GIRP comments on

Guidelines on the principles of Good Distribution Practices for active substances for medicinal products for human use submitted for public consultation

Introduction:
GIRP, the European Association of Pharmaceutical Full-line Wholesalers, represents around 750 pharmaceutical wholesale distributors in 31 European countries. The main activity of members' is to purchase, store and supply the full assortment of medicinal products (in range and depth) to pharmacies in their area of geographic activities (which can be national or regional). Wholesale distributors also purchase and store a number of active substances that they then supply to pharmacies for the preparation of magistral and officinal formulas.

Scope of the draft GDP guidelines:
GIRP is unsure whether these draft GDP guidelines apply to our members and seeks clarification on this point. According to paragraph 1 of the draft text, the guidelines apply to the distribution of active substances for medicinal products for human use. While magistral and officinal formulas can be considered medicinal products according to article 1, point 2 of Directive 2001/83/EC, the same Directive states in article 3, point 1 and 2 that it is not applicable to any medicinal product prepared in a pharmacy, i.e. magristral formula or officinal formula. The GDP guidelines must clarify the exact scope of their application.

Should the draft GDP guidelines for active substance apply to wholesale distributors, it is essential to expand paragraph 24 of the draft text to allow for the supply of active substances to pharmacies and other persons legally authorized in the Member States to retail supply to the public. Currently, paragraph 24 only allows supplies to be made to registered distributors of active substances or authorized manufacturers (according to articles 52a and 40 respectively of Directive 2001/83/EC). Pharmacies do not fall under either definition. In fact, article 40, point 2 of Directive 2001/83/EC on the authorization of the manufacture of medicinal products states that such an authorization is not required for preparations and other processes, where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorized in the Member States to carry out such processes.

In the same context if the proposed GDPs for active substances for medicinal products for human use are applicable only for active substances being supplied by their producers to medicinal product manufacturers then the following comments are not applicable.

Furthermore, if the GDP guidelines for active substances are applicable to wholesale distributors, GIRP has the following detailed comments:

Public consultation text	Suggested change	GIRP comment	Priority
5. The size, structure and complexity of distributor's activities should be taken into consideration when developing or modifying the quality system.	5. The quality system should be developed or modified independent of the size, structure and complexity of distributor's activities ~~should be taken into consideration when developing or modifying the quality system~~.	GDP guidelines have to ensure that every holder of a wholesale distribution authorisation adheres to the same standards and ensures the same quality independently of the size and complexity of the activities as risk is not related to size.	3

6. A management representative should be appointed in each distribution point, who should have defined authority and responsibility for ensuring that a quality system is implemented and maintained. He should fulfill his responsibilities personally.	6. A ~~management~~ company representative should be appointed in each distribution point, who should have defined authority and responsibility for ensuring that a quality system is implemented and maintained. He should fulfill his responsibilities personally.	The definition of management representative is unclear. If it is to be equated with responsible person, it would involve major additional costs for wholesale distributors. As GIRP members operate over 1,600 warehouses in Europe, this provision could lead to an annual cost increase of approximately 20 million Euro (detailed calculation can be provided), without improving the current well-functioning system.	2
13. Records should be kept of each purchase and sale, showing the date of purchase or supply, name of the active substance, batch number and quantity received or supplied, and name and address of the original manufacturer. Records should ensure the traceability of the origin and destination of products, so that all the suppliers of, or those supplied with, an active substance can be identified. Documents that should be retained and available include: - Identity of original manufacturer - Address of original manufacturer - Purchase orders - Bills of lading, transportation and distribution records - Receipt documents - Name or designation of active substance - Manufacturer's batch number - All authentic Certificates of Analysis, including those of the original manufacturer - Retest or expiry date	13. Records should be kept of each purchase and sale, showing the date of purchase or supply, name of the active substance, batch number of the last supplier, if delivered in an electronic format and printed on the product as a standard barcode, and quantity received or supplied, and name and address of the ~~original manufacturer~~ supplier. Records should ensure the traceability of the origin and destination of products, so that all the suppliers of, or those supplied with, an active substance can be identified. Documents that should be retained and available, if delivered in electronic format, include: - Identity of ~~original manufacturer~~ supplier - Address of ~~original manufacturer~~ supplier - Purchase orders - Bills of lading, transportation and distribution records - Receipt documents - Name or designation of active substance - ~~Manufacturer's~~ Supplier's batch number, if delivered in an electronic format and printed on the product as a standard barcode - ~~All authentic~~ Certificates of Analysis, where accessible ~~, including those of the original manufacturer~~ - Retest or expiry date	The name and address of the original manufacturer and the batch number are not usually known to wholesale distributors. They mostly know the name and address of their supplier – usually an importer of APIs. The details of the original manufacturer, who is often based in a country outside Europe, as well as the batch number are often printed on a label contained within the packaging of the product. As wholesale distributors may not interfere with the packaging of a product, they cannot access this information. This 'inside label' usually also contains a link to the Certificate of Analysis of the original manufacturer, which can be retrieved from the internet.	1

18. Active substances should normally be stored apart from other goods and under the conditions specified by the manufacturer (e.g. controlled temperature and humidity when necessary). These conditions should be monitored periodically and records maintained. The records should be reviewed regularly by the person responsible for the quality system.	18. Active substances do not need to ~~should normally~~ be stored apart from other goods unless they require special ~~and under the~~ conditions specified by the manufacturer (e.g. controlled temperature and humidity when necessary). These conditions should be monitored periodically and records maintained. The records should be reviewed regularly by the person responsible for the quality system.	Active substances are normally not stored apart from other products on stock such as medicines, unless they require special storage conditions like temperature control. This requirement is impossible to implement as all products in the warehouses that do not require special storage conditions are stored according their frequency in demand. Cross-contamination is not a problem as active substances come in appropriate packaging.	1
23. Shortages that requires registered importers to notify relevant customers of any interruption to supply that the importer or distributor becomes aware of.	(23. Shortages that requires registered importers to notify relevant customers of any interruption to supply that the importer or distributor becomes aware of.)	This sentence seems truncated. Please clarify its meaning.	3
28. A system should be in place by which the distribution of each batch of active substance can be readily determined to permit its recall.	28. If the batch number is delivered in an electronic format and printed on the product as a standard barcode, ~~A~~a system should be in place by which the distribution of each batch of active substance can be readily determined to permit its recall.		
29. Distributors should transfer all quality or regulatory information received from an active substance manufacturer to the customer, and from the customer to the active substance manufacturer.	29. Distributors should transfer all quality or regulatory information received from an active substance manufacturer to the customer, and from the customer to the active substance manufacturer, if such information is supplied to them in electronic format.	Wholesale distributors do not usually receive quality or regulatory information from their suppliers. Some such information, such as the Certificate of Analysis, is contained within the packaging of the active substance, but is not usually accessible to wholesale distributors.	1

30. The distributor who supplies the active substance to the customer should provide the name and address of the original active substance manufacturer and the batch number(s) supplied. A copy of the original Certificate of Analysis from the manufacturer should be provided to the customer.	30. The distributor who supplies the active substance to the customer should provide the name and address of the ~~original active substance manufacturer~~supplier and the batch number(s) supplied, if delivered in an electronic format and printed on the product as a standard barcode. A copy of the original Certificate of Analysis from the manufacturer should be provided to the customer, if delivered in electronic format.	The name and address of the original manufacturer and the batch number are not usually known to wholesale distributors. They mostly know the name and address of their supplier – usually an importer of APIs. The details of the original manufacturer, who is often based in a country outside Europe, as well as the batch number are often printed on a label contained within the packaging of the product. As wholesale distributors may not interfere with the packaging of a product, they cannot access this information. This 'inside label' usually also contains a link to the Certificate of Analysis of the original manufacturer, which can be retrieved from the internet. Wholesale distributors cannot therefore provide this information to their customers, unless they receive it in electronic format first.	1
31. The distributor should also provide the identity of the original active substance manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorised agents, depending on the legal relationship between the authorised agents and the original active substance manufacturer. (In this context "authorised" refers to authorized by the manufacturer.)	31. The distributor should also provide the identity of the supplier ~~original active substance manufacturer~~ to regulatory authorities upon request. ~~The original manufacturer can respond to the regulatory authority directly or through its authorised agents, depending on the legal relationship between the authorised agents and the original active substance manufacturer. (In this context "authorised" refers to authorized by the manufacturer.)~~	The identity of the original manufacturer is not usually known to wholesale distributors. They mostly know the identity of their supplier – usually an importer of APIs. The details of the original manufacturer, who is often based in a country outside Europe, are often printed on a label contained within the packaging of the product. As wholesale distributors may not interfere with the packaging of a product, they cannot access this information. The interaction of original manufacturer and regulatory authority should not be part of the GDP guidelines. It should be regulated in the GMP guidelines.	1
32. The specific guidance for Certificates of Analysis is included in Section 11.4 of Part II of the EU-GMP.	~~32. The specific guidance for Certificates of Analysis is included in Section 11.4 of Part II of the EU-GMP.~~	This is a reference to GMP requirements. It should not be part of the GDP guidelines.	3

35. Active substances which have left the care of the distributor, should only be returned to saleable stock if: a) the active substance is in the original unopened container(s) and in good condition; b) it is demonstrated that the active substance have been stored and handled under proper conditions; c) the remaining shelf life period is acceptable; d) they have been examined and assessed by a person authorised to do so.	35. Active substances which have left the care of the distributor, should only be returned to saleable stock if: a) the active substance is in the original unopened container(s) and in good condition; b) it is demonstrated by the customer that the active substance have been stored and handled under proper conditions; c) the remaining shelf life period is acceptable; d) they have been examined and assessed by a person authorised to do so.	Wholesale distributors cannot know how products were handled while outside their control. The customer returning the active substance should guarantee that it was correctly handled.	1
37. Records of returned active substances should be maintained. For each return, documentation should include: - Name and address of the consignee - Active substance batch number and quantity returned - Reason for return - Use or disposal of the returned active substance	37. Records of returned active substances should be maintained. For each return, documentation should include: - Name and address of the consignee - Active substance batch number, if delivered in electronic format, and quantity returned - Reason for return - Use or disposal of the returned active substance	The batch number is not known to wholesale distributors. The batch number is often printed on a label contained within the packaging of the product. As wholesale distributors may not interfere with the packaging of a product, they cannot access this information, unless it is delivered to them in electronic format.	1
39. All quality related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.	39. All quality related complaints, whether received orally or in writing, should be recorded ~~and investigated~~ according to a written procedure.	Wholesale distributors cannot conduct quality related investigations. This is a task for the original manufacturer or competent authority under GMP rules.	2

42. If the situation warrants, the distributor should review the complaint with the original active substance manufacturer in order to determine whether any further action, either with other customers who may have received this active substance or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.	42. If the situation warrants, the distributor should review the complaint with the ~~original active substance manufacturer~~supplier in order to determine whether any further action, either with other customers who may have received this active substance or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.	The identity of the original manufacturer is not usually known to wholesale distributors. They mostly know the identity of their supplier – usually an importer of APIs. The details of the original manufacturer, who is often based in a country outside Europe, are often printed on a label contained within the packaging of the product. As wholesale distributors may not interfere with the packaging of a product, they cannot access this information.	2
43. Where a complaint is referred to the original active substance manufacturer, the record maintained by the distributor should include any response received from the original active substance manufacturer (including date and information provided).	43. Where a complaint is referred to the supplier~~original active substance manufacturer~~, the record maintained by the distributor should include any response received from the supplier~~original active substance manufacturer~~ (including date and information provided).	The identity of the original manufacturer is not usually known to wholesale distributors. They mostly know the identity of their supplier – usually an importer of APIs. The details of the original manufacturer, who is often based in a country outside Europe, are often printed on a label contained within the packaging of the product. As wholesale distributors may not interfere with the packaging of a product, they cannot access this information.	2

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