Comments from the European Industrial Pharmacists Group on the Commission's Revised Guidelines on Good Distribution Practice of Medicinal Products for Human Use

The updating of the Guidelines on Good Distribution Practices[1] by the European Commission is a process that is long overdue, and therefore the European Industrial Pharmacists Group is pleased to see that this procedure is close to implementation. Recent developments in legislation concerning medicinal products have highlighted the importance of the need to ensure that Europe's patients are not exposed to falsified medicinal products. One critical step in ensuring this objective is the strengthening of the pharmaceutical supply chain through good distribution practices of the highest order. The European Industrial Pharmacists Group (EIPG) has always viewed the wholesale distribution of pharmaceuticals to be a natural extension of the process of manufacture of medicinal products, and consequently, the standards that should be applied in distribution activities should be no less than those applied in manufacturing – it is merely the reduced range of activities and lower complexity of the processes involved that make the application of principles of GDP less demanding than those of GMP, and not any misconception that GDP standards are less than those of GMP.

EIPG has always believed that the position of Responsible Person should be filled by a pharmacist, the class of professional whose training best encompasses knowledge of the necessary legislation, quality assurance and quality management principles, and an understanding of medicinal products at such a level as to be able to implement the conditions necessary for their safe transport and storage. As a compromise, EIPG had recommended that the proposed legislation should introduce minimum standards of qualifications and practical experience for the Responsible Person, in a manner concordant with those for the Qualified Person. This recommendation was not taken on board during in the final version of Directive 2011/62/EU[2], and EIPG is *greatly pleased to note the Commission's recommendation that the Responsible Person should preferably be a graduate in pharmacy*. EIPG understands that the GDP guidelines cannot impose requirements that exceed those of the Directive, but notes that in certain instances as outlined below, the guidelines are excessively prescriptive, possibly to account for the implementation of GDP in those Member States where the Responsible Person does not possess the expertise and training of a pharmacist. This approach of attempting to shut the stable door after the horse has bolted has, in certainly instances, the potential to be unnecessarily restrictive on pharmacist Responsible Persons and to deprive them of the ability to apply their professional judgment in the implementation of GDP.

Finally, with regards to the issue of falsified medicinal products, although EIPG notes that this document attempts to introduce a greater level of alertness in GDP standards to prevent

[1] Guidelines on Good Distribution Practice of Medicinal Products for Human Use (Text with EEA Relevance) (94/C 63/03)

[2] Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products.

penetration into the supply chain, in the absence of the necessary delegated acts, currently the subject of a separate consultation process, certain aspects of GDP entrenched in new requirements imposed by the Directive, such as the checking of security features on medicinal products, could not be included. EIPG therefore *strongly recommends that consultation on the necessary delegated acts and on the guidelines for GDP be carried out in as holistic a manner as possible*, in order to ensure that the requirements for the implementation of GDP provide the necessary guidance to entities engaging in wholesale distribution of medicinal products, at such a level as will ensure compliance with the new requirements of the amended Directive 2001/83/EC[3].

Specific Points of Note

Introduction

Article 77, Par 1 of Directive 2001/83/EC, as amended, provides that "Member States shall take all appropriate measures to ensure that the wholesale distribution of medicinal products is subject to the possession of an authorization to engage in activity as a wholesaler in medicinal products" However, Par 3 of the same Article allows that "Possession of a manufacturing authorization shall include authorization to distribute by wholesale the medicinal products covered by that authorization". Albeit that both these provisions are mentioned in the Introduction, the EIPG feels that the paragraphs could benefit from greater clarity if reworded as follows:

> "*Only persons or entities that are authorized to distribute medicinal products by wholesale are entitled to engage in such activity. Such authorization may either be through the holding of a wholesale distribution authorization or through possession of a manufacturing authorization, the latter including an authorization to distribute by wholesale the medicinal product covered by the authorization.*"

Chapter 2

The role of the Responsible Person in a licence for wholesale distribution parallels that of the Qualified Person in manufacturing and importation: he/she bears the final responsibility in ensuring that the activities carried out under the licence are done within the framework of a quality system consistent with the legislation and that guarantees the quality, safety and efficacy of the medicinal product. The EIPG is aware, as previously mentioned, that the functions of the Responsible Person are, in some countries, being carried out by individuals that are not subject to professional regulation. However, on the other hand, this is insufficient justification for excessive, and at times inconsistent, restrictions in the provisions governing the activities of professional individuals functioning as Responsible Persons – restrictions that in some cases exceed even those currently in force for Qualified Persons.

a) Item 2.1 states that the Responsible Person should fulfill his/her responsibilities personally whereas Item 2.4 states that the Responsible Person should carry out his/her activities personally. When dealing with individuals who are as high up within the

[3] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

hierarchy of a Quality Management System as the Responsible Person, one ceases to talk in terms of activities, but deals in terms of responsibilities.

b) In Item 2.3 albeit that the proposed guidelines state that the qualifications of the Responsible Person should meet the conditions provided by the legislation of the Member State, a degree in Pharmacy is then listed as being merely "desirable". EIPG feels that such a statement has the potential to undermine the legal position in those Member States which believe, as does EIPG, that the Responsible Person should be a pharmacist, and therefore it should be specified that the degree in Pharmacy is desirable, as opposed to required, only for those Member States where the Responsible Person is not required to be a pharmacist.

c) As is the case for Qualified Persons, it is perfectly acceptable for a Responsible Person to delegate activities to suitable personnel within the organization, so long as the Responsible Person retains personal responsibility for such delegated activities within a defined quality system.

d) Article 48 Par 1 of the Directive speaks of the Qualified Person being permanently and continuously at the disposal of the manufacturing licence holder, rather than being permanently available. The EIPG believes that the same terminology should be used when making provisions for the availability of the Responsible Person.

e) In larger organizations, as is the case for Qualified Persons, a single licence holder may have more than one Responsible Person nominated on the licence, and delegation of duties to other Responsible Persons may occur not due to the absence of the main Responsible Person but, appropriately, to ensure that the responsibilities placed on any individual are not so extensive as to present an unacceptable risk to product quality.

The EIPG therefore recommends the following amendments:

2.1 The wholesale distributor must designate a person as Responsible Person[6]. The Responsible Person should fulfill his/her responsibilities personally and should be permanently ~~**available**~~ *and continuously at the disposal of the licence holder*. The Responsible Person should meet the conditions provided for by the legislation of the Member State concerned.

2.3 The qualifications of the Responsible Person should meet the conditions provided by the legislation of the Member State concerned and should be appropriate to fulfill the assigned ~~**duties**~~ *responsibilities*. ~~**A**~~ *In those Member States where the Responsible Person is not required by legislation to be a pharmacist, a* degree in Pharmacy is desirable. He/she should have appropriate competence and experience as well as knowledge and training on GDP.

2.4 The Responsible Person should ~~**carry out**~~ *fulfill* his/her ~~**activities**~~ *responsibilities* personally in order to ensure the wholesale distributor can demonstrate GDP compliance and that public service obligations are met.

2.5 x) delegating his/her duties when ~~**absent**~~ *necessary* and keeping appropriate records relating to any delegation;

Chapter 3

The potential implementation of checking of the security feature and unique identification number on medicinal products raises new information technology challenges in GDP-related activities. It is thus more important than ever to ensure the security and fidelity of data in computer systems and the failure of these guidelines to address the issue of audit trails is surprising. The EIPG therefore recommends the addition of the following item.

3.26 *Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GDP-relevant changes and deletions (a system generated "audit trail"). For change or deletion of GDP-relevant data the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed.*

Chapter 6

Item 6.3 requires that the national competent authority be informed without delay in the event of any complaint concerning a potential product defect or a potential falsified product. This provision goes beyond the scope of Article 80, Sub-paragraph (i) of Directive 2001/83/EC as amended by Directive 2011/62/EU, which only provides that wholesale distributors should "immediately inform the competent authority and, where applicable, the marketing authorisation holder, of medicinal products they receive or are offered which they identify as falsified or suspect to be falsified". Insofar as product defects as concerned, the provisions of Item 8.8 of Volume 4, Part I, Chapter 8 of the EudraLex, which provides that the competent authorities are to be informed if a manufacturer is considering action following detection of serious quality problems with a product.

As regards returns of medicinal products, the guidelines once again seek to establish a gold standard for returns of medicinal products from customers not holding a wholesale distribution authorization, and consequently fail to take into account a number of scenarios:

a) Hospitals are not normally licensed as wholesale dealers, but may, by virtue of a Quality Management System implemented as part and parcel of their activities and their specific licences, apply standards of storage and handling of medicinal products that are comparable to those of GDP
b) Stating that a medicinal product may be returned to saleable stock if it is returned within five days undermines the professional role of the pharmacist responsible person, who may believe, for a particular medicinal product under specific circumstances, that five days is an unacceptable time period.
c) No mention is made of the unacceptability of returning products to saleable stock if these are returns by patients to pharmacies.

The EIPG therefore recommends the following amendments:

6.3 Any complaint concerning a ~~**potential product defect or**~~ a potential falsified product should be recorded with all the original details and investigated. The national competent authority should be notified without delay.

6.5 If necessary, appropriate follow-up actions should be taken after investigation and evaluation of the complaint. *The competent authorities should be informed without delay if a wholesale distributor is considering action following any potential defect that may compromise the quality, safety and efficacy of the product.*

6.9 ii) Medicinal products returns from a customer not holding a wholesale distribution authorization *but authorized to administer or dispense medicinal products* should only be returned to saleable stock if they were returned within ~~**five days of**~~ *a suitable timeframe* from original dispatch *and are not returns from a patient*.

Chapter 7

The activities that are outsourced by the holder of a wholesale distribution licence may not be simply those of the distribution of medicinal products. They may include pest control, transportation, maintenance, calibration of equipment, and so on. The providers of these services may not necessarily have a wholesale distribution as this may not be their specific activity. Consequently, it is impractical to propose that when outsourcing activities both parties must hold a distribution authorization. Moreover, as in the Introduction, it is proposed to clarify the term distribution authorization to include entities that are entitled to distribute medicinal products by virtue of a manufacturing licence. In view of this consideration, Item 7.5 also needs to be adjusted to clarify the fact that it is referring to contracted activities that relate exclusively to distribution of medicinal products.

EIPG therefore proposes that the **Principle** section of Item 7 be reworded as follows:

"When outsourcing activities a written contract should be drawn up. Both the contract giver and the contract acceptor must ~~**hold a distribution authorization**~~ *be suitably authorized to perform the contracted activities*. The written and signed contract should cover all ~~**wholesale distribution**~~ *the necessary activities to ensure that there are no gaps or unexplained overlaps with regard to the application of Good Distribution Practices* and clearly establish the duties and responsibilities of each party. Written contracts should be established for any activity likely to impact on GDP related activities.

Moreover, Item 7.5 should be reworded as follows:

7.5 ~~**The**~~ *A* Contract Acceptor carrying out activities falling under the definition of wholesale distribution of medicinal products is ~~**a wholesale distributor**~~ *an entity authorized to distribute medicinal products by wholesale*. As such, he is subject to all obligations for wholesale distribution of medicinal products.