pharmaceutical customer, information about the original manufacturer may also be provided in other ways or on other documents than the labels.
12.3	The supplier of the materials should ensure that the contract acceptor for transportation of the materials is aware of and provides the appropriate storage and transport conditions.	The supplier should provide the contract acceptor with information about any special requirements for appropriate transport and storage conditions. The ability of the contract acceptor to comply with these requirements should be evaluated.
12.4	Procedures should be in place to ensure proper cleaning and prevention of cross-contamination when liquids (tanks) and bulk or packed materials are transported.	Best practice for bulk transport is to use dedicated equipment and defined handling processes. If this is not possible, the type of transport equipment and suitable supplies (e.g. seals, fittings, hoses, pumps) should be specified. The materials used should be compatible with the transported excipients. Possible incompatibilities between sealing materials or hoses and the product transported should be taken into account especially for solvents. Cleaning procedures with documented evidence of their efficiency should be used between loadings of different materials. Consideration has to be given to previous cargoes. A list of restricted or

	Good trade and distribution practices for pharmaceutical starting materials (GTDP), **WHO Technical Report Series, No. 917, 2003**	***IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006***
		acceptable previous cargoes should be communicated to and agreed upon with the transport companies. Changes to bulk transport equipment and supplies should be well controlled, evaluated and finally approved by the contract giver.
12.5	The bulk transport of pharmaceutical starting materials requires numerous precautions to avoid contamination and cross-contamination. The best practice is to use dedicated equipment, tanks or containers.	*See section 12.4*
12.6	Packaging materials and transportation containers should be suitable to prevent damage to the pharmaceutical starting materials during transport.	*Self explanatory*
12.7	For bulk transport, validated cleaning procedures should be used between loadings, and a list of restricted previous cargoes must be supplied to the transport companies.	*See section 12.4*
12.8	Steps should be taken to prevent unauthorized access to the materials being transported.	Consideration should be given to security aspects. For example, transportation of bulk excipients should have a sealing system in place. Containers should bear tamper evident seals.
12.9	General international requirements regarding safety aspects (e.g. prevention of explosion and of contamination of the environment, etc.) should be observed.	*Self explanatory*
13	**Contract activities**	
13.1	Any activity performed, as referenced in the GMP and GTDP guidelines, delegated to another party, should be agreed upon in a written contract.	Responsibilities for such activities should be referenced in a contract and/or technical agreement.
13.2	The contract giver should evaluate the proposed contract acceptor's compliance with GTDP before entering into an agreement.	The evaluation should include an audit of the contract acceptor's premises and quality system.
13.3	All contract acceptors should comply with the requirements in these guidelines. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.	*See 12.4*
13.4	There should be a written and approved contract or formal agreement between the contract giver and contract acceptor that addresses and defines in detail the responsibilities, GTDP and which party is responsible for which quality measures.	*Self explanatory*
13.5	Subcontracting may be permissible under certain conditions, subject to approval by the contract giver, especially for activities such as sampling, analysis, repacking and relabelling.	*Self explanatory*

APPENDIX A GLOSSARY

Acceptance Criteria
Numerical limits, ranges, or other suitable measures of acceptance for test results. [4]

Active Pharmaceutical Ingredient (API)
Any substance or mixture of substances intended for use in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the body of man or animals. [4]

Agreement
Arrangement undertaken by and legally binding on parties. [1]

Batch (Lot)
A specific quantity of material produced in a process or series of processes so that it can be expected to be homogeneous. In the case of continuous processes, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. [2]

Batch Number (Lot Number)
A unique combination of numbers, letters and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined. [4]

Batch Process
A process that produces the excipient from a discrete supply of raw materials that is present before the completion of the reaction. [2]

Batch Record
Documents that provide a history of the manufacture of a batch of excipient. [2]

Broker / Broking
Brokers resell excipients without conducting physical handling of the product such as warehousing, transport, repackaging etc..

Bulk excipient
Excipient in any transportation or storage equipment (tanks, silos, ISO-Containers, tank/silo trucks etc.) to be filled/repackaged into others (tanks, silos, drums, bags, containers etc.).

Calibration
The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. [4]

Certificate of Analysis (COA)
A document listing the test methods, specification and results of testing a representative sample from the batch to be delivered. [2]

Certificate of Conformity (COC)
A document, which confirms that the product shipped to the customer, complies with a specific set of requirements or specifications. It does not contain actual test results.

Commingling
Unintended blending of traces of carryover material from one batch with another.

Consignment
The quantity of a pharmaceutical starting material made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch. [1]

Contamination
The undesired introduction of impurities of a chemical or microbiological nature, or foreign matter, into or onto a raw material, intermediate, or excipient during production, sampling, packaging, or repackaging, storage or transport. [2]

Continuous Process
A process that continually produces material from a continuing supply of raw material. [2]

Contract
Business agreement for supply of goods or performance of work at a specified price. [1]

Critical
A process step, process condition, test requirement or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the excipient meets its specification. [2]

Cross-Contamination
Contamination of a material or product with another material or product. [4]

Customer
The organization receiving the excipient once it has left the control of the excipient manufacturer; includes brokers, agents and users. [2]

Deviation
Departure from an approved instruction or established standard. [4]

Drug (Medicinal) Product
The dosage form in the final immediate packaging intended for marketing. [4]

Earliest expiry/first out principle concept (EEFO)
A distribution procedure to ensure that the stock with the earliest expiry date is distributed and/or utilized before an identical stock item with a later expiry date is distributed and/or utilized. [1]

Excipient
Substances other than the API which have been appropriately evaluated for safety and are intentionally included in a drug delivery system. [2]

Expiry (Expiration) Date
The date designating the time during which the excipient is expected to remain within specifications and after which it should not be used. [2]

First in/first out principle concept (FIFO)
A distribution procedure to ensure that the oldest stock is distributed and/or utilized before a newer and identical stock item is distributed and/or utilized. [1]

Good Manufacturing Practices (GMP)
That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use. Current Good Manufacturing Practices (cGMP) is the applicable term in the United States. For purposes of this guide the terms GMP and cGMP are equivalent.

Homogeneous material
Material of uniform consistency and composition throughout a batch. [1]

Impurity
A component of an excipient that is not intended to be present but arises as a consequence of the raw materials used or the manufacturing process. [2]

In-process Control / Testing
Checks performed in production to monitor and, if appropriate, to adjust the process and or to ensure that the intermediate or excipient conforms to its specification. [2]

Intermediate
Material that must undergo further manufacturing steps before it becomes an excipient. [2]

Labelling
The action involving the selection of the correct label, with the required information, followed by line-clearance and application of the label. [1]

Lot
See Batch.

Manufacture / Manufacturing Process
All operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage, and distribution of excipients and related controls. [2]

Material
A general term used to denote raw materials (starting materials, reagents, and solvents), process aids, intermediates, excipients and packaging and labelling materials. [4]

Non-conforming Material
Material that does not meet the manufacturer's specifications or has not been manufactured according to applicable GMPs.

Original Manufacturer
Person or company manufacturing a material to the stage at which it is designated as a pharmaceutical starting material. [1]

Packaging Material
A material intended to protect an intermediate or excipient during storage and transport. [2]

Pharmaceutical Starting Material
A pharmaceutical starting material is an active pharmaceutical ingredient (API) or an excipient intended or designated for use in the production of a pharmaceutical product. [1]

Procedure
Written, authorized instruction for performing specified operations.

Processing
Operations to change product characteristics by mainly physical treatment through e.g. milling, sieving, distilling, filtration, blending.

Production
Operations involved in the preparation of an excipient from receipt of materials through processing and packaging of the excipient. [2]

Quality Assurance
The sum total of the organised arrangements made with the object of ensuring that all excipients are of the quality required for their intended use and that quality systems are maintained. [2]

Quality Control
Checking or testing that specifications are met. [4]

Quality Critical
Describes a material, process step or process condition, test requirement or any other relevant parameter that directly influences the quality attributes of the excipient and which must be controlled within predetermined criteria. [2]

Quarantine
The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection. [4]

Raw Material
A general term used to denote starting materials, reagents and solvents intended for the use in the production of intermediates or excipients. [2]

Recall (USA: see Retrieval)
A process for withdrawing or removing a pharmaceutical material from the distribution chain because of defects in the materials or complaints of a serious nature. The recall might be initiated by the manufacturer/importer/distributor or a responsible agency. [1]

Record
Documents stating results achieved and/or providing evidence of activities performed. The medium may be paper, magnetic, electronic or optical, photography etc. or a combination thereof . [2]

Re-evaluation Date (Retest Date)
The date when the material should be re-examined to ensure that it is still suitable for use. [4]

Relabelling
The process of putting a new label on the material (see also *labelling*). [1]

Repackaging
The action of changing the packaging of the material. [1]

Retained Sample
Representative sample of a batch/delivery that is of sufficient quantity to perform at least 2 full quality control analyses and will be kept for a defined period of time.

Retest Date
The date when a material should be re-examined to ensure that it is still suitable for use. [1]

Retrieval (especially in the USA)
Process for the removal of an excipient from the distribution chain. [2]

Sampling
Operations designed to obtain a representative portion of a pharmaceutical starting material based on an appropriate statistical procedure, for a defined purpose, e.g. acceptance of consignments, batch release, etc. [1]

Skip Lot (periodic) Testing
The performance of specified tests at release on pre selected batches and/or at predetermined intervals, rather than on a batch-to-batch basis, with the understanding that those batches not tested must still meet all the acceptance criteria established for that product. This represents a less than full schedule of testing and should therefore be justified, presented to, and approved by, the regulatory authority before implementation. When tested, any failure of the starting material to meet the acceptance criteria established for the periodic (skip lot) test should be handled by proper notification of the appropriate regulatory authority (authorities). If these data demonstrate a need to restore routine testing, then batch-by-batch release testing should be reinstated. [1]

Specification
A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the tests described for a material. [2]

Stability
Continued conformance of the excipient to its specifications. [2]

Supplier
Person or company providing pharmaceutical starting materials on request. Suppliers may be distributors, manufacturers, traders, etc. [1]

Supply Chain
For the purpose of this guideline supply chain is defined as all steps in the entire chain of distribution starting from the point at which an excipient is transferred outside the control of the original manufacturer's material management system downstream to the final user of the excipient.

Top Management
Person or group of people who direct and control an organization at the highest level. The highest level can either be at the site or corporate level and will depend on the way that the quality management system is organized. [2]

Traceability
Ability to determine the history, application or location that is under consideration, for example, origin of materials and parts, processing history or distribution of the product after delivery. [2]

Trader / Trading
See Broker/Broking.

Validation
A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria. [4]

APPENDIX B BIBLIOGRAPHY

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