Principles to be applied for the implementation of the
HMA/EMA Guidance on the identification of CCI and PPD
in MA Applications

Introduction

The general public expectations over the transparency of the European Medicines Regulatory System and the increasing number of requests on access to documents correspond to an increasing trend in the release of information contained in the Marketing Authorisation Application (MAA) after its granting, particularly when it comes to clinical and safety data. Companies are aware that parts of the MA dossier may be released upon request after the granting of the MA.

As agreed in April 2011 by HMA, the Guidance Document on the Identification of Commercially Confidential Information and Protected Personal Data in the Marketing Authorisation Applications was on a three month consultation (1st June – 1st September 2011). During this period comments were received from twenty four associations and organisations. The general tone of these comments was very positive and supportive, welcoming the EMA/HMA initiative and the efforts to promote a more transparent and consistent approach across the European Medicines Regulatory Network. It is apparent that companies and authorities are well aware of transparency responsibilities, while protecting Commercial Confidential Information (CCI) and Personal Data when appropriate.

In general the pharmaceutical industry highlighted concerns in regard to the release of contractual arrangements between companies, personal data of experts and clinical and non-clinical data. Pharmaceutical companies raised special concerns with regard to the disclosure of non-clinical data, while the release of clinical data was supported by most stakeholders.

This summary of the main concerns, combined with some proposals to address them, has been prepared by the HMA/EMA Working Group on Transparency to facilitate review of the Guidance document and to provide additional guidance on implementation.

As stated in the introduction of the guidance document, it should be stressed that the principles laid out in therein will only apply to dossiers for authorised medicinal products.

The guidance document has been revised to reflect the comments received during the consultation period and the explanations outlined below in this paper.

It should be further noted that the intention is to provide a harmonised guidance to facilitate a consistent approach across the network. In case of disclosure of personal data, national or community legislation as well as the legislation on the protection of personal data (Dir. 95/46/EC) have to be taken into account.

1 Commercial Confidential Information shall mean any information which is not in the public domain or publicly available and where disclosure may undermine the economic interest or competitive position of the owner of the information, as per the definition agreed by HMA and EMA in November 2010 (EMA/48411/2010).
1) Applicability to MA applications submitted/approved before the publication of this guidance

*Status: Item agreed in HMA/EMA Transparency WG*

There are concerns that MA applications submitted or approved prior to the publication of the guidance document will not have been organised and prepared in accordance with the new agreed European principles.

**Approach Agreed:**

We believe that there are no constraints on using the principles outlined in this guidance when dealing with a request for access to MAA submitted/approved before the publication of this guidance.

2) Applicability of the Guidance document to refused or withdrawn MAAs

*Status: Item agreed in HMA/EMA Transparency WG*

There are concerns that disclosure of information regarding refused or withdrawn MAA applications may undermine potential new submissions of the MAA.

**Approach Agreed:**

The HMA/EMA guidance document is intended to apply to data provided in the MA dossier after a Marketing Authorisation is granted. Hence, the discussion about information to be disclosed when dealing with refused/withdrawn MAA (namely the reasons for refusing an application) is beyond the scope of this guidance. Nonetheless, competent authorities may apply the principles in the guidance to information in refused or withdrawn applications.

3) Applicability of the Guidance document to Orphan designation applications and Paediatric Investigation Plans

*Status: Item agreed in HMA/EMA Transparency WG*

It is mentioned in the last version of the document that “this guidance addresses the approach to provide access to different information in the MA dossier as high-level principles. This guidance document follows the structure of the Common Technical Document (CTD). However the principles outlined should be equally applicable to other formats and applications (e.g. Orphan designation, Paediatric Investigation Plans)”.

**Approach Agreed:**

Considering the comments received and the particularities of the applications for Orphan Designation and Paediatric Investigation Plans, we believe that we should defer the inclusion of this type of applications for the near future. Therefore, we proposed to remove the applicability to applications for Orphan Designation and Paediatric Investigation Plans, but to highlight that this will be addressed in the future.

4) Contractual arrangements between companies and other organisations

*Status: Item agreed in HMA/EMA Transparency WG*

The comments received to the consultation showed concerns about disclosure of contractual arrangements between companies and organisations. Companies, in particular generic companies, are concerned that disclosure of contractual arrangements exposes CCI.

It was agreed that there should be a distinction between contractual arrangements between companies included in Module 3, which the group considered to be CCI, and contractual arrangements with study centres and Contract Research Organisations (CROs) which are
typically in Modules 4 and 5 where it was understood that public scrutiny over situations of possible conflicts of interests may constitute an overriding reason to disclose some of this information. In the guidance document categorisation shall be changed accordingly. In any case overriding public health reasons to release information will prevail.

**Approach Agreed:**

Information on contractual arrangements in Module 3 of the dossier will be considered commercial confidential information in line with the agreed EU definition used in the guidance document; “any information which is not in the public domain or publicly available and where disclosure may undermine the economic interest or competitive position of the owner of the information”.

With regard to information in modules 4 and 5 of the dossier, it is considered that contractual information with companies responsible for non-clinical and clinical studies, including CROs can be released, as they may contribute to and be responsible for important information included in the dossier. The names of these CROs are therefore considered as information which can be released (CBR).

5) **Definition of the criterion “Protected Personal Data” (PPD) and disclosure of such data**

**Status:** Item agreed in HMA/EMA Transparency WG

The need for a clear definition of PPD and its applicability was pointed out by several stakeholders. In addition, there were a large number of requests disagreeing with the current proposals for PPD.

**Approach Agreed:**

The specific considerations on Protected Personal Data (PPD) are given in section 3 (as modified) of the guidance.

According to article 2(a) of the Directive 95/46/EC and article 2(a) of Regulation (EC) No 45/2001 of the European Parliament and of the Council, “personal data shall mean any information relating to an identified or identifiable natural person (‘data subject’); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity”, it is agreed that this definition should be added to the guidance document. However, there is a need to start to define PPD, Protected Personal Data, i.e. which personal data should be protected from disclosure.

Section 3 will be modified in line with the principles described below:

It has been agreed that all sections currently marked as PPD shall be redesignated because there are differences in the implementation of Directive 95/46 at national level and because different applicants have historically applied different approaches to the inclusion of personal data.

The following principles have been agreed and the designation indicated is subject to the provisions listed:

HMA/EMA considers that very little information in the application dossier should be considered as personal data that should be protected from disclosure. Personal data in the dossier mainly falls into the following categories:

A. Personal data relating to experts or designated personnel included in the dossier
B. Personal data relating to other staff included in the dossier
C. Personal data related to patients included in clinical trial study reports
D. Personal data related to pharmacovigilance information on individual patients
Notwithstanding specific national legislation on the protection of personal data, such as secrecy, processing and transferring of personal data (based on Directive 95/46/EC), the following policy will be applied to the four categories identified above.

A. Personal data related to experts or designated personnel - CBR

In general, it is considered that names of experts or designated personnel with legally defined responsibilities and roles with respect to aspects of the Marketing Authorisation dossier (e.g. QP, QPPV, Clinical expert, Investigator) are included in the dossier because that have a legally defined role or responsibility and it is in the public interest to release this data. Applicants are advised that non-essential information (e.g. personal addresses, personal phone numbers) should not be included in the dossier. For dossiers prepared before the application of this guidance document, such personal data will be redacted only if disclosure could lead to infringement of personal integrity or cause personal harm.

EMA/HMA aims to work with stakeholders to develop a plan to ensure that such data will no longer be included from an agreed date.

In addition, certain competent authorities may redact names of experts involved in animal studies where it can be considered that disclosure of such information may present a security risk to those individuals in the country concerned.

B. Personal data relating to other staff included in the dossier - PPD if included

HMA/EMA does not consider that names or personal details of other staff need to be included in the dossier. Applicants are therefore advised that such data should not be included in the dossier. For dossiers prepared before the application of this guidance document, such personal data will be redacted.

EMA/HMA aims to work with stakeholders to develop a plan to ensure that such data will no longer be included from an agreed date.

C. Personal data related to patients included in clinical trial study reports - PPD if included

The current European legislation requires patient information to be included in non-identifiable form in the marketing authorisation application submitted to competent authorities. Therefore applicants should ensure that the dossiers submitted meet legislative requirements. The applicant remains responsible for compliance with the legislation in cases where such data is inadvertently included in the dossier.

D. Personal data related to pharmacovigilance information on individual patients - PPD

Although it is not expected that much pharmacovigilance information related to individual patients will be provided as part of the initial MAA, this cannot be excluded. In addition a request may cover an application in the post-authorisation phase. In these cases the principles outlined in the HMA/EMA recommendations on the handling of requests for access to period safety update reports EMEA/74133/2009 will be applied. Where necessary at least dates of birth, reporting country information and patient identification code will be redacted before release.

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2 Some Member States have specific legislation and/or specific national rules, guidances or practices on the protection of personal data and therefore, in these countries, this data may be redacted.
6) Release of signatures of experts/designated personnel in the dossier  

*Status: Item agreed in HMA/EMA Transparency WG*

Different national practices apply to the release or disclosure of signatures included in the marketing authorisation dossier. Release of signatures is considered as Case-by-Case (CBC) to take into account these differences.

7) Disclosure of Pharmacovigilance system details  

*Status: Awaiting implementation of pharmacovigilance legislation*

There are concerns that disclosure of the Pharmacovigilance system reveals commercially sensitive information on company structures.

**Approach Agreed:**

Since this is currently being worked on in the context of the new pharmacovigilance legislation, we propose to defer this discussion until this work has been completed.

8) Risk Management Plans  

*Status: Awaiting for implementation of pharmacovigilance legislation*

There are concerns that disclosure of the company’s Risk Management Plan might be premature and confusing, as it is likely to differ from the final agreed and published summary.

**Approach Agreed:**

Since this is currently being worked on in the context of the new pharmacovigilance legislation, we propose to defer this discussion until this work has been completed. In any case, summaries of risk management plans will be published.

9) Environmental Risk Assessments (ERA)  

*Status: Approach for medicinal products for human use agreed at HMA/EMA Transparency WG 9/12/11. Discussion on veterinary dossiers will be separately considered.*

**Approach Agreed:**

In general, information on ERA in the human medicines fields is not confidential and can be released (CBR).

10) Possibility of consultation procedure with industry prior to disclosure  

*Status: Item agreed in HMA/EMA Transparency WG*

**Approach Agreed:**

The decision on what to disclose or not, lies with the regulatory authority. However, efforts can be made to inform or consult the Marketing Authorisation Holder (MAH) prior to publication or responding to a request of access to documents. This will depend on legal national frameworks.

11) Possibility that the information published or disclosed may be abused by companies and regulators where equivalent patent requirements or intellectual property protection to those in the EU do not apply.  

*Status: Item agreed in HMA/EMA Transparency WG*
Approach Agreed:
While the regulators understand the concerns raised, they do not expect that the guideline proposals will have a major impact in other regions. Manufacturing and quality information will be maintained as confidential and a summary of the remaining information is already published in EPAR’s or NPAR’s. As a general policy, in order to facilitate international collaboration, EU regulators would like to promote greater reliance on assessments performed by EU regulators. Publication or access to this information will facilitate this and help to avoid duplication of efforts. Data and market exclusivity as well as protection of other property rights are covered by separate legislation. An action to improve the public assessment reports in these areas could be envisaged. Similarly, companies should consider carefully how they present data in this section.

12) Potential conflict with publication in medical journals
Status: Item agreed in HMA/EMA Transparency WG

A number of responders to the consultation expressed the concern that publication of the clinical part of the dossier could prevent the acceptance of publications by investigators on data submitted as part of the dossier.

Approach Agreed:
Since the guideline addresses access to data after the granting of the marketing authorisation, it is difficult to see how this is a real concern. In addition, it should be clarified that publication is currently not in the scope of this document. The issue of publication is separate and should not interfere with the responsibilities of competent authorities to give appropriate access to information. However, following recent discussions from EMA with editors of medical journals, the release of this information is not normally considered a pre-publication. Discussions with medical journal editors will continue.

13) List of references and original manuscripts
Status: Item agreed in HMA/EMA Transparency WG

The concern was raised that the list of references and/or the detailed publications may provide competitors with insights into the quality and manufacturing processes and/or regulatory approaches and therefore they should be classified as CCI.

Approach Agreed: The list of references of the publications included in the dossier is not considered as confidential and can be released.

However, if the actual manuscripts are included, these may be subject to copyright. If there is no copyright, the manuscripts may be released upon request.

14) Scientific advice
Status: Item agreed in HMA/EMA Transparency WG

There are concerns that disclosure of information regarding scientific advice may affect new submissions of MA applications and the company’s research and development strategy.

Approach Agreed:
The release of information on an authorised therapeutic indication should not be regarded as Commercially Confidential Information after the conclusion of the procedure. However, all the information related with new developments and formulations should be protected.

15) GMO (Genetically Modified organism)  
Status: Item agreed in HMA/EMA Transparency WG

When a medicinal product contain GMOs, an Environmental Risk Assessment (ERA), should be provided in the section 1.6.2 of the Module 1 of the dossier.

Approach Agreed:
According to Notice to Applicants, the “information shall be presented in accordance with the provisions of Directive 2001/18/EC, taking into account any guidance documents published by the Commission in connection with the implementation of the said Directive. The information shall consist of:
• an introduction;
• a copy of any written consent or consents to the deliberate release into the environment of the GMO(s) for research and development purposes according to Part B of Directive 2001/18/EC;
• the complete technical dossier supplying the information required by Annexes III and IV to Directive 2001/18/EC;
• the environmental risk assessment in accordance with the principles set out in Annex II to Directive 2001/18/EC;
• the results of any investigations performed for the purposes of research or development;
• taking into account the above information and the ERA, a conclusion which proposes an appropriate risk management strategy which includes, as relevant to the GMO and product in question, a post-market monitoring plan and the identification of any special particulars which need to appear in the Summary of Product Characteristics, labelling and package leaflet;
• appropriate measures in order to inform the public.
A dated signature of the author, information on the author's educational, training and Occupational experience (CV), and a statement of the author's relationship with the applicant, shall be provided.”

At EU level there is a strong pressure for the release of information of GMOs. According with the EU legislation, information on GMOs should be public. Therefore, we propose to maintain the criterion “Can be Released and/or CBC” in this section of the guidance document. However, it is acknowledged that certain information may be CCI and should not be disclosed and further consultation with experts might be helpful to understand the legal requirements.

16) Reviewing CTD format in ICH and/or with other international pharmaceutical regulatory authorities  
Status: Item agreed in HMA/EMA Transparency WG

The idea of having a new format of CTD in order to have a confidential section in the MA dossier has been put forward by several stakeholders. However, there are concerns that a change at level of ICH may undermine the harmonised ICH regions approach to the agreed format of MAA. However, it is perceived that on the long-term this would be of benefit for all parties. EU will raise this issue at ICH.

Approach Agreed:
EU agencies will continue the discussion at ICH level and/or with other international pharmaceutical regulatory authorities on the proposed approach. Considering the administrative burden for regulatory agencies, the preparation of a non-confidential version of a dossier should be considered in the future. It was agreed that the EU agencies may well raise this issue at future
ICH meetings. In addition to this, pharmaceutical companies should be made aware that information from dossiers will be disclosed and they should not submit (patient) data that are not requested in the CTD. The CTD format will be strictly followed. It should be noted that there is no intention to create a European only version of the CTD.

17) Non-clinical data
Status: Item agreed in HMA/EMA Transparency WG 9/12

A number of respondents expressed concern about release of information in the non-clinical part of the dossier, on the grounds that the data presented was either commercially confidential as it revealed development or regulatory strategy approaches, or contained other proprietary information. Respondents also referred to the fact that non-clinical data might include experimental approaches which applied to a number of applications, not just the application under consideration.

**Approach Agreed:**
In principle, non-clinical study data is considered as data that can be released (CBR). In the case of exceptional and substantiated cases, for example, where innovative study designs and/or innovative analytical methods have been used, consideration will be given to the need for redaction.

18) Clinical data
Status: Item agreed in HMA/EMA Transparency WG

Although there was in general a very positive move towards increasing awareness expressed in the responses received, some stakeholders highlighted concerns towards the release of clinical data and documentation on the basis that this may reveal insights to competitors, and/or may bring disadvantages to researchers when publishing manuscripts from public clinical data and/or may have an impact on the way intellectual property rights are enforced worldwide.

**Approach Agreed:**
The concerns about intellectual property and medical journals are addressed separately.

In general, the data included in clinical trial study reports is considered as data that can be released as such data is not considered either commercially confidential or personal data that should be protected (see point 5 above). In addition, there are increasing demands from the public to put as much clinical data as possible in the public domain.

It should be noted that in order to reinforce transparency and public confidence in the European Medicines Regulatory System, NCAs are intending to develop strengthened efforts to release (either on request or proactively) growing amounts of clinical data.

19) Veterinary comments
Status: Item under discussion

The same principles should apply. However further discussion of specific veterinary considerations including the difference between CTD and NTA formats will need to be taken into account. Discussion deferred to separate Veterinary document which is expected to be developed during 2012.

HMA/EMA Working Group on Transparency
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