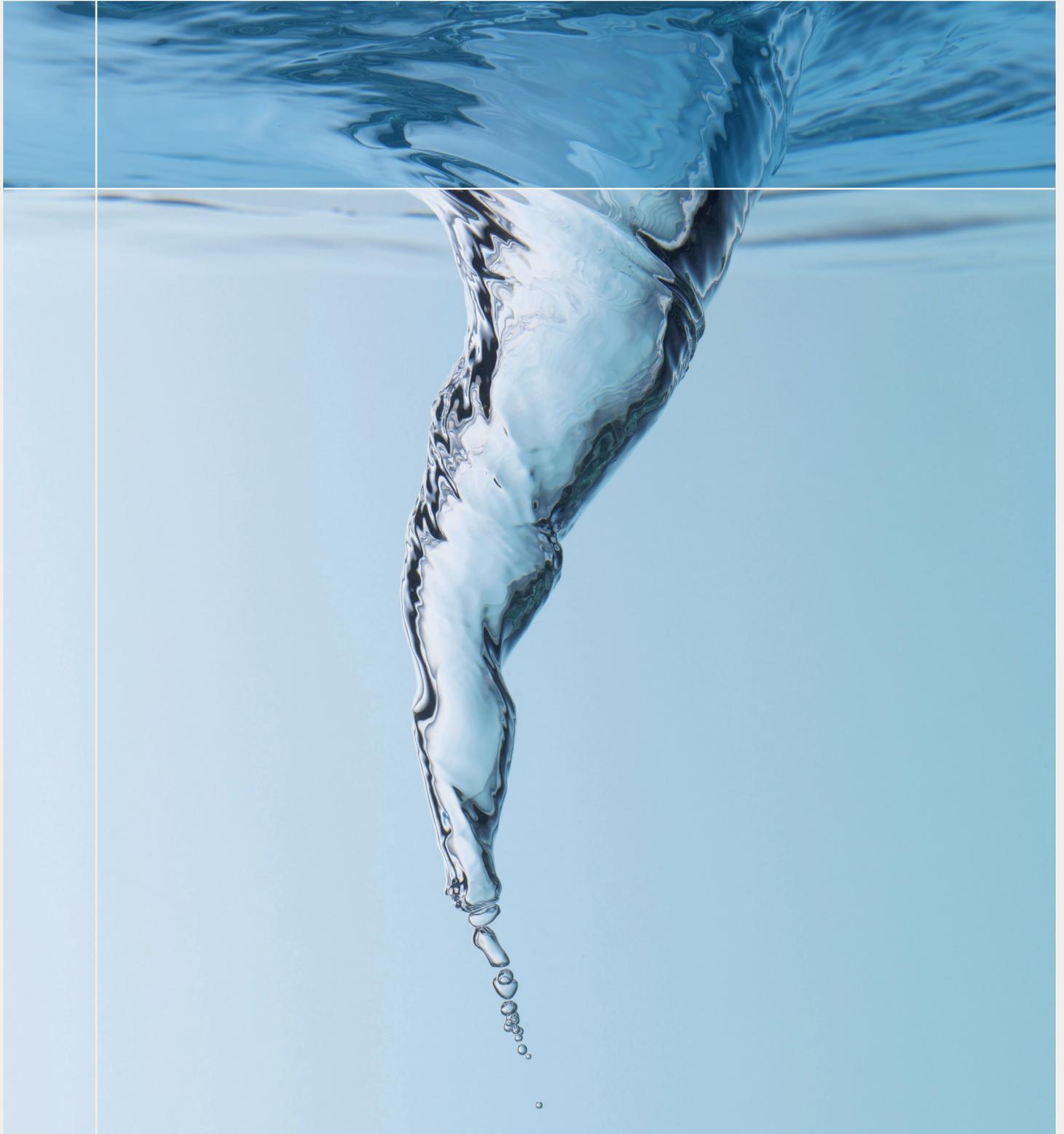


Propylene Oxide / Propylene Glycols Sector Group

Guidelines for Handling and Distribution
of Propylene Glycol USP / EP

Revision 2.2 - May 2013



Member companies

Company

BASF SE

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Contents

1	Introduction	5
1.1	Purpose	5
1.2	Scope	6
1.3	Existing regulations	7
1.4	Product Stewardship	8
2	General Characteristics of the Propylene Glycol USP/EP Distribution Chain	10
2.1	Product traceability	10
2.2	Inspection and testing	10
2.3	Control of non-conforming products & product recall	13
2.4	Handling and storage equipment	13
2.5	Shelf life	14
2.6	Quality records and samples retention time	14
2.7	Personnel qualification & training	14
2.8	Reviews and self-assessments	15
2.9	Change control	15
3	Bulk Storage	16
3.1	General	16
3.2	Basic design and construction	16
3.3	Storage tank operations	17
3.4	Cleaning and maintenance	17
3.5	Returned product	17
4	Loading	18
4.1	General	18
4.2	Basic design and construction	18
4.3	Operations	19
5	Bulk Transportation	20
5.1	General	20
5.2	Basic design and construction	20
5.3	Prior and adjacent cargoes	21
5.4	Sealing	22
5.5	Cleaning	22
5.6	Traceability	22
6	Unloading	23
6.1	General	23
6.2	Basic design and construction	23
6.3	Operations	23

7	Packaging Operations	24
7.1	General conditions	24
7.2	Basic design and construction	25
7.3	Container specifications	25
7.4	Unloading equipment and procedures	26
7.5	Packaging facilities	26
7.6	Marking, sampling, quality control and certificate of analysis	27
7.7	Storage of containers	27
7.8	Loading for shipments	27
8	Traders/Re-sellers, Brokers	28
9	Customer pick-ups	29
	Appendix 1	30
	Product information	
	Appendix 2	32
	Assessment questionnaire for bulk storage/packaging	
	Appendix 3	38
	Assessment questionnaire for warehousing companies	
	Appendix 4	41
	Assessment of Traders/Re-sellers, Brokers	
	Appendix 5	43
	List of References	
	Appendix 6	44
	Definitions	
	Appendix 7	46
	Symbols for Use on Packed Product	

1 Introduction

These Guidelines have been prepared by the European manufacturers (see page 1) of Propylene Glycol USP/EP (Pharmaceutical Grade) under the direction of the Cefic Propylene Oxide/Propylene Glycols Sector Group, following the Responsible Care® programme for the handling and distribution of their products.

1.1 Purpose

Propylene Glycol USP/EP is used as an excipient (inactive ingredient) for the manufacturing of pharmaceutical products. It can also be applied to the production of food, flavours, animal feed and cosmetics. Propylene Glycol USP/EP is a high purity product which has to meet all specification items of the current United States and/or European (USP/EP) pharmacopoeias. The manufacturers of this high quality product are firmly committed and all actors in the supply chain should comply with Quality Management Systems, such as ISO 9000: 2001, ISO 22000, with appropriate principles of current Good Manufacturing Practices (GMP) applicable to excipients, with the programme for food components of Hazard Analysis and Critical Control Points (HACCP) and with Responsible Care® programmes.

Before reaching the final consumer, Propylene Glycol USP/EP is distributed through a chain of operations (handling, storing, transport, packaging, etc) often performed by several successive actors. Current Good Trade and Distribution Practices (GTDP) as published by WHO and IPEC should be considered by all partners involved in the distribution chain.

The purpose of this document is:

- 1) to raise the awareness of each person involved in the distribution chain;
- 2) to provide handling guidelines in order to preserve the initial quality of the product from the manufacturer's bulk tanks to the final customers for their sensitive applications;
- 3) to ensure a high level of protection of public health.

Contamination or mislabelling may lead to potentially severe consequences for human life, especially pharmaceuticals like injection fluids and orally administered drugs, dermal creams and food applications.

All parties involved in the manufacturing and distribution chain of Propylene Glycol USP/EP are responsible for its safe, proper and hygienic handling.

Any company which transports, packages and/or stores, either bulk or packed, Propylene Glycol USP/EP must have in place a system that protects the end users from any quality alterations of the product from the initial manufacturing stage to its final destination.

The Cefic Propylene Oxide/Propylene Glycol Sector Group recommends that these Guidelines be adopted by all parties involved in Propylene Glycol USP/EP distribution, as an Industry Code of Practice. These Guidelines apply to all commercial transactions, including swaps, processing, re-sales and customer product pick-ups and transportation arrangements. Application of SQAS (Safety & Quality Assessment System) is strongly recommended for all logistical service providers and ESAD II Appendix F & G (European Single Assessment Document) for distributors handling Propylene Glycol USP/EP.

1.2 Scope

This document only refers to mono propylene glycol USP/EP (Pharmaceutical Grade). Dipropylene glycol and tripropylene glycol are not classified as pharmaceutical grade products, and therefore are not within the scope of these Guidelines.

Propylene Glycol is also placed on the market as “Industrial/Technical Grade” for various industrial/technical applications. The manufacturing and distribution process of propylene glycol “Industrial/Technical Grade” does not meet the high standards required by USP/EP and therefore must not be used for sensitive applications such as but not limited to pharmaceuticals, food, animal feed, flavours and cosmetics. It is mandatory to use Propylene Glycol USP/EP rather than Propylene Glycol Industrial/Technical Grade in such sensitive applications to avoid any adverse health effects caused by potential impurities.

These Guidelines are mainly concerned with the distribution chain, starting after the manufacturer’s final storage tank and ending at the final user’s storage facilities.

These guidelines are applicable to each step in the supply chain as visualised in Figure 1, such as:

- Bulk storage
- Loading/ unloading
- Transportation
- Filling packages
- Warehousing

Typical actors involved in these operations are:

- Manufacturers
- Transporters
- Terminal operators
- Distributors
- Packaging companies
- Warehousing companies
- Traders/Re-sellers, Brokers

The Guidelines define minimum requirements such as:

- Quality certification
- Traceability and product recall
- Transportation/Distribution controls
- Goods-receipt control
- Intermediate recertification
- Equipment selection and controls
- Personnel qualification

Chapter 2 refers to general principles of current Good Manufacturing Practices (cGMP) which must be applied to all operations of the distribution chain. Chapters 3 to 7 refer to each operation one by one to which specific practices must be applied in addition to the general practices described in Chapter 2.

1.3 Existing regulations

Legislation varies from country to country; it is not the purpose of these Guidelines to take into account all legislation worldwide.

Propylene Glycol is subject to the new legislation for chemicals in Europe, (REACH), which has entered into force on 1st June 2007. Some applications of Propylene Glycol, however, referred to in this document are outside the scope of REACH, such as pharmaceuticals, cosmetics, food and feed.

Even though there are a number of pharmacopoeias, e.g. the United States Pharmacopeia, the European Pharmacopoeia, the Pharmacopoeia of Japan, etc, these Guidelines only refer to the United States and European Pharmacopoeias and are not intended to be comprehensive, even with respect to those two pharmacopoeias.

A number of guidelines relevant to Propylene Glycol USP/EP have been published; see references in Appendix 5. All these documents, with focus on pharmaceutical applications may serve as additional general guidance for the manufacture and distribution of excipients such as Propylene Glycol USP/EP:

- Joint IPEC – PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients, published in 2006, with a corresponding Good Manufacturing Practices (GMP) Audit Guideline published in 2008 by the International Pharmaceutical Excipients Council (IPEC), in collaboration with the Pharmaceutical Quality Group (PQG).
- Good Trade and Distribution Practices for Pharmaceutical Starting Materials, published by World Health Organization (WHO) in 2003.
- The IPEC Good Distribution Practices Guide for Pharmaceutical Excipients, published in 2006, with a corresponding Good Distribution Practices Audit Guideline for Pharmaceutical Excipients, published in 2011 by The International Pharmaceutical Excipients Council.
- The European Single Assessment Document for Chemical Distributors (SQAS – ESAD II), published by Cefic /FECC in 2006, which includes supply chain aspects and a third party assessment scheme. Appendix F has been developed for food, pharmaceutical and/or cosmetic type products, and is based on these Cefic PG USP/EP guidelines. A sub-section G has been added for pharmaceutical excipients.
- ICH – Q7, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, published by the International Conference on Harmonisation (ICH) in 2000. This guide has been taken over in European legislation as part II of EU Guidelines to Good Manufacturing Practices for Medicinal Products for Human and Veterinary Use, 2005.
 - EXCiPACT™, the certification standards for pharmaceutical excipients, published in 2012 by EXCiPACT, a subsidiary of IPEC
 - FSSC 22000 (HACCP, ISO 22000), the certification standard for food materials
 - GMP+ / QS / Ovocom Feed Safety Assurance schemes, the certification standards for feed materials

The Cefic Guidelines for Handling and Distribution of Propylene Glycol USP/EP are focused on the risks in the distribution chain.

Unlike the United States, Propylene Glycol USP/EP is currently not cleared in countries of the European Union as a multi-purpose direct food additive.

In the European Union, several regulations are relevant for Propylene Glycol USP/EP:

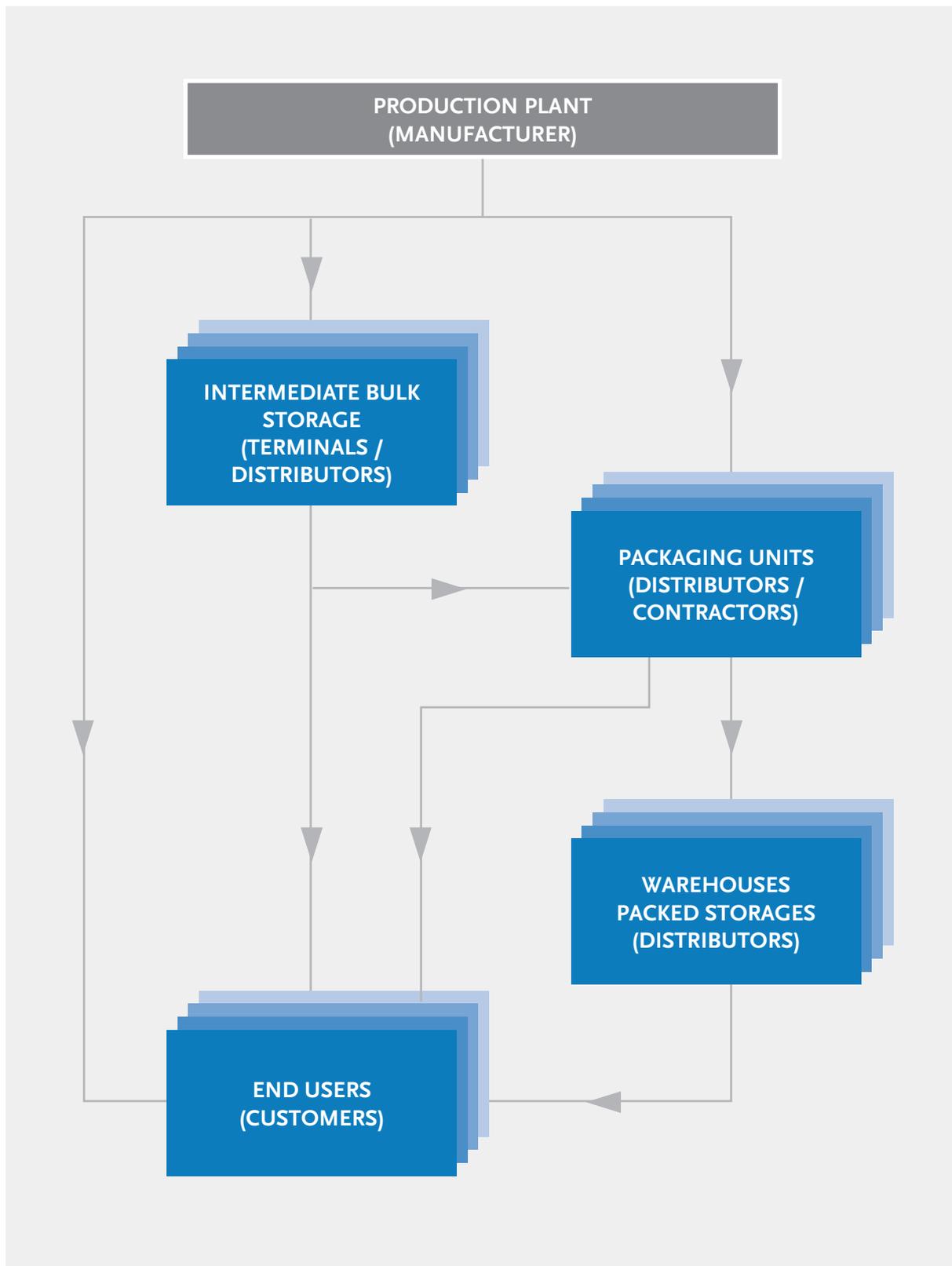
- Commission Regulation (EC) No 1333/2008 on food additives: Propan-1,2-diol (propylene glycol) is listed as food additive in Annexes II+III under E 1520.
- Propan-1,2-diol (propylene glycol), E 1520, is cleared as carrier and carrier solvent for colours, emulsifiers, antioxidants and enzymes (max. 500g/kg in the enzyme preparation), with a maximum allowed content in the final foodstuff of 1 g/kg, allowed in:
 - Flavourings for foodstuff with a maximum level of 3 g/kg
 - Flavourings for beverages with a maximum level of 1 g/l
- Purity criteria for E 1520 are published in Regulation (EU) No 231/2012, laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008.
- Propylene glycol was used as feed additive (E-490) according to regulation EC 1831/2003. From November 2010 propylene glycol is considered a feed material in the EU. This means that all the rules and restrictions for feed materials apply to propylene glycol. The most recent regulation of feed materials is Regulation (EC) No 767/2009. Propylene glycol is not suitable for use in cat feedstuff.
- Propylene Glycol complies with Commission Regulation (EC) No 1223/2009 on cosmetic products and is not included in any of the lists of restricted or banned substances.

Final end-users have the obligation to consult with applicable national government regulations for confirmation of approved and appropriate uses of propylene glycol.

1.4. Product Stewardship

Product Stewardship is one of the fundamentals of Responsible Care®. The whole distribution chain for Propylene Glycol USP/EP must be controlled in order to maintain quality and purity, traceability and safety. If several parties are involved in the distribution chain, everyone should make downstream parties aware of the existence of and need for adherence to and compliance with these Cefic guidelines and should emphasise the importance of Propylene Glycol USP/EP being handled according to these Guidelines at every stage all the way through to the end-user.

Figure : Distribution chain



2 General Characteristics of the Propylene Glycol USP/EP Distribution Chain

This Chapter describes the general handling and distribution principles, applicable to all stages of the distribution chain of Propylene Glycol USP/EP. More detailed practices, specific to each handling stage, are described in Chapters 3 to 7. All practices of this Guideline comply with current Good Manufacturing Practices (cGMP) and recommendations of the ISO 9000 series, or equivalent quality management system as described in Chapter 1.3.

2.1 Product traceability

Traceability requires having a process in place in order to track the history of the material, from the manufacturer's final storage, including the raw materials used for production and the type of packaging, to the final delivery to customers, by means of a recorded identification.

The entire distribution chain must make provisions for a full traceability in order to allow a fast and efficient investigation of any quality issue and/or product recall when required.

To be traceable, each delivery must be identified by product name, origin and lot number together with appropriate shipping and quality documentation too. Mixing of lots from different manufacturers must not be done. See the definitions of "lot" and "lot number" in the Glossary (Appendix 6).

The distribution records must indicate all Propylene Glycol USP/EP shipments and be properly filed. These records must, as a minimum, identify by batch or lot where and to whom the product was shipped, its quantity, carrier and date of shipment.

2.2 Inspection and testing

All Propylene Glycol USP/EP lots must be checked and tested, as described below, before being released for shipment and at the receiving site before being unloaded. These checking/testing records must be kept in writing by the manufacturing plants, the terminals, the distributors and the end customer.

Each time Propylene Glycol USP/EP is transferred from one container to another in the distribution chain (tank, iso-container, drum, etc.) it must be sampled to allow further investigation in case of a quality claim.

Upgrading or otherwise certifying Propylene Glycol Industrial/Technical grade to Propylene Glycol USP/EP is forbidden at any point of the distribution chain, even if the quality certificate shows full compliance.

Analytical testing should be carried out based on documented test methods and procedures, in compliance with cGMP and the applicable current edition of the appropriate pharmacopeia, or any other accepted standard. Non-compendial test methods may be used as long as such analytical tests are demonstrated to be at least equivalent to those in the compendia, and the test method should comply with applicable general chapters and notices. Documented procedures should include laboratory controls as defined in the cGMP.

The following paragraphs describe the minimum checking and testing requirements for either bulk or packed shipments and receptions. They also describe the quality re-certification process in case of intermediate operations (intermediate bulk storage, packaging or repackaging operations, warehousing) in case of mixing of different lots.

2.2.1 Sampling procedure

The following applies to all required points of sampling as outlined in the next chapters of these guidelines:

- Written procedures must be in place, describing in sufficient detail the sampling process, as well as the sample storage conditions.
- All samples must be representative and properly labelled.
- For sampling, only clean odourless glassware, aluminium or stainless steel must be used. Sampling devices should be dedicated to Propylene Glycol USP/EP and labelled.
- Samples must be stored under proper conditions (see Appendix 1, section 2) to preserve the quality of the product and retained in accordance with the provisions of § 2.5 and 2.6 of this Chapter.
- Sample size should be the amount required to perform at least two specification tests. The volume may vary based on the type of analysis required, as detailed in the following paragraphs.

2.2.2 Quality control

For each product lot there must be an appropriate quality certificate such as a certificate of analysis or a certificate of conformity (see Glossary) issued by a qualified laboratory (in-house or outside), certifying conformity to all items of the USP/EP requirements. A certificate of analysis should clearly indicate if analytical test results were obtained from a specific lot or from periodical, statistically based testing.

Key point controls are simple tests performed to identify the product and check for possible contamination. Their purpose is not to modify the initial quality certificate unless USP/EP specification limits are exceeded.

Key points for product identification can be any characteristic test such as density, refractive index, GC, IR spectrum or others. The test must be performed both after each bulk loading and prior to each bulk unloading, as detailed in the following paragraphs.

Key points for contamination detection must include, as a minimum, a visual detection of colour and suspended matter, and a check for unusual odours. It is recommended to also analyse for water content. These tests must be performed each time after the product is transferred into a different tank or container.

If key point controls are in compliance with sales specifications, operations are performed in accordance with these guidelines, and if there is no mixing of different lots, the analytical data of the quality certificate of the upstream materials can be carried over to the downstream lot.

2.2.3 Bulk Receiving controls

For all bulk receptions, the identity of the product must be checked against the delivery documents and the manufacturer's quality certificate. The integrity of the seals must also be checked.

Key point control analysis for contamination detection and for positive product identification must be performed before the material is released for unloading, in accordance with a documented procedure.

In case of non-conformance, the received lot must be carefully segregated and labelled pending further investigations.

2.2.4 Propylene Glycol USP/EP re-certification

Propylene Glycol USP/EP received in bulk can either be stored in an intermediate bulk tank for further use or packed in drums, IBCs or smaller packaging before being stored in warehouses, re-shipped or repacked. In such cases of intermediate handling, a re-certification process must be applied as follows:

2.2.4.1 INTERMEDIATE BULK STORAGE

If the product is unloaded into an intermediate and not emptied (drained) storage tank and/or mixed with another lot, the initial analytical data are no longer valid. A new lot number must be assigned and a new certificate of conformity issued in compliance with the USP/EP requirements. If a certificate of analysis is required, new analyses must be performed, reporting actual test results. In such cases, the remaining shelf life (refer to definition in Appendix 6) of the oldest lot applies.

2.2.4.2 PACKAGING OPERATIONS

When bulk product is packed in drums, IBCs or smaller packaging, each packed lot must be sampled in accordance with an adequate and documented sampling technique (see Chapter 7) and key point controls must be performed on a composite sample representative of the whole lot. If these key point controls are in accordance with sales specifications and there has been no mixing with another lot, the data mentioned in the certificate of analysis of the bulk product from which the packaging was performed can be passed over to the packed lot and used for further shipments.

2.2.5 Shipment controls

2.2.5.1 BULK SHIPMENTS

A sample must be taken from the bulk transport equipment after the filling as indicated above (§ 2.2.1), according to precise procedures to ensure it is representative.

Key point control analysis as indicated above (§ 2.2.2) must be performed for each loading.

As long as key point analyses are performed with positive results, the quality certificate may refer to the tank from which the shipment is done.

2.2.5.2. PACKED PRODUCT SHIPMENTS (DRUMS AND IBCS)

The quality certificate of each lot remains valid during the shelf life period and as long as the packaging is not unsealed. Under these two conditions, the quality certificate of the initial packed lot can be used for each shipment.

2.2.6. Sealing of shipments

All tank trucks, rail cars and containers must be properly sealed with tamper-evident devices. It is recommended that seal numbers be recorded on shipping documents. (For more details see Chapter 5). Identification and integrity of seals must be checked at both sending and receiving locations. Any product received with violated or broken seals must be considered no longer as USP/EP.

2.3 Control of non-conforming products & product recall

If any material fails to conform to the USP and/or EP specifications, or has otherwise been found to be adulterated, contaminated, or mislabelled, such material must be clearly identified and segregated to prevent inadvertent use or delivery. A system should be in place to record any non-conformity and take appropriate action immediately.

In such cases, product quality investigations as well as health risk assessment must be conducted promptly and, when necessary, the non-conforming shipment must be recalled as well as possibly the entire lot. For this purpose, a product recall procedure must be in place, describing responsibilities and required actions to ensure a prompt notification to all parties involved and, if necessary, an immediate recall of the whole lot. The downgrading to technical grade or disposal of such product should be documented. Non-conforming materials must never be blended with materials that do comply with specifications. The effectiveness of the recall procedure should be evaluated regularly.

Records must be kept showing final destination and utilisation (for instance downgrading or destruction of the product) of all non-conforming quantities as well as the root cause analyses and the corrective action applied to avoid re-occurrence.

2.4 Handling and storage equipment

All equipment surfaces in contact with Propylene Glycol USP/EP must be made of a material that does not affect its quality and must be easy to clean. Aluminium, stainless steel, coated carbon steel or food-approved, non-transparent (opaque) plastics are recommended.

Each piece of equipment in contact with Propylene Glycol USP/EP must be solely dedicated to Propylene Glycol USP/EP, or as a minimum to food grade products or Propylene Glycol Industrial/Technical Grade and properly labelled. When cleaning is necessary (for instance in case of product change or maintenance activity) a documented cleaning procedure, validated for effectiveness, must be applied. In all circumstances, stringent restrictions must be applied to the last product handled, and efficient inspection must be performed, in accordance with written procedures, before putting the equipment in service (see following chapters).

Any substance required for the operations such as for example lubricants or coolants, must not come into contact with Propylene Glycol USP/EP. Substances acceptable for food grade applications must be used where contamination is possible.

It is recommended to avoid contact of the product with air and moisture as much as possible.

Maintenance activities should be carried out according to written instructions, which should include considerations to minimize the risks for product contamination. Records of major equipment maintenance & cleaning operations must be maintained.

A clean environment must provide protection from foreign materials such as dust, insects, odorous and/or toxic compounds as much as possible.

2.5 Shelf life

Information concerning shelf life or expiry date of Propylene Glycol USP/EP should be given based on the manufacturer's own stability tests. Storage conditions, recommended by the manufacturers should be followed (see Appendix 1, section 2). Even with nitrogen blanketing, the shelf life of Propylene Glycol USP/EP should not exceed the manufacturer's recommendation. Manufacturers do not support shelf life extension but do recommend downgrading to Propylene Glycol Industrial/Technical Grade.

2.6 Quality records and samples retention time

Quality records (e.g. but not limited to certificate of analysis, traceability documents, inspection reports, analytical records) must be kept as a minimum for the recommended product shelf life plus one year.

Samples taken for each lot quality certification must also be retained during the product recommended shelf life plus one year.

Samples taken for key point controls must be retained for a minimum of 3 months, but a longer storage period is recommended.

2.7 Personnel qualification & training

Operation & maintenance personnel engaged in product sampling, handling, storage, packaging and transportation & equipment maintenance operations which may affect the quality of the Propylene Glycol USP/EP, must:

- Be aware of the principles of cGMP and cGTDP.
- Be qualified for the tasks to be performed in accordance with company policies.
- Receive appropriate information and/or training for working in sensitive product applications and for using job-specific procedures on a regular basis, with training records being archived.
- Demonstrate good hygiene and health.
- Wear clean clothing adequate for the duty performed.

Access to areas where the product is exposed to a risk of contamination must be limited to authorised personnel.

Also non-operational personnel (e.g. logistics, marketing, etc.) involved in the administration of the Propylene Glycol USP/EP distribution chain must have received a proper training focused on the sensitivity of the product applications.

2.8 Reviews and Self-assessments

All Cefic PO/PG members support and strongly recommend the application of the SQAS – ESAD II third party assessment scheme, specifically section F for the handling of Propylene Glycol USP/EP by supply chain parties. ESAD II section F, including the assessment questionnaires apply more generally to food/pharma and/or cosmetic grade products. They consist of a comprehensive assessment scheme, originally developed based on the Cefic Propylene Glycol USP/EP guideline, with added contents, e.g. a sub-section G for pharmaceutical application.

Application of the individual Propylene Glycol USP/EP assessment questionnaires as proposed in Appendices 2 and 3, is still considered a minimum requirement in cases where an ESAD II section F assessment has not been completed by the supply chain operator.

The results of these reviews must be brought to the attention of all parties involved. When necessary, action plans to correct instances of non-conformance must be defined and proper execution followed up, and documented.

In the absence of ESAD II assessment all parties involved in the Propylene Glycol USP/EP distribution chain must periodically perform self-assessment to evaluate their compliance with these guidelines.

If the reviewed company refuses to correct its deficiencies within an acceptable timeframe, the manufacturer must refuse delivery of Propylene Glycol USP/EP for the non-conforming operation.

Assessment questionnaires are proposed in Appendices 2 and 3. Appendix 2 is dedicated to intermediate storage and/or packaging activities, while Appendix 3 has been developed for warehouse activities.

A minimum compliance of 90 % on these questionnaires (Appendix 2) is recommended throughout the whole supply chain (manufacturers, distributors engaged in intermediate bulk storage and/or packaging). In addition all the parties should comply with all the principles considered as essential minimum requirements (**questions marked in bold – see Appendix 2**).

Distributor warehouse locations should also comply with certain minimum requirements **as marked in bold in Appendix 3**.

2.9 Change control

Effective control of change should be managed by the principles of the cGMP of IPEC, further detailed in the (IPEC Americas) Significant Change Guide whenever the product is used as a pharmaceutical excipient. Furthermore, if the product is used in food or feed, the applicable principles of the programmes of HACCP or Iso 22000 may be required. Changes that may impact the quality of Propylene Glycol USP/EP should be evaluated and approved before implementation. Significant changes shall be communicated to the customer and, as applicable, to the regulatory authorities in a timely manner before implementation.

3 Bulk Storage

3.1 General

Propylene Glycol USP/EP presents no unusual storage problems since the product does not freeze at ambient temperature and has a low vapour pressure and high flash point, which makes handling relatively easy. Product does, however, become viscous at low temperatures and the storage system may need to be designed for this possibility. Special care must be taken to avoid any contamination of the product while in the bulk storage tank and piping system. The recommendations of Chapter 2 must also be considered.

3.2 Basic design and construction

It is recommended that the entire storage equipment, including storage tank, piping system, pumps and filters is dedicated for usage of Propylene Glycol USP/EP and clearly labelled. Alternatively, the last utilisation of the entire equipment should be as a minimum for Propylene Glycol Industrial/Technical Grade, or other USP/EP or food grade material. In any case, a written cleaning procedure, validated for effectiveness, must be used whenever a change in product service is necessary.

Storage tanks should be located in contained areas, which should be preferably covered by concrete, asphalt or similar materials.

The bulk storage tank and piping system of a distributor or terminal location should be inspected on site and approved for operations by the Propylene Glycol USP/EP manufacturer or their authorised third party prior to receiving product for the first time.

The design of the sample point at a storage tank and the sample method should ensure that a representative sample can be obtained.

3.2.1 Materials of construction

A full stainless steel, aluminium or food grade approved non-transparent plastics system is recommended for Propylene Glycol USP/EP storage equipment. Contact with carbon steel should be avoided for the risk of iron contamination and deterioration of product colour.

3.2.2 Coating

As an alternative to stainless steel or aluminium, a carbon steel tank, lined with a food grade approved epoxy/phenolic or phenolic resin coating may also be used for product storage.

3.2.3 Storage atmosphere

Propylene Glycol USP/EP is hygroscopic. Atmospheric vents should be equipped with drying devices to protect product from humidity. Product degradation leading to increased levels of oxidation products may occur if Propylene Glycol USP/EP is stored with exposure to air over long periods of time.

Nitrogen blanketing is the preferred means of keeping the product dry and ensuring the shelf life. The quality of the blanketing gas must be controlled and be compatible with USP/EP requirements, especially regarding absence of dust.

If the system is shared with multiple products, steps should be taken (provision should be made) to prevent cross-contamination such as by use of regularly maintained check valves.

3.2.4 Heating/Insulation

The storage temperature of Propylene Glycol USP/EP should not exceed 40°C. In cold climates, external electric heating systems or heat exchangers and/or tank insulation have to be installed. Heat exchangers should then be constructed of stainless steel on the product side and preferably operated with hot potable water. Direct heating with high-pressure steam should be avoided due to risk of local product overheating.

3.3 Storage tank operations

Written operating procedures must be established for the storage tank operations of Propylene Glycol USP/EP. Quality control must be performed according to Chapter 2.

3.4 Cleaning and maintenance

Cleaning and maintenance activities of Propylene Glycol USP/EP storage equipment should be carried out according to written procedures and documented. Only hot potable water or condensate must be used as the last cleaning agent. All activities must be performed without any risks of product contamination. Before return to operation, the equipment should be flushed with the product and the last flush should fulfil the requirements of the Propylene Glycol USP/EP specification.

3.5 Returned product

Any Propylene Glycol USP/EP returned with the security seals not intact must not be fed back into the USP/EP distribution chain. In order to avoid any risk of undetected contamination, it is recommended to downgrade any returned product from Propylene Glycol USP/EP to Propylene Glycol Industrial/Technical grade.

4 Loading

4.1 General

Propylene Glycol USP/EP is not classified as a hazardous product according to EU criteria. Bulk loading into tank trucks, ISO tank containers, rail tank wagons, barges or vessels presents no specific safety hazard. However, loading facilities should be designed and constructed in such a way as to ensure product quality is maintained and to avoid product contamination during the loading process. Recommendations of Chapter 2 must also be considered.

4.2 Basic design and construction

It is highly recommended that the entire loading equipment, including the piping system, pumps, valves, flow elements, rigid loading arms or flexible hoses be in dedicated usage for Propylene Glycol USP/EP and clearly labelled. Alternatively, direct prior use of the entire equipment should have been, as a minimum, for Propylene Glycol Industrial/Technical Grade, acceptable food grade or pharmaceutical products. In any case, a written cleaning procedure, validated for effectiveness, must be used whenever a change in product service is necessary.

The preferred material of construction for the piping and loading arm is stainless steel, but carbon steel coated with an approved food grade lining (see Chapter 3.2.2) can also be used.

The entire loading area should be clean and preferably equipped with a roof and weather protection.

Loading of tank trucks, railcars and ISO tank containers is preferably carried out in a dedicated loading bay via a dedicated loading arm through the bottom valve. In case of loading through the top dome, it should be covered during the loading process to avoid contamination by dust or water. Loading through dedicated flexible hoses may also be done, as long as they are properly stored to avoid contamination and misuse.

The entire equipment including all connections and hoses must be immediately drained and capped and in case of irregular use preferably sealed after usage in order to protect the product against dust and moisture.

4.3 Operations

All loading activities should be described in written procedures.

It is recommended to use a loading checklist, signed by the loading operator and filed. Special attention should be given to excluding filling mistakes. In particular, the following controls should be performed as a minimum:

- review of certificate of adequate cleaning and pre-load restrictions for transport equipment (see Chapter 5).
- visual inspection for cleanliness and dryness of transport equipment and its accessories (like valves, outlets etc.).
- cleanliness of loading equipment.
- proper connection(s) between loading and transport equipment.
- proper closing and sealing of all valves and openings after completion of loading.

For loading of larger product volumes (capacity higher than 100 metric tons) into ships and barges, it is recommended to use a modified procedure, controlled by an independent surveyor, including the following steps:

- visual inspection of tank compartment, loading lines, manifolds and pumps to ensure these are clean, dry and odour free.
- if the compartment is not dedicated to Propylene Glycol USP/EP service, the compartment needs to be washed (see Chapter 5).
- a review for acceptable prior cargoes must be carried out to ensure compatibility with Propylene Glycol USP / EP. (see Chapter 5.3).
- the material of the compartment should be confirmed to stainless steel or coated as per Chapter 3.2.2.
- loading of a small initial amount of material (approximately 20 metric tons).
- circulation of this material through all lines, tanks and accessories, used for the corresponding shipment.
- taking a sample of this material and performing key point control analysis for contamination detection.
- continuation of the loading process till completion, if the key point controls are in compliance with the Propylene Glycol USP/EP sales specification. Otherwise remove the initial amount and repeat the operation.
- after completion of the loading, all compartments and dedicated lines and pumps linked to the compartment are to be sealed.

Sampling and key point control analyses after the completed loading process must be performed as outlined in Chapter 2.

5 Bulk Transportation

5.1 General

Transportation of Propylene Glycol USP/EP requires high quality standards in order to avoid product contamination. Transportation companies should demonstrate a proven commitment to these standards, using quality management systems as described in Chapter 1.1. Typical means of transport for Propylene Glycol USP/EP in bulk are ships, barges, tank trucks, ISO tank containers and rail tank wagons. It is recommended that hauliers for road transportation be evaluated in accordance with the Safety and Quality Assessment System (SQAS) or similar schemes. Ships used for the transportation of Propylene Glycol USP/EP should be evaluated by CDI (Chemical Distribution Institute) or a similar organisation. Rail companies should also have quality management systems in place. Recommendations of Chapter 2 must also be considered.

Contractual arrangements with transportation companies must explicitly ensure transportation is not sub-contracted, unless specific controls are satisfied, ensuring the same level of quality and product purity. The contract acceptor should inform of subcontracting and seek the approval of the contract giver before start of any sub-contracting transport activities.

Trans-loading or trans-boarding between intermediate vessels like for instance from ship to barge should be avoided. Where trans-loading is unavoidable the vessels and hoses used must follow current prior cargo requirements, and the operation must be reviewed and approved by the Quality Assurance Manager or designated personnel.

5.2 Basic design and construction

5.2.1 Truck/Railcar/Container

Stainless steel, aluminium or food grade approved coated carbon steel are recommended as tank materials. Teflon, Gylon 3500, Garloc 900, Viton (vapour space only) or similar should be used for all gaskets, whereas Neoprene or natural rubbers are to be excluded due to intense swelling, deterioration and risk of cross contamination.

The same type of gaskets should also be applied, as required, for other equipment in contact with Propylene Glycol USP/EP, see Chapter 3, Bulk Storage, Chapter 4, Loading, Chapter 6, Unloading and Chapter 7, Packaging operation.

It is recommended to use similar technology as for food grade trucks, containers and railcars.

5.2.2 Ship/Barge

Although stainless steel is the best material of construction, ship and barge tanks may also be made of carbon steel, coated with a Propylene Glycol USP/EP manufacturer approved epoxy/phenolic or phenolic resin.

5.3 Prior and adjacent cargoes

A documented prior and adjacent cargo policy must be developed and applied for all shipments in non-dedicated transportation equipment to protect end-users from product cross contamination. This policy must include either a positive or a negative list (allowed or prohibited last cargoes), and should be applied for the last previous cargo as a minimum.

The following criteria should serve as guidance to develop a positive list with permitted prior cargoes:

- A food grade material with the exception of those originating from animal substances (applicable whenever the product is certified to meet Kosher or Halal requirements).
- A material not classified as toxic, carcinogen, teratogen, mutagen or reproductive toxin by any respected publication or authority.
- A material not classified as insecticide, pesticide, herbicide, biocide or fungicide.
- A material not reactive with Propylene Glycol USP/EP.

It is recommended that for coated/lined tanks, the three prior cargoes comply with the list of permitted prior cargoes.

It is highly recommended that any exception to these criteria should be tolerated only if approved by competent quality assurance personnel, based on application of specific risk analysis criteria. This evaluation might involve consideration about for example physical properties of the material in question and application of specific cleaning procedures and surveillance activities.

5.3.1 Tank Truck/Railcar/Container

It is highly recommended to only use tank trucks, containers and railcars, dedicated to Propylene Glycol USP/EP.

If not product dedicated the transportation equipment should preferably be in dedicated use for food grade products. A specific cleaning procedure, preferably for food grade materials, must be used, with documented evidence of its efficiency. The actual previous last cargo must be mentioned on the cleaning certificate, which should be issued as European Cleaning Document (ECD).

In addition, a list of prohibited or allowed last cargoes must be defined on the basis of the acceptability criteria as stated above and applied to shipments in non-dedicated transport equipment.

5.3.2 Ship/barge

A similar or same previous cargo restriction or allowance policy as for land transport in non-dedicated equipment should be applied for non-dedicated ships and barges, ensuring that the product is not loaded after compounds that would affect the quality even at very low levels of contamination.

It is recommended that multi-compartment deliveries be carried out with only Propylene Glycol USP/EP compatible products in the adjacent tank compartment in accordance with the prior cargo list.

5.4 Sealing

Loading and unloading valves and domes (as well as the tube boxes) of transportation equipment, used for bulk transportation of Propylene Glycol USP/EP, must be sealed after loading, using tamper-evident and preferably numbered seals in order to ensure that impurities cannot be introduced either inadvertently or on purpose during transport. A way to ensure this is to record seal numbers on the shipping documents, so that the offloading site is able to match the numbers against the incoming papers. If the shipment arrives at the final destination with one or more of these seals broken, replaced or missing, the incident should be documented and the supplier informed. The product must no longer be used as Propylene Glycol USP/EP grade material. When trucks and railcars, exclusively dedicated to Propylene Glycol USP/EP are used, the same sealing procedures should be applied to the empty, returned transport equipment (i.e. sealing must be done immediately after loading is completed). Sealing of ships and barges is also required.

5.5 Cleaning

Proper cleaning and inspection of the non dedicated transportation equipment coming back from maintenance is of the utmost importance and must be performed on every tank truck/container/rail car prior to loading, including pumps, hoses, seals and other equipment, coming into contact with the product. Cleaning of tank trucks and containers should be carried out in SQAS assessed cleaning stations. The cleaning procedure should be documented, verified for efficiency and must not be changed without proper notification and approval. It is highly recommended to apply cleaning standards for food grade products, EFTCO-codes F. A cleaning certificate must be provided, including the type of last cargo, preferably in the format of the ECD.

It is highly recommended that ships and barges be inspected and analytically tested for prior cargo according to written procedures, by an authorised laboratory or an independent surveyor, before the loading of Propylene Glycol USP/EP is allowed (see Chapter 4, § 4.3).

Tank trucks, rail cars and containers, used in dedicated transport for Propylene Glycol USP/EP, may not need to be cleaned before being reloaded, if all valves are immediately resealed after unloading at the offloading site and after return are proven to be undamaged. It is recommended to take a sample of the heel and to test for contamination or product degradation prior to reloading. However, to avoid any risk of cross contamination, possibly caused during the unloading process at the customer, at least a simplified cleaning may be considered.

5.6 Traceability

Distribution records should be kept for all Propylene Glycol USP/EP shipments, including as a minimum lot number, name and location of receiving party, quantity, carrier and date of shipment (see also Chapter 2, § 2.1).

6 Unloading

6.1 General

Propylene Glycol USP/EP is typically unloaded from bulk transportation in tank trucks, ISO tank containers, rail tank wagons, ships or barges into a storage tank, for repackaging into smaller containers such as IBCs, drums or smaller packages or for end-use at final customers. Unloading facilities and operations must be designed and constructed in such a way as to maintain product quality and to avoid any product contamination during the unloading process. The recommendations of Chapter 2 must also be considered.

6.2 Basic design and construction

It is recommended that the entire unloading equipment, including piping systems, pumps, filters, valves, flow measuring elements, is dedicated for usage of Propylene Glycol USP/EP and clearly labelled. Alternatively, the last use of the entire equipment should be as a minimum for Propylene Glycol Industrial/Technical grade, acceptable food grade or pharmaceutical grade products. In any case, a written cleaning procedure, validated for effectiveness, must be used whenever a change in product service is necessary.

Preferred material of construction for the piping is stainless steel.

Unloading is preferably carried out by using a pump, and a dedicated arm or a flexible hose (see Chapter 4 § 4.2) connected to the bottom valve of the bulk transportation equipment. A filter on the vapour phase inlet is recommended to avoid ingress of particles during unloading. Alternatively, unloading may be achieved by pressurising the transport equipment with clean nitrogen or dry, filtered air.

The entire unloading equipment including all flexible connections and hoses should be immediately drained and capped and preferably sealed after usage to protect the product against dust and moisture. Flexible hoses must be properly stored to avoid contamination and misuse. It is recommended to use the customer's own dedicated hoses.

6.3 Operations

All unloading activities should be described in written procedures.

It is recommended that an unloading checklist is used, signed by the unloading operator and filed.

Prior to unloading, all seals must be checked for correctness and the material identified based on shipping documents. A representative sample must be taken, analysed for key point control items, as detailed in Chapter 2 § 2.2, and released for unloading with corresponding proper documentation. See Chapter 2 § 2.2.1 and § 2.5 for minimum sample size and storage time.

7 Packaging operations

In these guidelines packaging is defined as filling containers such as 200/250 litre steel or plastic drums and 1 m³ IBCs and smaller packaging from a bulk Propylene Glycol USP/EP storage tank or directly from bulk transport equipment (eg. tank trucks).

The requirements of this Chapter do not apply to the filling of sampling bottles.

Documented procedures must be applied and adequate equipment must be used to protect the quality and purity of the product and to ensure that the correct labels are applied to each container.

The following covers the operation chain from the reception of the bulk materials to the dispatch of container lots (drums or IBCs) loaded in a truck or a dry container, ready to be shipped out of the packaging and storing site.

The recommendations of Chapter 2 must also be considered.

7.1 General conditions

Sites where such operations are performed must comply with the following:

- a. The site must be efficiently secured. Access to the site must be limited to authorised persons only.
- b. The areas dedicated to Propylene Glycol USP/EP handling and storing must be clearly marked, preferably dedicated to compatible products such as USP/EP compliant or food grade material and effectively separated from other types of products.
- c. The presence of any toxic product in or near the packaging area must be identified and recorded. Any risk of cross contamination and handling mistakes with a toxic product must be evaluated and proper prevention enforced. The use of insecticides etc. needs to be controlled.
- d. All operational, technical and administrative personnel involved in those operations must be fully aware of the requirements of these guidelines, and be trained accordingly. Personnel should wear clean clothes as specified, practice personal hygiene and be regularly trained.
- e. The site must be kept in clean and orderly conditions, and industrial hygiene must be maintained.

7.2 Basic design and construction

All equipment in contact with the product (pipes, hoses, pumps, etc) must comply with requirements of Chapter 2 § 2.4 (Handling and Storage equipment).

It is recommended that every piece of equipment in contact with the product, including piping systems, hoses, pumps, filters, valves, flow measuring elements, be dedicated for usage of Propylene Glycol USP/EP and clearly labelled. Alternatively, the direct prior use of the relevant equipment should be as a minimum for Propylene Glycol Industrial/ Technical grade, or USP/EP compliant or food grade material. In any case, a written cleaning procedure, (see Chapter 3.4) validated for effectiveness, must be used whenever a change in product service is necessary.

This equipment must be made of easy to clean material. Stainless steel or coated steel is recommended (see Chapter 2.4 and Chapter 3.2).

All accessories such as gaskets or pump seals must be made of food/pharmaceutical compatible material (asbestos is forbidden).

All products such as for example pump lubricants or greases on loading arm joints which might contaminate the Propylene Glycol USP/EP in the event of mechanical failure must be food grade approved.

7.3 Container specifications

7.3.1 Drums

The manufacturing and handling of empty containers should be considered as an important part of the distribution chain of Propylene Glycol USP/EP. As a consequence, attention must be paid to the following requirements:

- Reconditioned drums must not be used.
- On each empty drum, the drum manufacturing lot number and the supplier identification must be marked to provide complete quality traceability along the distribution chain.
- The internal cleanliness of the drums must be controlled according to written procedures, with special care to prevent dust, foul odours, insects or foreign matter.
- Drums must be closed at the drum manufacturing facilities and opened just before filling in the packaging area.
- The drum manufacturer needs to be informed of the sensitive usage of the supplied drums. It is recommended to regularly assess packaging suppliers. Packaging specifications should be agreed in writing with suppliers.
- All steel drums must be internally coated with a food grade approved material.
- Plastic drums must be made of a food grade approved material. Non-transparent (opaque) plastics must be used to protect the product against any sunlight induced decomposition.
- Consideration should be given to potentially reduced shelf life or stability of the product when stored in plastic containers.
- It is recommended to perform shelf life testing to evaluate potential influences of the packaging material when the packaging supplier and /or the type of packaging are changing.
- As indicated in sections 7.7 and 3.2.4, the packed product should be shielded against direct sunlight and rain, and the temperature should be kept below 40° C. In case symbols are used on drums and IBCs, Appendix 7 shows the recommended symbols.

7.3.2 IBC's

Propylene Glycol USP/EP may also be delivered in intermediate bulk containers (IBC's), typically of 1 m³ size.

Specifications as described in 7.3.1 are also applicable for IBCs.

Stainless steel IBCs dedicated to Propylene Glycol USP/EP may be reused as long as either heels are analysed for contamination or degradation, or IBCs are cleaned according to validated cleaning procedures for food grade products prior to refilling. It is not recommended to return plastic IBCs for reuse with Propylene Glycol USP/EP.

7.4 Unloading equipment and procedures

The unloading station must provide easy access to the bulk transport equipment (road tanker, ISO containers, rail tank cars) with proper identification and specific connections. The requirements of Chapter 6 must be applied.

Prior to discharge, the product must be quality tested and released (see Chapter 6 § 6.3).

The transport equipment can be discharged either with a dedicated pump or by pressurising with high purity and filtered nitrogen (purity above 99.95 %) or dry, filtered air.

It is recommended to filter the product with a Propylene Glycol USP/EP compatible filter (in the range of 25 microns made of non-fibre-releasing material). The filter should be regularly maintained based on a written procedure and documented.

7.5 Packaging facilities

The packaging operation must be conducted in a clean environment, preferably in a positive air pressure room of appropriate quality to ensure product integrity during the filling operation. Adequate control of dust, dirt, insects, chemical vapours, exhaust fumes from vehicles, etc. must be maintained to prevent contamination. Personal hygiene requirements of operational personnel must be followed.

Opening of empty containers, sampling and sealing of the bungs must be done in the clean environment before releasing for storage. It is recommended to apply a packaging checklist with appropriate documentation.

7.6 Marking, sampling, quality control and certificate of analysis

The lot number and container reference number must provide full traceability, allowing the identification of the packaging site, the packaging date and the origin of the product. It is recommended that the filling and marking operations be done simultaneously.

Each lot/batch of filled containers must be sampled in accordance with written procedures, which can be based on a statistical method.

Quality controls must be performed according to Chapter 2 § 2.2.

It is recommended that production and expiry date or shelf life be indicated on each container.

Written procedures for labelling operations such as generating, printing, storage, usage and destruction of labels and labelling of containers should be implemented with sufficient documentation to avoid wrong labelling. Pre-printed labels should be stored in a secure location, excess labels should be destroyed with documentation. A sample label of each batch should be kept.

7.7 Storage of containers

Containers must be stored in dedicated areas, with adequate separation from toxic products.

Rejected, recalled, returned or damaged containers should be marked and segregated in a quarantine area.

First in - first out inventory (FIFO) management or equivalent must be applied for the control of shelf life.

Avoidance of light exposure and maximum temperature conditions as indicated by the manufacturer must be respected.

Any opening of the containers in the storage area is prohibited.

A written programme for pest control should be implemented for storage, re-packaging and loading/unloading areas. Inspection records should be kept.

7.8 Loading for shipments

Loading operation of trucks or dry containers should be performed according to a written checklist with final inspection for conformance to avoid any misloading. The checklist and packaging list should be verified for correctness and checked and signed by two persons.

8 Traders/Re-Sellers, Brokers

Due to the sensitive applications of Propylene Glycol USP/EP it is highly recommended to keep the supply chain as transparent and short as possible. As a minimum, quality and traceability must be controlled throughout the supply chain to the end-user.

If traders and brokers cannot be avoided, the same requirements as for chemical distributors apply. Such parties, even if they are “office-only” companies are requested to be assessed according to Safety, Quality and Assessment System (SQAS) for distributors/ESAD II. Application of sections F and G for food, cosmetic or/and pharma is requested. All questions of this part related to processes or operations contracted out to service partners are not applicable.

9 Customer Pick-Ups

Customer pick-ups/collections of Propylene Glycol USP/EP in either bulk or original packaging should only be accepted if the principles of the CEFIC Propylene Glycol USP/EP guidelines are followed.

The Propylene Glycol USP/EP manufacturer should ensure that procedures are agreed in writing with the pick-up partner and followed. These procedures should specifically define as a minimum

- use of approved carrier
- inspection of truck prior to loading
- carrier provides a cleaning certificate if no dedicated transport equipment
- copy of cleaning records
- verify food grade wash
- use of proper transportation equipment
- adhere to prior cargo restriction policies for non-product dedicated equipment
- application of proper sampling prior to sealing and sealing practices
- appropriate documentation to allow complete traceability
- samples and records should be retained as described in 2.6.

Appendix 1 Product Information

Product and toxicology information mentioned in this Appendix is mainly based on the working group members' Material Safety Data Sheets.

Additional information about Propylene Glycol USP/EP is available in the IUCLID Data Set, including full toxicological information.

1 GENERAL DATA

EINECS NUMBER	CAS-NUMBER	USP/NF, EP NAME	IUPAC-NAME	SOME SYNONYMS	E NUMBER
200-338-0	57-55-6	Propylene Glycol	Propane-1,2-Diol	1,2-Propylene Glycol 1,2-Propanediol 1,2-Dihydroxypropane	E 1520, Propan-1,2-diol (propylene glycol) (food additives) E 490, Propan-1,2-diol (animal feed additives)

2 PHYSICAL PROPERTIES

FORMULA	MOLAR MASS	TYPICAL VALUES, COMMONLY IN USE:	
$\begin{array}{c} \text{HO} \quad \text{OH} \\ \quad \\ \text{H}_2\text{C} - \text{CH} - \text{CH}_3 \end{array}$	76.1	Melting point (101.3 kPa)	(-60 °C) Supercools
		Pour point	< -57°C
		Boiling range (101.3 kPa)	186-190 °C
		Flash point (closed cup, Pensky Martens)	99 - 103 °C
		Ignition temperature	370 - 420 °C
		Explosive limits in air	
		- lower	2.6 vol%
		- upper	12.6 vol%
		Solubility in water at 20 °C	soluble (in all proportions)
		Specific gravity d(25/25) (USP)	1.035 - 1.037
		Vapour pressure at 20 °C	0.08 - 0.106 hPa
		Viscosity at 25 °C (Brookfield)	46 mPa s
		Dynamic viscosity (20 °C)	55 mPa.s
Refractive index at 20 °C	1.430 - 1.434		
Log Pow	ca. -1		

Additional data are given in the manufacturers' technical data sheets and Safety Data Sheets.

Propylene Glycol USP / EP is a colourless, almost odourless liquid.

The product is hygroscopic and sensitive to sunlight, air, oxidising agents, acids, bases and high temperatures. Partial oxidation in the presence of oxygen may lead to the formation of aldehydes, ketones, acids and dioxolanes. The rate of product degradation, indicated by increasing colour, UV absorption, acidity and odour, increases with higher temperatures, the presence of metals and / or product exposure to sun (UV) light when stored outside in transparent plastic containers. It is generally recommended to store product in approved, closed containers at temperatures not exceeding 40 °C.

The manufacturer's shelf life is only applicable if the storage conditions as described in the guideline are followed.

Other data such as assay, values tested by infrared absorption, content of oxidising and reducing substances, acidity, water content, residue on ignition, sulphated ashes, chlorides, sulphates, heavy metals, and residual solvents are specified in the current EP and USP monographs and must be met.

3 HAZARDS AND CLASSIFICATIONS

HAZARDS IDENTIFICATION

Under normal use conditions no specific health or environmental hazards.

Safety: Not flammable, but may burn.

Propylene Glycol USP/EP is not subject to classification according to the EU's Dangerous Substances Directive.

The Globally Harmonized System (GHS) for classification and labelling came into force on 31 December 2008 as the "CLP Regulation" (Classification, labelling and Packaging of Substances and Mixtures) and will apply to substances by 30th November 2010 in the EU. No classification is anticipated.

WARNING PROPERTIES/RISK PHRASES/HAZARD STATEMENTS (CLP)

None

TRANSPORT REGULATIONS

Propylene Glycol USP/EP is not classified as hazardous under EU transportation regulations.

Appendix 2 Assessment Questionnaire for Bulk Storage/Packaging

Purpose

The purpose of this questionnaire is to evaluate the extent to which operations in various phases of the distribution chain comply with the Cefic Guidelines for Handling and Distribution of Propylene Glycol USP/EP. It should be applied as a minimum requirement in the absence of a completed SQAS/ESAD II, section F assessment.

It can be used either as a self evaluation tool by any company involved in the distribution chain, or as pre-audit protocol, to help manufacturers of Propylene Glycol USP/EP assess the ability of their contractors to handle this product safely.

This questionnaire covers only the basic precautions recommended by the Cefic guidelines, and is intended for use as a preliminary conformity evaluation. Completion of the questionnaire will increase the company's awareness on the most important concerns and will help identify quickly any significant weaknesses.

For evaluation, please consider the requirements as described in Chapter 2.8.

However, the questionnaire gives no detailed information on the Cefic guidelines and how to implement them. If any shortcomings are identified as a result of this evaluation, further investigation must be carried out and possible actions taken.

N.B.:

- A separate questionnaire should be completed for each site or part of the company involved in the handling and distribution of Propylene Glycol USP/EP.
- "Product" refers to Propylene Glycol USP/EP.
- Words in italics are defined in the Glossary.
- Please tick either YES or NO or N/A (not applicable) in each question. Some questions require a more detailed answer; space is provided in the COMMENTS column.
- **Questions considered as essential, minimum requirements are marked in bold.**

Company references and activities (product related)

COMPANY NAME _____

CONTACT PERSON _____

SITE ADDRESS _____

ACTIVITY

- | | | | |
|-----------------------|--------------------------|----------------------|--------------------------|
| - Bulk storage | <input type="checkbox"/> | - (Re-) Packaging | <input type="checkbox"/> |
| - Bulk loading | <input type="checkbox"/> | - Packed Warehousing | <input type="checkbox"/> |
| - Bulk transportation | <input type="checkbox"/> | - Final usage | <input type="checkbox"/> |
| - Bulk unloading | <input type="checkbox"/> | - Other | <input type="checkbox"/> |

Description _____

ASSESSMENT QUESTIONS				
	YES	NO	N/A	COMMENTS
1 GENERAL				
1.1				Please specify which activity and standard?
1.2				Which criteria?
1.3				Which subjects and time spent?
1.4				How?
1.5				
1.6				Which analytical tests?
1.7				How ?
1.8				Describe:
1.9				How long are they retained?
1.10				Describe:
1.11				Describe:
1.12				Which materials? Describe:

ASSESSMENT QUESTIONS				
	YES	NO	N/A	COMMENTS
2 BULK STORAGE				
2.1 Is the storage tank material compatible with the Product?				Which material?
2.2 Is the storage tank equipped with a nitrogen blanketing system or a drying equipment to protect the Product against oxidation and/or moisture?				Describe your system :
2.3 Is the quality of the blanketing gas, if used, compatible with the Product?				Which quality?
2.4 Do you ensure your sampling installation can provide a representative sample?				How?
2.5 If material of different lots is mixed in the storage tank, do you : - take a representative sample of the ix? - assign a new lot number? - carry out a re-certification with corresponding analytical testing?				Which tests?
3 BULK LOADING AND UNLOADING				
3.1 Do you have written procedures and documentation for bulk loading/unloading of the Product?				
3.2 Is the entire equipment in contact with the Product : - located in a clean area? - labelled? - drained and capped after the operation, according to written procedures?				
3.3 Before loading do you : - inspect the cleanliness of the transport equipment? - keep the inspection documents?				How? Which ones?
3.4 After loading do you : - retain a sample, taken from the filled transport equipment? - perform key points analysis for positive identification and contamination detection? - seal all valves and openings?				For how long? Which ones?
3.5 Before unloading do you : - check the integrity of the seals? - perform key points analysis for positive identification and contamination detection? - retain a sample?				Which ones? For how long?

ASSESSMENT QUESTIONS				
	YES	NO	N/A	COMMENTS
4 BULK TRANSPORTATION				
4.1 Do you evaluate your transporters in accordance with SQAS or similar schemes? Do you ascertain that the truck drivers are trained for handling of Propylene Glycol USP/EP?				
4.2 Do you prohibit sub-contracting: - under all circumstances? - is all sub-contracting reported and approved by the contract giver?				
4.3 If you use non-dedicated equipment, do you require : - a specific cleaning procedure with a cleaning certificate? - a list of prohibited or allowed last cargoes?				Describe: Attach your list
4.4 With your transportation companies, do you have a formal agreement detailing : - your sealing requirements? - the suitable materials in contact with the Product?				Describe: Describe:
5 PACKAGING				
5.1 Is the entire equipment in contact with the Product : - fully dedicated (or at least dedicated to Propylene Glycol industrial grade, other USP/EP compliant or food grade products)? - clearly labelled? - cleaned according to written and validated procedures? - made of approved materials? - are pipelines and equipment connected to pipelines for other products e.g. through a manifold?				Describe: Which materials? If yes, how is risk of cross contamination managed?
5.2 Is the Product filtered prior to the packaging operation? - does documentation include - filter type? - filter size? - change frequency? - filter condition? - date of inspection/replacement? - responsible individual?				
5.3 Is the environment of the packaging operation : - separated from other operations (or at least devoted to compatible products)? - clean and dust free? - pressurised with filtered air?				Describe:
5.4 If toxic products are present on the site, do you have a written procedure for cross contamination prevention?				Describe

ASSESSMENT QUESTIONS				
	YES	NO	N/A	COMMENTS
5.5 Is each packed lot : - fully traceable (including the origin of the empty container)? - homogeneous in quality? - sampled and checked for positive identification and contamination according to written procedures? - do you retain a sample?				For how long?
5.6 Is the expiry date or the shelf life mentioned on each container (drums, IBCs, etc)?				
5.7 Are you controlling the cleanliness of containers prior to filling, at least on a statistical basis?				How? Which method?
5.8 For each cleanliness inspection, do you keep a written report, e.g. in a checklist?				For how long?
5.9 Do you have written container specifications, including, for all parts in contact with the product, an approval of material for food grade products?				
5.10 Are container suppliers : - selected according to quality criteria? - periodically assessed? - informed of the sensitive usage of the product?				Which criteria? How frequently?
5.11 Are you prohibiting : - reconditioned containers? - IBCs made of translucent plastics? - non coated steel drums?				
6 RECEPTION, WAREHOUSING AND SHIPMENTS OF PACKED PRODUCTS				
6.1 Are receptions performed : - according to written procedures? - with conformity inspection, including the seals? - with control of the existence and the quality of the appropriate documentation?				Describe:
6.2 Are containers stored : - in dedicated areas with adequate separation from other products for the prevention of errors? - with a shelf life control system? - with protection from direct sun light? - with maximum temperature conditions and control, as applicable?				

ASSESSMENT QUESTIONS				
	YES	NO	N/A	COMMENTS
6.3 If you have to open a container : - do you have a written procedure to prevent contamination? - do you have a quality re-certification procedure? - do you re-seal the container?				
6.4 For container loading on trucks or in dry containers : - do you use a check list for final inspection? - is the packaging list signed by at least 2 people?				
TOTAL				

ASSESSMENT SCORE: Number of YES/Number of (YES + NO) x 100 = _____ %

COMMENTS _____

COMPLETED BY _____

DATE _____

SIGNATURE

Appendix 3

Assessment Questionnaire for Warehousing Companies

Purpose

The purpose of this questionnaire is to evaluate the extent to which operations in various phases of the distribution chain comply with the Cefic Guidelines for Handling and Distribution of Propylene Glycol USP/EP. It should be applied as a minimum requirement in the absence of a completed SQAS/ESAD II, section F assessment.

This questionnaire is specifically designed for warehousing companies, which exclusively handle Propylene Glycol USP/EP in original manufacturer packed and sealed drums and IBCs only.

It can be used either as a self evaluation tool by any company involved in the distribution chain, or as pre-audit protocol, to help manufacturers of Propylene Glycol USP/EP assess the ability of their contractors to handle this product safely.

This questionnaire covers only the basic precautions recommended by the Cefic guidelines, and is intended for use as a preliminary conformance evaluation. Completion of the questionnaire will increase the company's awareness of the most important concerns and help to identify quickly any significant weaknesses. For evaluation of the questionnaire please consider the requirements described in Chapter 2.8.

However, the questionnaire does not give detailed information on the Cefic guidelines and on how to implement them. If any shortcomings are identified as a result of this evaluation, further investigation must be carried out and possibly actions taken.

N.B.:

- A separate questionnaire should be completed for each site or part of the company involved in the handling and distribution of Propylene Glycol USP/EP.
- The word "Product" refers to Propylene Glycol USP/EP.
- Words in italics are defined in the glossary.
- Please tick either YES or NO or N/A (not applicable) in response to each question. Some questions require a more detailed answer, for which space is provided in the COMMENTS column.
- **Questions considered as essential, minimum requirements are marked in bold.**

Company references and activities (product related)

COMPANY NAME _____

CONTACT PERSON _____

SITE ADDRESS _____

ACTIVITY

- Packed Warehousing

Description _____

ASSESSMENT QUESTIONS				
	YES	NO	N/A	COMMENTS
1 GENERAL				
1.1				Specify which activity and standard?
1.2				Which criteria?
1.2 Have all personnel involved in handling the Product : - been made aware of the risks to human health? - been formally qualified according to written criteria?				
1.3				Which subjects and time spent?
1.3 In your qualification process, do you require a specific training?				
1.4				How?
1.4 Are you able to provide full traceability : - on Product origin? - in your operations? - on Product destinations?				
1.5				
1.5 Do you keep distribution records for every product shipment, including name and location of receiving party, quantity, lot number, carrier and date of shipping?				
1.6				
1.6 Is every Product lot accompanied by a quality certificate?				
1.7				Describe:
1.7 Do you have written procedures on how to handle non-conforming lots?				
1.8				Describe:
1.8 Do you have written procedures on how to handle product, received in original packaging with broken or violated seals?				
1.9				Describe:
1.9 Do you have a written procedure for Product recall with defined responsibilities in case of a quality concern?				
6 RECEPTION, WAREHOUSING AND SHIPMENTS OF PACKED PRODUCTS				
6.1				Describe:
6.1 Are receptions performed : - according to written procedures? - with conformity inspection, including the seals? - with control of the existence and the quality of the appropriate documentation?				

ASSESSMENT QUESTIONS				
	YES	NO	N/A	COMMENTS
6.2 Are containers stored : - in dedicated areas with adequate separation from other products for the prevention of errors? - with a shelf life control system? - with protection from direct sun light? - with maximum temperature conditions and control, as applicable?				
6.3 In case you apply additional label(s) on the original, sealed packaging do you have a written procedure for label creation and control?				What additional labels do you apply?
6.4 Can you confirm that you do not open original packed and sealed containers and resell the material as Propylene Glycol USP/EP?				
6.5 For container loading on trucks or in dry containers : - do you use a check list for final inspection? - is the packaging list signed by at least 2 people?				
TOTAL				

ASSESSMENT SCORE: Number of YES/Number of (YES + NO) x 100 = _____ %

COMMENTS _____

COMPLETED BY _____

DATE _____

SIGNATURE

Appendix 4

Assessment for Traders/Re-sellers/Brokers

In a standard supply chain operation the manufacturer of Propylene Glycol USP/EP sells product in bulk or in original packaging directly to the final end users or to qualified distributors. These distributors, assessed and approved by the manufacturers, may store the product in intermediate storage tanks and/or repackage it, or store original packed material in warehouses, before shipping the product to their final end-use customers. In these cases the supply chain operations are usually transparent to the Propylene Glycol USP/EP manufacturer. Compliance with the Cefic Propylene Glycol USP/EP Guidelines, including traceability can be clearly established by means of Cefic self-assessments and manufacturer reviews.

On the other hand Propylene Glycol USP/EP manufacturers may decide to sell product in bulk or in original packaging to traders/brokers/distributors who act as re-sellers of the material to other distributors/traders/brokers, establishing a new supply chain. In most cases the original Propylene Glycol USP/EP manufacturer has only limited knowledge about those parties involved and their compliance with the Cefic PG USP/EP Guidelines.

The purpose of this chapter is to emphasise the main principles of the Cefic Propylene Glycol USP/EP guideline and to strive for its consistent implementation for **all** supply chain operations in Europe.

The Cefic MPG USP working group recognises that all Cefic member companies will seek to comply with all applicable competition laws. The working group also recognizes that there is a high risk of losing traceability of the product when sold to traders/re-sellers/brokers. The group views this as a gap in the ongoing implementation efforts of the Cefic guidelines in Europe and as an unacceptable risk. It is therefore recommended that Cefic members who act as manufacturers/sellers for the product ensure awareness for and application of the Cefic guidelines by establishing a system of full traceability for Propylene Glycol USP/EP throughout the supply chain whenever it is sold.

Therefore, the following **3-step process** should be applied for both existing and intended new sales of Propylene Glycol USP/EP:

- 1) Manufacturer to send letter with major Cefic guideline requirements to trader/re-seller/broker.
- 2) Trader/re-seller/broker to complete the Cefic self-assessment, as applicable, and to confirm compliance with the Cefic guideline in writing to the manufacturer.
- 3) Manufacturer to confirm results in a review.

More details are given in the following paragraph.

Step 1

The manufacturer should specifically emphasise the following critical requirements of the Cefic Propylene Glycol USP/EP guideline in writing to the trader/re-seller/broker, as applicable:

- Product traceability: proper distribution records, Cefic guideline, Chapter 2.1.
- Appropriate inspection, testing and sampling, Chapter 2.2.
- Upgrading of industrial to pharmaceutical grade quality strictly forbidden at any point of the supply chain
- Appropriate handling and storage equipment and procedures.
- Appropriate bulk transport equipment: prior cargo restriction policy.
- Appropriate repackaging facilities: clean environment conditions, Chapter 7.5.
- Mixing of different lots from different manufacturers is a non supported practice. In such cases traceability is compromised and the trader / re-seller / broker takes all responsibility for the purity and GMP compliance of this material and is now the manufacturer of the material.
- For mixing of lots from the same manufacturer as a minimum, key point control testing according to Chapter 2.2.4. should be done and, if in compliance, a certificate of conformity may be issued. If the customer requires a certificate of analysis the product must be re-analysed and released in compliance with Propylene Glycol USP / EP specification requirements and a new COA be created with the new analytical data. A new lot number should be assigned to re-establish traceability from this point of the supply chain further downstream.

Step 2

Traders/re-sellers/brokers should provide the manufacturer/seller with a letter, containing the following points:

- Provide the manufacturer with a filled in Cefic self-assessment form, as applicable.
- Confirm their compliance with the Cefic guidelines for the handling and distribution of Propylene Glycol USP/EP, especially the critical points, mentioned above.
- Agree on Responsible Care® practices and Product Stewardship aspects, which include that every party in the distribution chain of Propylene Glycol USP/EP takes responsibility for its safe, proper and hygienic handling. Using Responsible Care® ethics, every party ensures that downstream supply chain partners are aware of the Cefic guidelines and are striving to meet those guidelines.

Step 3

The manufacturer verifies the results of this self-assessment, as a minimum the guaranteed traceability, in a review at the trader/re-seller/broker. The questionnaire for bulk/repackaging distributors should be used, as applicable.

This 3-step process should be applied for both new and already existing business.

In case of potential new sales to a trader/re-seller/broker, steps 1 and 2 should be completed first prior to start of product supply with step 3 being finalised within a 6 months period afterwards.

For already existing business completion is suggested in a shorter proposed time frame of 3 months.

If identified and addressed instances of critical non-conformances to the Cefic Propylene Glycol USP/EP guidelines are not corrected by the trader/re-seller/broker within an acceptable time frame the manufacturer should not start or stop the sales of Propylene Glycol USP/EP to the corresponding company.

Appendix 5

List of References

1. The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients, The International Pharmaceutical Excipients Council (IPEC) – Pharmaceutical Quality Group (PQG), 2006
2. ICH – Q7, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use 2000
3. European Single Assessment Document for Chemical Distributors (ESAD), Cefic /FECC, March 2006
4. Good Trade and Distribution Practices for Pharmaceutical Starting Materials, World Health Organization, 2003
5. The IPEC Good Distribution Practices Guide for Pharmaceutical Excipients, The International Pharmaceutical Excipients Council (IPEC), 2006
6. The IPEC Good Distribution Practices Audit Guideline for Pharmaceutical Excipients, The International Pharmaceutical Excipients Council (IPEC), 2008
7. Responsible Care Status Report 2007, International Council of Chemical Associations (ICCA), 2007
8. Current United States Pharmacopeia (USP)
9. Current European Pharmacopoeia (EP)
10. Current Pharmacopoeia of Japan (JP)
11. Current Safety Data Sheets according to 1907/2006/EC of Member Companies of the Working Group (see also Appendix 1)
12. European Standard ISO 9000:2000 series

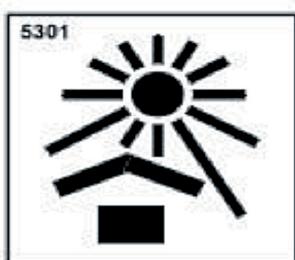
Appendix 6 Definitions

TERM	DEFINITION
Adulterated Substance	Material which has either been contaminated with a foreign substance or not manufactured using good manufacturing practices.
Certificate of Analysis (COA)	A document which reports actual analytical data obtained from testing a representative sample of the product lot to be shipped to the customer.
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.
Clean area/environment	An area with defined environmental control of contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants in the area.
Conformity	The fulfilment of specified requirements.
Contaminant	An impurity not intended to be present in the product that may be introduced through such things as poor cleaning, processing, lack of appropriate environmental and personnel controls during the manufacturing process, handling and distribution.
Continuous Process	A manufacturing process which continually produces Propylene Glycol USP/EP from a continuous supply of raw materials.
Contract Review	The systematic activities carried out before the contract is signed by the supplier. They must ensure that the customer's requirements for quality are clearly defined, unambiguous, documented, and achievable by the supplier.
Cross-Contamination	Contamination of a material with another product during production, handling and distribution.
Excipient	Any substances other than the active pharmaceutical ingredient (drug) and packaging materials, which have been appropriately evaluated for safety and are included in a drug delivery system.
Expiry Date	The date until which a product is expected to remain within specification if stored correctly. It is established for every lot by adding the shelf-life period to the manufacturing date.
FIFO (First In First Out)	A distribution procedure which ensures that the oldest stock (lot) is distributed and/or utilised before a newer and identical stock (lot) item is distributed and/or utilised.
IBC	Intermediate Bulk Container.
Impurity	A substance contained in a product other than the desired substance.

TERM	DEFINITION
Lot	A defined quantity of raw material, intermediate material, packaging components or final product processed so that it can be expected to be homogeneous. In a continuous process, a lot corresponds to a defined portion of the production, based on a fixed quantity or time interval (e.g. tank or vessels volume, one day's production, etc.).
Lot number	A distinctive combination of numbers and/or letters from which the complete history of the manufacture, processing, packing, coding and distribution of a lot can be determined.
Nonconforming Material	Any material that does not meet manufacturer's specifications or has not been manufactured according to applicable GMPs.
Packaging	The act of filling and labelling a container with a product.
Packaging Material	The containers, closures, and labels employed in the packaging of a product.
Quality Assurance	All those planned and systematic actions necessary to provide confidence that a product or a service will satisfy given requirements for quality.
Quality Control	The operational techniques and activities (preventive, supervisory and corrective action) that are necessary in fulfilling quality requirements.
Recall	Decision taken by a company to call back a product batch which has been put on the market.
Retest Date	The date when a material should be re-examined to ensure that it is still suitable for use.
Shelf Life	The length of time during which the product meets specifications.
Specifications	A list of tests, references to analytical procedures, and appropriate acceptance criteria for a material, which serve as a basis for quality evaluation.
Validation	A documented programme that provides a high degree of assurance that a specific procedure, process, equipment, material or activity will consistently produce a result meeting pre-determined acceptance criteria.

Appendix 7 Symbols for Use on Packed Product

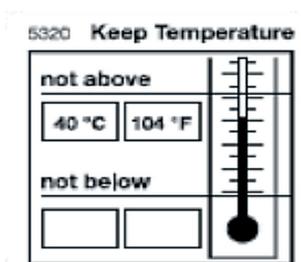
Protection against direct sunlight



Protection against rain



Maximum storage temperature





Cefic AISBL - European Chemical Industry Council

Avenue E. van Nieuwenhuyselaan 4

1160 Brussels - Belgium

T +32 2 676 72 11

F +32 2 676 73 00

www.cefic.org