UK comments on the European Commission's concept paper for the

**"Implementing Act on the requirements for the assessment of the regulatory framework applicable to the manufacturing of active substances of medicinal products for human use"**

*(SANCO/D3/(2011)ddg1.d3. 1438409)*

**Concept paper for "third country assessment" consultation topics:**

1. The concept paper deals with five main topics, which will be dealt with individually in the rest of this paper:

    - Equivalence assessment of the rules for GMP
    - Equivalence assessment of the regularity of inspections to verify compliance with GMP and the effectiveness of enforcement of GMP
    - Regularity and rapidity of information provided by the third country relating to non-compliant producers of active substances
    - "Other issues" which includes:
        - Form of assessment
        - Interface with existing mechanisms
        - Regular verification
        - Date of application
    - Any other comments or issues not already covered in the concept paper.

2. Unless otherwise noted, any further references to the Articles of Directive 2001/83/EC in the remainder of this paper are to the text amended by Directive 2011/62/EU.

*Equivalence assessment of the rules for GMP*

3. Article 111b(1)(a) of Directive 2001/83/EC obliges the Commission, in its equivalence assessment, to take particular account of the third country's rules for GMP.

4. Pending the adoption of the delegated act relating to GMP for active substances, it is proposed that Part II of the current EU GMP be used as the standard for assessment.

5. Currently where the MHRA undertakes inspections of active substance manufacturers, either on request of the active substance manufacturer or on a for-cause basis, the standards described in Part II form the basis of that inspection and a GMP certificate (or statement of non-compliance as appropriate) is issued to the inspected party.

6. Part II of the EU GMP is based on the content of ICH Q7 ("Good Manufacturing Practice for Active Pharmaceutical Ingredients"). ICH Q7 was adopted by the European Medicine Agency's Committee for Proprietary Medicinal Products in November 2000. The standards described therein are widely accepted in the EU and are also well established.

7. On this basis the MHRA supports the proposal to use Part II as the benchmark for equivalence assessment, pending the adoption of the delegated act on GMP for active substances. Comments for the concept paper on GMP for active substances will be submitted to the Commission separately.

*Equivalence assessment of the regularity of inspections to verify compliance with GMP and the effectiveness of enforcement of GMP*

8. Article 111b(1)(b) of Directive 2001/83/EC obliges the Commission, in its equivalence assessment, to take particular account of:

   - the regularity of inspections to verify compliance with GMP; and
   - the effectiveness of enforcement of GMP.

9. Article 111(1)(1b) places an obligation on Member States to "…have a system of supervision including by inspections at an appropriate frequency based on risk, at the premises of the manufacturers, importers or distributors of active substances, located on its territory, and effective follow up thereof."

10. Article 111(1)(1h) states that "Inspections shall be carried out in accordance with the guidelines referred to in Article 111a." Article 111a states "The Commission shall adopt detailed guidelines laying down the principles applicable to inspections referred to in Article 111."

11. The rules relating to the current inspection strategy are set out in the "*Compilation of Community Procedures on Inspections and Exchange of Information*" (currently EMA/INS/GMP/459921/2010 Rev 13), in particular the chapter on "*Guidance on the Occasions When It Is Appropriate for Competent Authorities to Conduct Inspections at the Premises of Manufacturers of Active Substances Used As Starting Materials*". Commission considers that this document provides a suitable basis for the establishment of a risk-based inspection programme.

12. Commission proposes to use the audit checklist currently employed by the Joint Audit Programme for GMP Inspectorates[1] as the basis for the equivalency assessment of the third country's regulatory framework. This audit checklist is described in an annex to the concept paper.

13. Whilst the audit checklist describes the components of the assessment, their relative importance, and the method by which the component is to be assessed, the MHRA considers there would be merit in the publication of acceptance criteria associated with the individual components of the checklist. It is considered that the publication of acceptance criteria would assist third country Competent Authorities with the internal assessment of their regulatory frameworks, and provide transparency in the assessment process.

14. There appears to be a discrepancy between the level of oversight expected for active substance manufacturers operating in Member States, and those operating in third countries.

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1 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/joint_audit_programme.jsp&mid=WC0b01ac058006e06f&murl=menus/regulations/regulations.jsp&jsenabled=true

15. Historically the obligation for direct oversight of the active substance manufacturer rested with the authorized manufacturer of the medicinal product (Article 46(f) before amendment). Directive 2011/62/EU has retained this in principle, and extends the obligation on the medicinal product manufacturer to ensure that the active substances used are themselves manufactured **and** distributed in accordance with good manufacturing practice and good distribution practice for active substances.

16. Article 8(3)(ha) makes explicit the requirement for written confirmation that the manufacturer of the medicinal product has verified compliance of the active substance manufacturer with the relevant GMP by way of audit (interpreted as being the "QP declaration").

17. Member States exercise indirect oversight of GMP for active during the assessment of marketing authorizations/variations, and the inspection of manufacturing authorization holders. Nevertheless, inspection of active substance manufacturing sites is risk-based and may be triggered if there are concerns with the quality of an active substance.

18. As a generality, active substance manufacturers globally are not currently routinely inspected by Member States, and not necessarily re-inspected once they have received a GMP certificate.

19. Since Member States will not be required to subject active substance manufacturers on their territory to regular and repeated inspection, it is considered that Article 46b(2)(ii) places a substantially greater duty on third country Competent Authorities than that placed on Member States through Article 111(1)(1b).

20. The MHRA considers that there could be issues where a third country's framework is assessed and found to be lacking when compared to European standards, particularly as there is no requirement or mechanism for a Member State to confirm the veracity of any written statement issued by a third country Competent Authority to the importer of an active substance.

21. Where a framework does not meet European standards it is clear that the country could not be named on Commission's list. However, it would also be the case that at least one of the requirements described in Article 46b(2)(b) could not be met, as for any particular manufacturing plant the third country Competent Authority would not be able to confirm with confidence that:

    - the standards to which the plant has been assessed are comparable to European standards;
    - the plant is subject to regular, strict and transparent controls and effective enforcement;
    - findings of non-compliance at the plant are reported to the Union without delay.

22. A problem then arises with the application of Article 46b(2)(b), as the third country Competent Authority will not be able to provide a written statement absolutely confirming that:

    - standards at the active substance manufacturing site are comparable to EU GMP.
    - the manufacturing plant is subject to regular, strict and transparent controls equivalent to those applied in the EU.
    - findings of non-compliance are supplied to the EU without delay.

23. In such a situation it is considered that the only recourse would be the inspection of individual active substance manufacturing plants by a Member State. This will have very significant resource

implications, particularly if the country is a significant source of active substances. All EU inspection resources are sized for the routine inspection of sites within the EU and in third countries with a relatively small contingency for triggered inspections.

24. It is understood that, to date, no third countries have expressed an interest in being assessed.

*25.* There is no requirement for third countries to indicate whether they are prepared to issue written confirmations before implementation in July 2013. Member States will not therefore know before the implementation date whether the lack of availability of written statements will present a particular issue, and as a consequence whether to notify Commission on exceptional grounds under Article 46b(4).

*Regularity and rapidity of information provided by the third country relating to non-compliant producers of active substances*

26. The MHRA supports the proposal that third country Competent Authorities participate in the "Procedure for Handling Rapid Alerts Arising from Quality Defects" described in the Compilation of Community Procedures. This is particularly as the procedure already provides a well established means of communication between authorization holders, Member States, MRA countries, PIC/S participants and other International organisations.

*Other issues: Form of assessment, Interface with existing mechanisms, Regular verification, Date of application*

27. The MHRA considers that the "Form of assessment" should take account of experience already accumulated as part of Member State's third country inspection programmes, for both active substances and medicinal products. The assessment should also include a review of a cross section of inspection reports issued by the third country Competent Authority.

28. The MHRA also considers that an appropriate number of observed inspections should be performed before acceptance onto Commission's list, rather than simply "…if necessary, an observed inspection of one or more of the…". The number of observed inspections should be commensurate with the compliance history of the third country.

29. It is not clear whether the re-assessment cycle will include a full repeat assessment, or be risk-based in nature. It is also not clear whether MRA agreements covering active substances will slot into the re-assessment process, or remain distinct.

30. The MHRA considers that implementation date may be unduly optimistic given the length of time typically seen for comparable assessment systems (e.g MRA agreement, PIC/S accession).

31. It is considered that the process of third country assessment and entry onto Commission's list could take around three years, and may significantly exceed that, the result being that at the time these requirements come into effect that there will be no 3rd countries on the list and that written statements (or inspection of active substance manufacturing sites) will be required to maintain importation.

*Other comments*

32. The concept paper seems to focus almost exclusively on the process of third country assessment. Other mechanisms need to be in place for the practical implementation of this system by all parties, that is:

- Third country competent authorities,
- Industry,
- Member State medicines Competent Authorities, and
- Customs Authorities.

These mechanisms should include:

- the need or otherwise for an original written statement to accompany each shipment of active substance from the manufacturer;
- the need for an original statement or copy to accompany sub-parts of any shipments if they are split at point(s) along the supply chain;
- the location and accessibility to the original statement where copy statements are allowed;
- identifying which personnel in the supply chain are required to review the written statement accompanying a shipment, and any authority they have or will need to take actions such as stopping shipments.

33. The requirement for both assessment and the provision of written statements is described as being for the third country concerned. It is clear that the most significant third country suppliers of active substances operate at a provincial level (States or Provinces forming individual regulatory entities within the countries as a whole). The Directive and concept paper does not appear to acknowledge the finer structure of third country regulatory systems, or its potential impact on the proposed systems.

34. There appears to be no substantial incentive for third countries to participate in the proposed systems. The systems could be construed as presenting a barrier to a widening legitimate global trade, particularly in emerging markets. At the extreme, the additional burden of obtaining a written confirmation from a third country Competent Authority could make it easier for manufacture of the medicinal product to take place in a third country. This is because the manufacturer of the finished dosage form in the third country would not be burdened with obtaining a written confirmation before (importing and) using the active substance. Reliance instead would be placed on Articles 8(ha) and 46(f), covered by obligations on the manufacturer of the medicinal product importing the product into the Community. If this were to be the perverse incentive created by Directive 2011/62/EU, it could seriously harm the European pharmaceutical industry and further reduce finished dosage form manufacture in Member States. It may be necessary for Commission to consider how this issue can be addressed.

35. Whilst raising GMP standards at third country manufacturing sites is a laudable aim, and is being pursued through other international fora, it is not clear what substantial benefit the written statement from the third country Competent Authority will provide in this respect. Article 46b(2)(a) requires as a matter of fact that the active substance is required to be manufactured to the relevant standards of EU GMP, 2(b) simply provides a level of reassurance that the third country has in place a regulatory framework comparable to (or indeed exceeding) that in Member States.

36. Article 46(f) and the "QP declaration" have provided the mechanism for the assurance of active substance quality, particularly obliging the manufacturer of the medicinal product to use active substances which have been manufactured to the relevant standards of EU GMP. Directive 2011/62/EU creates a specific legislative reference for the QP Declaration (by way of Article 8(ha)), and also makes explicit the requirement for the manufacturer of the medicinal product to have audited his suppliers (by way of a revised Article 46(f)). Chapter 5 of the EU GMP is also being revised to further support these changes by introducing the concept of "supply chain traceability" for starting materials.

37. It is estimated that around 60% of UK authorized medicinal products use active substances sourced from third countries, with around 7% of those active substances coming from MRA countries. China and India are by far the largest suppliers of active substances intended for use in the manufacture of UK authorized medicinal products. There are around 940 third country sources of active substances named on UK Marketing Authorizations, compared with 1675 located within Member States.

38. If a third country is not named on Commission's list and refuses to provide a written statement to the EU-based importer then it will fall to Member States to conduct inspections of active substance manufacturing sites in that third country to prevent potential stock shortages. Having to undertake such inspections in order to ensure continuity of supply will have a significant impact on Competent Authority inspection resources, and may have a knock-on effect for the resourcing of other GMP inspection programmes.

39. The reliance on GMP certification in Article 46b(4) does not align with the approach described in guidance issued by the European Medicines Agency[2], where it states:

> Manufacturing authorisation holders sometimes confuse the role of inspectorates with their own obligations but nevertheless, when inspection reports or GMP certificates issued by EEA, MRA partners or other recognised authorities are available, these can provide useful information to manufacturing authorisation holders. However, these alone cannot fulfil the statutory obligations of the manufacturing authorisation holder or the requirements of section 5.25 of the GMP Guide, but the results of inspections, may be used together with other supporting information in a risk-based approach by the manufacturer in establishing priorities for its own audit programme of active substance suppliers.

40. The MHRA considers that the current approach to GMP certification supports the following solution to the problem of an active substance importer not being able to obtain a written confirmation of standards.

41. In order to address this potential problem in a risk-based, proportionate and constructive manner, the MHRA suggests that in the absence of a written statement from a third country the QP declaration and manufacturer's audit may provide an adequate interim assurance of active substance quality, for those active substance manufacturing sites with a well established history of supply to the EU. This is

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2 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800296ca#section3

particularly in the light of the requirements of Article 46b(2) being without prejudice to Articles 8(ha) and 46(f).

42. The MHRA acknowledges that importers of active substances into the Community for subsequent export to a third country will not have available the assurances provided for by Articles 8(ha) and 46(f) if this approach is taken. It would be helpful to the UK's understanding of the Directive if Commission could confirm whether or not the requirements of Article 46b are intended to be applied to active substances imported into the Community, where those substances are subsequently exported to third countries and not used in Community manufacture of medicinal products.

43. In the UK it is the case that, because of the derogation provided for in Article 5(1), active substances intended for use in the manufacture of medicinal products exempt from the need for a marketing authorization do not need to be manufactured to the standards described in EU Good Manufacturing Practice.

44. Active substances may be imported with the intention for use in both veterinary and human medicines. It seems unlikely that, as they stand, Customs controls on importation will have enough discriminatory power to prevent the importation of active substances without the necessary accompanying written confirmations. This is particularly as the requirements introduced by Directive 2011/62/EU are not applicable to veterinary medicines.

45. With these last three points in mind, it is suggested that the controls on importation should rest with obligations placed on the manufacturer of the medicinal product rather than with border controls.

46. The MHRA suggests that clear incentives for third countries to participate in the assessment programme should be considered, perhaps mirroring the advantages granted to industry by the Mutual Recognition Agreement process.

47. The MHRA suggests that there may be merit in phasing-in the assessment scheme and requirement for written confirmation, to allow time for third countries to express an interest in either participating or not. This would allow industry time to identify alternative sources of active substances, ensuring continuity of the supply of medicinal products in the Community.

48. The MHRA will continue to support international initiatives in the development and mutual recognition of manufacturing standards.