Malta's Comments on the concept paper regarding implementing measures in order to harmonise the performance of the pharmacovigilance activities provided for in Directive 2011/83/EC and Regulation (EC) No 726/2004

The Maltese Medicines Authority welcomes this opportunity to comment on the draft implementing measures for pharmacovigilance.

Malta supports the need for improving and rationalising as well as simplifying the current legislative framework in this regard. However, Malta believes that, this should be reached through a reduction of administrative burden for both the pharmaceutical industry and the competent authorities whilst strengthening added value activities in protecting public health.

Overall, Malta is positive towards the proposed implementing measures, however, maintians certain concerns described in detail below.

A. Pharmacovigilance system master file

Consultation item no. 1: Should additional processes and pharmacovigilance tasks be covered?

The following additional processes and pharmacovigilance tasks need to be covered in the pharmacovigilance system master file;

- Monitoring and fulfilment of conditions of marketing authorisations issued as an Annex in Community Decisions.
- Implementation and reviews of Pregnancy Prevention Plans if applicable.
- Post-Authorisation Safety Studies production and submission

Fulfilment of Annex II and III of community decisions is a statutory obligation for marketing authorisation holders. The Pharmacovigilance system Master File should, therefore, cover these obligations.

Products authorised that have a high teratogenic potential require a pregnancy prevention plan. The monitoring of its implementation should be described in the system master file so as to enable Pharmacovigilance inspectors to be able to inspect the implementation of such programs.

Consultation item no. 2: The aim of the pharmacovigilance master file is two-fold: to concentrate information in one global document and to facilitate maintenance by uncoupling it from the marketing authorisation. Therefore changes to the content of the master file will be no longer subject to variation obligations. Would it be nevertheless appropriate to require the marketing authorisation holder to notify significant changes/modifications to the master file to the competent authorities in order to facilitate supervision tasks? If so, how should this be done? Should the master file contain a date when it was last reviewed?

Master files need to be submitted to the competent authorities either upon request (or a national obligation to submit these) or in preparation of an inspection. Malta would prefer that master files are submitted if requested and in preparation for an inspection. Preferably, transmission

should be in an electronic format. The Master file should be dated with its version number as well as information when it was last reviewed by the Marketing Authorisation Holder**.**

Consultation item no. 3: Is it necessary to be more precise on potential delegation, e.g. in the case of co-marketing of products? Please comment.

Malta believes that when any delegation within the distribution chain occurs, any third party will need to have a technical agreement signed and in place between the marketing authorisation holder and the said third party. Details of these technical agreements as well as the responsibilities of pharmacovigilance duties should be clearly laid out. These duties should be included in the both the technical agreement (signed by the qualified person for pharmacovigilance) as well as the master file.

Consultation item no. 4: Should a copy of the audit report be retained in the master file? Would it be appropriate to require documentation of audit schedules?

Malta is of the opinion that copies of all audit reports should be kept in the master file. Furthermore audit schedules are usually requested during inspections. The audit schedules could be part of an annex of the master file. An element of flexibility should be introduced so as not to make updating the master file an administrative burden.

Consultation item no. 5: Overall, do you agree with the requirements as regards the content and maintenance of the pharmacovigilance master file? Please comment.

Please refer to Malta's reply to consultation item no. 1 with respect to contents of the master file.

B. Quality systems for the performance of pharmacovigilance activities – Common obligations

Consultation item no. 6: Is there a need for additional quality procedures, e.g. in relation to study reporting in accordance with Article 107p of the Directive, in relation to communication on pharmacovigilance between the marketing authorisation holder and patients/health professionals; in relation to processes for taking corrective and improvement actions or in relation to the detection of duplicates of suspected adverse reaction reports in the Eudravigilance database?

Reporting serious and non-serious adverse events within statutory timelines is an obligation. However, at the point where Marketing Authorisation Holders receive the first piece of information of an adverse event, the quality system should not be detrimental to public health. The point to be made here is that, Marketing Authorisation Holders have the obligation to report complete information on the Adverse Events as well as revert to the reporter (either a patient or health care professional) with medical advice such as to stop the medicine or to go to hospital etc.

In order for appropriate transmission of individual case summary reports to Eudravigilance, Marketing Authorisation Holders must populate eudravigilance product dictionary with information on their medicinal products. In line with the new pharmacovigilance Regulation and Directive this is now an EU obligation. Therefore, there is a need for additional quality procedures to report information to eudravigilance product dictionary (EVMPD). However, to be able to populate EVMPD, due to the number of data entry requirements, the technical

specifications need to be as simple as possible and the reporting of one product should be completed within 1 hour. Across the EU, there are thousands of medicinal products (each marketing authorisation in each member state needs to be inputted in the database as a separate entry), therefore if very detailed technical specifications are adopted, thousands of hours as well as euros will be spent transmitting to EVMPD. The administrative burden for the public health benefit achieved is not justified.

Consultation item no. 7: Do you agree with the requirements for marketing authorisation holders? Please comment

Overall, Malta agrees with the requirements for marketing authorisation holders apart from those highlighted in response to Consultation item no. 6. In order for appropriate transmission of individual case summary reports to Eudravigilance, Marketing Authorisation Holders must populate eudravigilance product dictionary with information on their medicinal products. In line with the new pharmacovigilance Regulation and Directive this is now an EU obligation. Therefore, there is a need for additional quality procedures to report information to EVMPD. However, to be able to populate EVMPD, the technical specifications need to be as simple possible and the reporting of one product should be completed within 1 hour. Across the EU there are thousands of medicinal products (each marketing authorisation in each member state needs to be inputted in the database as a separate entry), therefore if very detailed technical specifications are adopted, thousands of hours as well as euros will be spent transmitting to EVMPD. The administrative burden for the public health benefit achieved is not justified.

It is important to note that no provisions have been introduced if a Marketing Authorisation Holder ceases to exist (bankruptcy or take over). If a medicinal product is authorised for a paediatric indication and the marketing authorisation holder has benefited from rewards or incentives under Articles 36, 37 or 38 of the Paediatric Regulation according to article 35 of the aforementioned regulation, and periods of protection have expired, and if the marketing authorisation holder intends to discontinue placing the medicinal product on the market, the marketing authorisation holder shall transfer the marketing authorisation or allow a third party, which has declared its intention to continue to place the medicinal product in question on the market, to use the pharmaceutical, pre-clinical and clinical documentation contained in the file of the medicinal product on the basis of Article 10c of Directive 2001/83/EC. Therefore, provisions adopted by the Commission should be in line with what is required by other EU regulations on Human medicines particularly Regulations (EC) No 1901/2006 and 1394/2007.

Consultation item no. 8: Do you agree with the quality system requirements? Please comment, if appropriate separately as regards requirements for marketing authorisation holders, national authorities and EMA.

Overall, Malta agrees with the quality system requirements for marketing authorisation holders apart from those highlighted in response to Consultation item no. 6. In order for appropriate transmission of individual case summary reports to Eudravigilance, Marketing Authorisation Holders must populate eudravigilance product dictionary with information on their medicinal products. In line with the new pharmacovigilance Regulation and Directive, this is now an EU obligation. Therefore, there is a need for additional quality procedures to report information to EVMPD. However, to be able to populate EVMPD, the technical specifications need to be as simple possible and the reporting of one product should be completed within 1 hour. Across the EU, there are thousands of medicinal products (each marketing authorisation in each Member

State needs to be inputted in the database as a separate entry), therefore if very detailed technical specifications are adopted, thousands of hours as well as euros will be spent transmitting to EVMPD. The administrative burden for the public health benefit achieved is not justified.

With respect to National Competent Authorities and EMA, in order to fulfil certain obligations the National Competent Authorities rely on Eudravigilance and its product dictionary as well as eudravigilance signal detection software (EVDAS). As a National Competent Authority responsible for inspections, we would like to be able to have capability to extract information from EVMPD and eudravigilance without limitations of 100 entries. This is imperative for preparatory work which we need to be able to carry out inspections.

Consultation item no. 9: For efficiency reasons a 'work sharing' procedure could be appropriate for the monitoring of medicinal products or active substances contained in several medicinal product. However, do you see a risk in cumulating all tasks (for the authorisation, PSUR scrutiny and Eudravigilance monitoring) in one Member State, as thereby the benefits of parallel monitoring may be lost ("peer review" system)?

Additionally, it may be envisaged to extend 'work sharing' to all medicinal products (including all centrally approved products) and to appoint a lead Member State in addition to EMA (Article 28a(1)(c) of Regulation (EC) No 726/2004). Please comment.

Generally, Malta agrees with the concept of extending work sharing to all medicinal products (including all centrally approved products) and appointing a lead Member State. However, to allow for the best possible assessment work to be carried out, rapporteurships should not be a 'closed shop' pegged to the Member State who was a rapporteur for the marketing authorisation. Over a period of time, competent expertise on medicinal products could have been acquired by a new Member State, while assessors from the original rapporteur team could not be available. Therefore, a system where lead Member States are appointed based on the availability of a competent team to carryout the work should be adopted. This would enable better work sharing and give the opportunity for NCAs in newer Member States to participate.

Consultation item no. 10: In the Commission's view the aim of this part is to establish common triggers for signal detection; to clarify the respective monitoring roles of marketing authorisation holders, national competent authorities and EMA; and to identify how signals are picked up? Are the proposed provision sufficiently clear and transparent or should they be more detailed? If so, which aspects require additional considerations and what should be required? Please comment.

The Malta Medicines Authority agrees with the Commission's view in this regard. It is imperative that National Competent Authorities have full access (and even flexibility to programme their own modified reports to facilitate data mining and signal detection) to Eudravigilance data warehouse to be able to fulfil their roles and responsibilities.

Consultation item no. 11: Do you agree with the proposed terminology? Please comment.

The Malta Medicines Authority agrees with the Commission's view that relevant ISO standards as well as MEDDRA are adopted. However, it should be kept in mind in the design of the system made available by the European Medicines Agency to populate Eudravigilance

Medicinal Product dictionary that the administrative burden needs to be minimised and that the system is simple enough (from a burden point of view) for the effective transmission of the required data elements.

Consultation item no. 12: Do you agree with the list of internationally agreed formats and standards? Please comment.

The Malta Medicines Authority agrees with the Commission's view that relevant ISO standards are adopted. However, the Regulation and Directive on pharmacovigilance provide for the submission of ICSRs from consumers / patients directly. This legislative provision might be over and above the details considered in the ISO standard. However, Eudravigilance should be able to accept this information.

Consultation item no. 13: Is there additionally a need for transitional provisions as regards certain aspects of this implementing measure, especially in relation to the specifications on format and content? Please comment.

Malta agrees with the Commission's view.

Consultation item no. 14: Do you agree with the proposed format and content? Please comment.

Malta agrees with the Commission's view but would like to point out that the batch number is not always known by the national agency for medicinal products and it could be very difficult obtaining this information. Reporting of this field should not be mandatory.

Consultation item no. 15: Do you agree with the proposed format and content? Please comment.

Malta's Medicines Authority agrees with the Commission's view in general. However we recommend to have an additional (section VIII) detailing fulfilments by marketing authorisation holders of conditions of marketing authorisations set in annex II, III and IV of commission decisions. This information would probably need to be submitted during updates to the Risk management plans.

Consultation item no. 16: Do you agree with the proposed format and content? Please comment

The Malta Medicines Authority agrees with the Commission's view.

Consultation item no. 17: Do you agree with the proposed format? Please comment.

The Malta Medicines Authority agrees with the Commission's view.