

This document has been prepared on the behalf of  
the European Glaucoma Society (EGS)  
for the purpose of contributing to the consultation paper on  
the extension of Directive 2003/94/EC to active substances

ID of the EGS in the Transparency Register: 05697037283-66

The EGS is a society of ophthalmologists  
and it is committed  
to improve the mutual understanding  
and provide a rational approach to the diagnosis and management of glaucoma.

Appendix I contains brief information on the disease.

**1. Extension of the Directive on GMP for medicinal products to active substances  
Consultation item No 1: Do you agree with this appraisal and approach? Please  
comment.**

The European Glaucoma Society (EGS) agrees with and supports this appraisal and approach as it will secure the integrity of the supply chain by strengthening the verification requirements applicable to the manufacturer of the medicinal product and active substances.

The EGS feels that regulating the active ingredients without regulating the excipients will be counterproductive particularly as the excipients have an impact on the quality and safety of the active substance of a medicinal product playing an important role in guaranteeing the dose, stability and release of the active principle, and the patient's 'compliance'. Furthermore they may interact chemically<sup>1</sup> or physically<sup>2</sup> with active substances of the medicinal product creating incompatibility issues and altering the bioavailability and efficacy of the active ingredient and in some occasions posing serious risks to public health<sup>3</sup>. Although such cases are rare, it is nevertheless important to address them.

The EGS believes that the Directive 2003/94/EC should be extended to cover the excipient substances, including colouring and flavouring agents, to ensure an overall compliance to GMP of the finished product. Furthermore the excipients ought to be subjected to the same toxicity studies as those requested for active principles, so as to protect the population from undesirable effects. Although such action is not in the scope of this Directive, it should supplement it.

A large number of both active substances and excipients are imported from outside the EU, keeping costs low particularly for medicinal products that are manufactured by preparations made in pharmacies. The European Glaucoma Society is concerned about any increase in costs as a result of such extension of the Directive, particularly if additional inspections in the manufacturing of active substances are required. Keeping the costs to the lowest possible level is particularly crucial for essential medicines as defined and listed in the WHO Model list of Essential Medicines (17th list, March 2011). Essential medicines are selected with due regard to public health relevance, evidence on efficacy and safety and they are intended to be available with assured quality at a price the individual and the community can afford.

Members of the European Glaucoma Society have recently experienced short supplies of a common diagnostic tool in a number of Member States as manufacturers and

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<sup>1</sup> Chemical interactions between the active ingredient and excipient can lead to the degradation of the drug and/or the formation of the so-called degradation impurities, which in some cases can cause dangerous allergic reactions.

<sup>2</sup> Physical interactions between excipient and active substance can have an impact on the speed of dissolution or the uniformity of the dosage of a solid formulation thereby affecting bioavailability of the active ingredient, i.e. the degree to which a drug or other substance becomes available to the target tissue after administration

<sup>3</sup>Adverse reactions to the excipient itself in specific populations with allergies and intolerance have been reported due to genetically-transmitted pathologies of metabolic origin and pathologies due to genetic predisposition. [http://pla.ce.bo.free.fr/biblio/the\\_safety\\_of\\_pharmaceutical\\_excipients.pdf](http://pla.ce.bo.free.fr/biblio/the_safety_of_pharmaceutical_excipients.pdf)

distributors opted to discontinue the product instead of re-applying for authorisations due to costs involved. This situation is particularly frustrating as the product having the appropriate manufacturing and marketing authorisation in one Member State, lacks marketing authorisations for distribution in other Member States.

Steps must be taken to prevent the removal of medicinal products from the market or increase in their production costs in parallel to the extension of the Directive. A large number of active substances may already fall under the scope of REACH (Registration, Evaluation, Authorisation and restriction of CHemicals) and hence they may already be regulated. Instead of re-registering such active substances in another regulatory framework, provisions should be made for efforts that can supplement any existing registration in other frameworks.

There are a number of unlicensed products such as special medicinal products, for example those prescribed to meet the individual clinical need of a patient when a suitable licensed medicine is not available. This could be for example, a particular strength medicine, a preservative-free formulation, a particular product presentation or when a licensed product is temporarily unavailable or discontinued e.g. some eye droplets preservative free. The active ingredients in such products impose additional questions particularly as such unlicensed products are medicinal products but they are regulated under national rules and legislation that varies between Member States due to differences in cultures, attitudes and histories.

Failures in the distribution chain due to low standards or non-compliance with transport and distribution guidelines, particularly for substances that require specialised handling such as cold chain products and narcotics, will compromise the quality, efficacy and safety of such products.

Therefore and in order to achieve a balance between best care, costs and safety to patients, the EGS calls for a number of actions parallel to the extension of the Directive 2003/94/EC to active substances. More specifically the EGS calls for:

Increased efforts to link the various policy areas such as REACH, to protect the public, keep the production costs at the lowest possible level and avoid unnecessary duplication in documentation and efforts

Increased efforts to centralise the marketing authorisation of both medicinal products and active substances for products that already hold the appropriate manufacturing authorisations in at least one Member State in order to simplify distribution throughout the EU of both medicinal products and active substances, in order to meet patients' needs at a time of rising costs. Such efforts could be supplemented by Member States through a review of the distribution networks that supply their national markets with medicines and related products to identify where possible economies could be made

considerations for any active ingredient in unlicensed products used routinely in hospitals

full integration of the current proposed approach with Good Distribution Practice (GDP) in light of a large number of both active substances and excipients imported from outside the EU, and additional efforts to extend the scope of and strengthen

compliance with Good Distribution Practice (GDP) to active substances and other starting materials of medicinal products.

acknowledge the cold chain distribution process as an extension of the GMP<sup>4</sup> by making this explicit in the Directive, accompanied with the appropriate validation measures to ensure that there is no negative impact to the safety, efficacy or quality of the active ingredients (and excipients)

collaboration and coordination at EU level regarding inspections of manufacturing sites and improvements in access to any related information to decrease costs and speed up processes

## **2. Adaptation of regulatory requirements of Directive 2003/94/EC to active substances**

### **2.1. Provisions in Directive 2003/94/EC that would not apply to active substances**

**Consultation item No 2: Are there other aspects which should be considered? Please comment.**

Special provisions governing advanced therapy<sup>5</sup> medicines. Clarification is required as to whether these special provisions would/could apply or not to active substances of such medicinal products.

Any other provisions for active pharmaceutical substances particularly in the light of the recent efforts by the EU, the Food and Drug Administration (FDA) and the Therapeutic Goods Administration (TGA) to rationalise international GMP inspections of active pharmaceuticals/active substances manufacturers<sup>6</sup>.

### **2.2. Provisions in Directive 2003/94/EC that would need to be amended**

**Consultation item No 3: Do you consider this list complete? Please comment.**

**Active substance.** The European Glaucoma Society agrees that the definition of active substance should be added. Some clarifications however may be useful to avoid

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<sup>4</sup> The GMP environment requires that all processes that might impact the safety, efficacy or quality of the drug substance must be validated, including storage and distribution of the drug substance.

<sup>5</sup> Advanced therapy medicines are gene therapy medicinal products, somatic cell therapy medicinal products or tissue engineered products pursuant to Article 2, paragraph 1, letter a of Regulation (EC) No. 1394/2007 of the European Parliament and the Council of 13<sup>th</sup> November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No. 726/2004 (OJ L 324 of 10.12.2007, p. 121).

<sup>6</sup> 20 February 2012 EMA/INS/GMP/129953/2012 Compliance and Inspection; [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2012/02/WC500123489.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123489.pdf)

misinterpretations in the case of mixtures of active substances<sup>7</sup> particularly when only one substance is active at the human level as for example, in the amoxicillin-clavulanic acid preparations<sup>8</sup>; or active substances in topical antiseptics which fall under the medicines regulations, although their regulation may overlap with the Biocidal Products regulations, as their principal function is that of inhibiting or arresting the growth of micro-organisms.

The EGS suggests therefore to make explicit that the definition of active substance refers to a single substance and excludes “combination of substances”, the only exception being the cases where the active substance cannot exist on its own. It may also be useful to have clarifications on:

how the term active substance relates to the term (and definition) of active pharmaceutical ingredient (API) as the two terms are sometimes used interchangeably but sometimes a distinction is made between the terms

whether the term active substance includes naturally occurring active substances or only synthesized, as this will affect how far back one should audit for compliance with GMP; whether it includes sterile active substances, biological and/or immunological active substances such as those present in blood preparations, sera, vaccines, allergens, test sera, radiopharmaceuticals

whether a substance is considered active independent or dependent on the quantity that is required to have an effect, and whether it is found in finished and intermediate medicinal products intended for further processing by a manufacturer

whether the definition of active substance covers the active ingredients of a number of medicinal products that do not comprise by the rules on active pharmaceutical ingredients, such as clinical trial investigational medicinal products, for which a marketing authorisation has not been granted; medicinal products dispensed by special compassionate-use permits<sup>9</sup>; medicinal products prepared in accordance with a magistral formula

whether active substances in products that are on the medicines borderline, such as products aimed at sports people, as many companies are unaware that medicines regulations may apply to their business

clarifications regarding the atypical actives<sup>10</sup> such as glycerine

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<sup>7</sup> The World Health Organization are working on a revision of their definition of active pharmaceutical ingredient (APIs) that excludes mixtures of APIs to tackle misinterpretation related to commercially available premixes of APIs; WHO, Working document QAS/11.426/Rev.1 July 2011; [http://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/DefinitionAPI-QAS11-426Rev1-08082011.pdf](http://www.who.int/medicines/areas/quality_safety/quality_assurance/DefinitionAPI-QAS11-426Rev1-08082011.pdf)

<sup>8</sup> Amoxicillin is the active ingredient with antimicrobial activity and the clavulanic acid acts as an inhibitor of bacterial resistance to antibiotics

<sup>9</sup> Compassionate use' permits allow medicinal products that are not authorised, but are in the development process, to be made available to patients with a severe disease who have no other satisfactory treatment available to them.

<sup>10</sup> substances which are registered as the active ingredient in a medicine but whose primary industrial use is not as a pharmaceutical active substance.

Herbal medicinal products are regulated by a separate Directive. It is only reasonable that the active substances in herbal medicines should also be dealt with separately as the definition of active substance of ordinary medicinal products will not cover the active ingredients in the herbal medicinal products which are often more than one herbal substance or one or more herbal preparations<sup>11</sup>, or one or more such herbal substances in combination with one or more such herbal preparations and where the definition of herbal substances covers mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form. In case that the extension of this directive will also apply to the active substance of herbal medicinal products, then the definition should be reviewed to take into account the specifics in traditional herbal medicinal products, particularly as different herbal preparations may contain the same active ingredient in different amounts and such medicines often contain more than one active substance.

Homeopathic medicinal products present even a greater challenge as they are prepared from homeopathic stocks involving a number of raw materials and they are not normally approved with an indication of effect. Therefore it is more difficult to have a definition that will address the active substance in homeopathic product.

**Manufacturer.** The definition of manufacturer should be included with clarification as to the exact role of the manufacturing authorisation holders and their statutory obligations, to prevent confusion between their duties and those of the inspectors of EU or recognised national authorities. The definitions should include:

anyone manufacturing / importing/packaging the active substance,  
anyone in charge of repackaging / unpacking / mixing the active substances,  
anyone in charge of labelling / relabelling or providing supplementary labels for the active substances.

There should also be clarification as to the definition of the manufacturer of active substances, manufacturer of medicinal products and pharmaceutical manufacturer with clear description of their role and obligations in relation to GMP e.g audits, inspections, records, reports, GMP certifications, etc

#### **Other definitions.**

**Starting materials.** A definition should be added and it should be adapted to the specifics of active substances particularly if immunological active substances and other types (see above in clarifications of definitions) are included in the scope of the directive.

**Excipients.** Some excipients should also be added to the list of active substances and hence the definition of 'excipient' should be included.

**Distributor.** The definition of distributor should also be included particularly if the distribution is acknowledged as an extension of the GMP. Such definition should include a company in the distribution chain between the active substance manufacturer and the pharmaceutical manufacturer that stores and distributes the active ingredient.

**Auditors.** Definition of auditors of active substance manufacturers, particularly for third party auditors, should be included clarifying their relation to the company.

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Herbal preparations: preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

**Importers.** Definition of importers of active substances from third countries should also be included as in some countries such importers are considered identical with pharmaceutical manufacturers and confusion may arise in interpretation.

Each definition should also include indication as to who is responsible for the relevant documentation and issuing of certificates such as inspection reports, GMP certificates.

### **2.3. Other provisions on active substances that could be added to Directive 2003/94/EC**

**Consultation item No 4: Do you agree with this specific point? Do you consider that other provisions specific to active substances should be added?**

The extension of the Directive on GMP for medicinal products to active substances must have some additional provisions specific to active substances. The European Glaucoma Society agrees with the placement of an obligation on the manufacturer of the active substance to ensure that the starting material is sourced from the premises claimed by the manufacturer of the starting material. This is particularly important in the case of the multi-source (generic) finished active substances where there is blending with another active substance or with an excipient. Such obligation will put responsibility not only on the quality of the starting material but also on the determination of what is considered to be the first step in the manufacture of the final product, which defines the start of shelf-life of the finished dosage form where applicable. The EGS believes that it may be useful to consider additional provisions for:

- GMP inspections of active substance manufacturers at the request of the manufacturer with the award of a GMP certificate to increase integrity of the supply chain

- borderline products such as food supplements that may have a physiological effect to be considered case-by-case

- atypical actives to allow for case-by-case dealing given the small volume of business

- some form of manufacturing authorisations to be awarded for active substances; extra documentation may be required in the case of multi-sourced generic active substances

- the award of distribution certificates of compliance with Good Distribution Practices which may address a number of issues in the supply chain

- sterile active substances as starting materials and the type of documentation required in such cases, as the basis of the inspection of active substances may require modifications to take into account the stages prior to, during and after the sterilisation process of the active substance, as only the *GMP Basic Requirements*



*for Active Substances used as Starting Materials* (EU GMP guide Part II) apply<sup>12</sup>

actions that should be taken upon discovery of a medicinal product whose active substance(s) fails to comply with GMP, bearing in mind that one active substance may be present in a number of medicinal products

GMP and GDP practices to be also adopted for the excipients and their raw materials from manufacturing to distribution chain and transport, with information about the excipients on the packaging and the patient's information leaflet

### **3. Other issues**

#### **3.1. Date of transposition of the delegated act**

#### **3.2. Date of application of the delegated act**

**Consultation item No 5: Please comment on section 3. Please raise any other issues or add any other comments you wish to make which have not been addressed in the consultation items set out above.**

In addition to the need to maintain supplies for legitimate medicinal products, the Commission should take into account the administrative resources available in each Member State and issues with misinterpretation of the current regulations. Such and other practical issues may restrict the transposition into national law in some Member States as it will require a number of other changes before the extension of the Directive can be adopted.

There is a danger that if a manufacturer discontinues a product due to non-compliance with GMP, the distributor of such product may turn into online suppliers in order not to lose the customers. Online suppliers remain unregulated to a large extent and a number of inappropriate products may be entering the market through imports from outside EU. Provisions should therefore be in place for increasing the awareness amongst the users of the various medicinal products (physicians, hospitals, patient organisations) regarding the extension of the Directive to active substances, as they are the only ones who can challenge distributors regarding the origin of their products, contributing hence effectively, although indirectly, to compliance with legislative changes.

Care should also be taken that the extension of the Directive 2003/94/EC to active substances will be carried out without prejudice to customs legislation, to the distribution of competences between the Union and the Member States and to the distribution of responsibilities within Member States.

Some compounds are used both as food additives and as excipients in medicinal products. As a result the intake of excipients through medicinal products may result in intake values of the excipient in excess of those recommended by toxicological committees on Food additives. Increased intake may cause health risks and such risks

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<sup>12</sup> The sterilisation and aseptic processing of sterile active substances are covered by the GMP for medicinal products (Commission Directive 2003/94/EC; as interpreted in the Basic Requirements for Medicinal Products including annex 1 of the EU GMP guide Part I). This implies that for any active substance manufacturer who performs sterilisation and subsequent aseptic handling of the active substance, a valid manufacturing authorisation or GMP certificate from a relevant national authority.



will not be prevented by the extension of the Directive alone. Increased efforts should be made to link the various policy areas such as the frameworks on food additives to protect the public.

The compilation of an inventory of approved active substances, excipients and other starting materials, distinguished by a clear international nomenclature (International Non-proprietary Names INN system), and listing the relative maximum doses for each administration route, will greatly enhance all efforts to monitor the long and complex supply chains of medicinal products.

The extension of the Directive 2003/94/EC to active substances may require assignment of inspectors specific to active substances and who will be based at the national medicines agency of Member States. A coordinating structure within the European Medicines Agency should also be considered and provided for.

## APPENDIX I. Glaucoma and related facts

### BACKGROUND

**Glaucoma statistics.** Glaucoma is a chronic, neurodegenerative disease of the optic nerve and the leading cause of irreversible blindness worldwide. It accounts for 10 million of the estimated 83 million bilaterally blind people worldwide, with blindness being 10 times higher in the developing than in the developed world: glaucoma is responsible for up to 30% of blindness in Africa.<sup>13</sup> The disease affects over 2% of the population over the age of 40 years and 4% of those above 80 years in Europe and 4-10% of the total population older than 40 years in USA. The total number of suspected cases of glaucoma worldwide is estimated to be around 65 million, increasing to 79.6 million by 2020<sup>14</sup>.

**Glaucoma costs.** The annual total cost per patient is estimated to be between €11,758 and €19,111 (direct treatment cost for late-stage glaucoma and rehabilitation) in Europe<sup>15</sup> and \$9,200 in USA, with 80% of costs related to the increased rates of depression, hip fractures, and home health care associated with glaucoma vision loss. Aside from the effect on the resources of medical care, there is additional impact, that cannot be quantified, on the sufferers and their families (rehabilitation and life style adjustments to accommodate the afflicted member of the family) and on productivity of the working force (as a result of reduced working life). Such burdens can only increase with the shift towards older populations.

**Addressing glaucoma.** Although current treatments slow down disease progression, they do not cure glaucoma as the molecular causes remain poorly understood. The financial and social impact of glaucoma can be reduced if the disease is treated at its earlier stages, and once diagnosed, glaucoma can be efficiently managed at a reasonable cost<sup>16</sup>. It is estimated that early treatment to arrest the development of visual impairment of even 10% of the glaucoma population in UK can potentially result in a saving of £555million to £1billion in UK alone<sup>17</sup>. Glaucoma is associated with other chronic medical conditions such as diabetes, myopia, and possibly with obesity and chronic stress and anxiety. Preventing the progression of such a chronic illness will be particularly cost-effective when dealing with patients exhibiting multi-chronicity.

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<sup>13</sup> *Glaucoma in Africa: size of the problem and possible solutions*, Cook, C, J. *Glaucoma*, 2009, Feb; 18(2): 124-8

<sup>14</sup> *The number of people with glaucoma worldwide in 2010 and 2020*, *Br J Ophthalmol.* 2006 Mar;90(3): 262-7, HA Quigley, AT Broman.

<sup>15</sup> *Cost analysis of glaucoma-related blindness in Europe*, P.B. Poulsen, P. Buchholz, J.G. Walt, T.L. Chistensen, J. Thygesen, International Congress Series, Vol. 1282, September 2005, pp 262-266,

<sup>16</sup> *J Glaucoma.* 2007 Aug;16(5):471-8.

Glaucoma in the United States and Europe: predicting costs and surgical rates based upon stage of disease.

<sup>17</sup> *The Costs of Blindness*, Ethical Strategies Limited, July 2003

**Diagnostic limitations and management issues as a hindrance to addressing glaucoma.** The classification of glaucoma suffers greatly from a lack of sensitivity in identifying preclinical glaucoma, and a lack of specificity in defining glaucoma unequivocally, as present-day clinical testing is based on observational skills and laboratory tools. As a result glaucoma is often detected too late for effective management. In the light of the estimated statistics and some reports referring to certain forms of glaucoma reaching epidemic proportions in India, China and other parts of Asia, it is of paramount importance therefore to address these diagnostic limitations in glaucoma for an efficient, effective and timely resolution of this serious global health issue.