EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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External guidance on the implementation of the European Medicines Agency policy on the publication of clinical data for medicinal products for human use

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5505
Send a question via our website www.ema.europa.eu/contact

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General information

1. Introduction

The European Medicines Agency policy on the publication of clinical data for medicinal products for human use[1] (hereafter referred to as 'Policy 0070') was developed by the European Medicines Agency (EMA), in accordance with Article 80 of Regulation (EC) No 726/2004. Policy 0070 was adopted by the EMA Management Board on 2nd October 2014 and subsequently published on the EMA website.

Policy 0070 is composed of two phases. Phase 1 of Policy 0070 entered into force on 1st January 2015. Phase 1 pertains to publication of clinical reports only[2]. Phase 2, which will be implemented at a later stage, pertains to the publishing of individual patient data (IPD)[3]. Clinical reports and IPD are collectively referred to as "clinical data".

There is a need for further guidance in order to ensure that Policy 0070 meets its objectives. For this purpose EMA has prepared the following documents:

- External guidance on the procedural aspects related to the submission of clinical reports for the purpose of publication in accordance with EMA Policy 0070 (see Chapter 2).
- External guidance on the anonymisation of clinical reports for the purpose of publication in accordance with EMA Policy 0070 (see Chapter 3).
- External guidance on the identification and redaction of commercially confidential information in clinical reports submitted to EMA for the purpose of publication in accordance with EMA Policy 0070 (see Chapter 4).

2. Scope

The scope of this guidance document relates to phase 1 of Policy 0070.

Clinical reports will be published, under Policy 0070, following conclusion of the regulatory decision-making process in the frame of centralised marketing authorisation procedures, as follows:

- as part of a marketing authorisation application (MAA) with the exception of informed consent applications; effective date 1 January 2015, or
- as part of a procedure under Article 58 of Regulation (EC) No 726/2004; effective date 1 January 2015, or
- submitted by a third party in the context of a MAA: effective date 1 January 2015, or
- as part of extension of indication – understood as variations related to the "*addition of a new therapeutic indication or modification of an approved one"* as per the *Guidelines*[4] *on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008*[5] - and line extension applications relating to existing centrally authorised medicinal products; effective date 1 July 2015, or

[1] European Medicines Agency policy on publication of clinical data for medicinal products for human use (EMA/240810/2013)
[2] For the definition of "clinical reports", see section 3 - Definitions.
[3] For the definition of "IPD", see section 3 - Definitions.
[4] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c_2013_2008/c_2013_2008_pdf/c_2013_2804_en.pdf
[5] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:334:0007:0024:EN:PDF

- requested by EMA/submitted by the applicant/Marketing Authorisation Holder (MAH) as additional clinical data in the context of the scientific assessment process for the aforementioned situations.

Clinical reports contained in applications where the Applicant has notified EMA of the withdrawal of the MAA are also published under Policy 0070.

The effective date of Policy 0070 for all other post-authorisation procedures will be decided on by EMA at a later date.

Furthermore, EMA would like to clarify a number of specific situations:

Clinical reports submitted as part of previous/other regulatory procedures

The EMA's view is that clinical reports submitted as part of, or cross-referred to within a regulatory application will be subject to publication following the redaction of CCI and anonymisation of the clinical data. This includes CSRs previously submitted in the context of earlier regulatory procedures which form the basis of the regulatory decision for those applications falling in the scope of the policy. This publication is independent of who the author or party holding any rights to the documents may be. Any such rights remain a contractual issue between the applicant/MAH and any third party(ies).

For example, according to the submission requirements laid down in Article 46 of Regulation (EC) No 1901/2006, the results of studies involving the use of an authorised medicinal product in the paediatric population should be submitted to the competent authority within six months of completion of the clinical study. As a result, these same studies may not be resubmitted in a regulatory procedure to add or modify a paediatric indication, but instead be referenced to the data submitted in the context of an earlier Article 46 procedure. In such cases, the clinical data submitted in the context of Article 46 of Regulation (EC) No 1901/2006 to which reference is made in a regulatory procedure for the addition or modification of a paediatric indication is also subject to publication under Policy 0070.

Informed consent applications

For informed consent applications where only a complete module 1 is submitted, the applicant/MAH is not expected to submit any document as Policy 0070 does not apply.

Duplicate marketing authorisations

In order to avoid unnecessary work EMA will accept that, in the event of duplicate marketing authorisations, the clinical study report submitted by the applicant/MAH will be accompanied by a statement confirming that the same set of documents were filed for all duplicate marketing authorisations (bearing different invented names). Provided that there are no differences among the clinical study reports for all the concerned duplicate products, the submission of one redaction proposal for all such documents would suffice. Hence, the applicant/MAH will not have to replicate submission for the documents pertaining to the individual marketing authorisation concerned or to the second or the third etc.

3. Definitions

For the purposes of the implementation of Policy 0070 the following definitions[6] will apply:

- **Aggregated data:**

  Statistical data about several individuals that has been combined to show general trends or values without identifying individuals within the data.

[6] It should be noted that some definitions are already included in the published Policy 0070. For the sake of completeness they have been incorporated as well in this guidance document.

- **Anonymisation:**

  The process of rendering data into a form which does not identify individuals and where identification is not likely to take place.

- **Anonymised / de-identified data:**

  Data in a form that does not identify individuals and where identification through its combination with other data is not likely to take place.

- **Applicant / MAH:**

  Applicant/MAH shall mean the natural or legal person(s) or organisation(s) that submitted the clinical reports to EMA in the context of applications in support of centralised marketing authorisations (MAs)/post-authorisation submissions for existing centrally authorised medicinal products, or in support of an application for an opinion in accordance with Article 58 of Regulation (EC) No 726/2004, as well as any person(s) or organisation(s) who own(s) copyright or other intellectual property rights in the clinical reports.

- **Article 29 Data Protection Working Party (Art. 29 WP):**

  The Art. 29 WP was set up under Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. It has advisory status and acts independently. It is composed of a representative of the supervisory authority(ies) designated by each EU country, a representative of the authority(ies) established for the EU institutions and bodies, and a representative of the European Commission.

- **Clinical reports:**

  Clinical reports shall mean the clinical overviews (submitted in module 2.5), clinical summaries (submitted in module 2.7) and the clinical study reports (submitted in module 5, "CSR") together with the following appendices to the CSRs: 16.1.1 (protocol and protocol amendments), 16.1.2 (sample case report form), and 16.1.9 (documentation of statistical methods).

- **Clinical data:**

  Clinical data shall mean the clinical reports and IPD.

- **Clinical study:**

  Clinical study shall mean any investigation in relation to humans intended to:

  – discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;

  – identify any adverse reactions to one or more medicinal products; or

  – study the absorption, distribution, metabolism and excretion of one or more medicinal products;

  with the objective of ascertaining the safety or efficacy of those medicinal products.

- **Commercially Confidential Information (CCI):**

  CCI shall mean any information contained in the clinical reports submitted to EMA by the applicant/MAH which is not in the public domain or publicly available and where disclosure may undermine the legitimate economic interest of the applicant/MAH.

- **Data:**

  Data shall mean characteristics or information, usually numerical, that are collected through observation. The word can also be used to describe statistics (i.e. aggregations or transformations of raw data).

- **Data controller:**

  A person who (either alone or jointly or in common with other persons) determines the purposes for which and the manner in which any personal data are, or are to be, processed.

- **Data linkage:**

  A technique that involves bringing together and analysing data from a variety of sources, typically data that relates to the same individual.

- **Data mining:**

  Activity of going through big data sets to look for relevant or pertinent information.

- **Data processor:**

  An organisation that processes personal data on behalf of a data controller.

- **Data subject:**

  An individual who is the subject of personal data.

- **Disclosure:**

  The act of making data available to one or more third parties.

- **Individual patient data (IPD):**

  IPD shall mean the individual data separately recorded for each participant in a clinical study.

- **Protected personal data (PPD):**

  For the purpose of this guidance document the definition from Directive 95/46/EC applies: “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.

- **Pseudonymisation:**

  Consists of replacing one attribute (typically a unique attribute) in a record by another. The natural person is still likely to be identified indirectly. Pseudonymisation reduces the linkability of a dataset with the original identity of a data subject.

- **Publishing:**

  The act of making data publicly available.

- **Re-identification:**

  The process of analysing data or combining it with other data with the result that individuals become identifiable, sometimes also referred to as ‘de-anonymisation’.

- **Residual risk:**

  The risk that remains after controls are taken into account (the net risk or risk after controls).

- **Risk:**

  The probability of re-identifying a trial participant.

- **Study subject:**

  For the purpose of Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, a 'subject' is defined as 'an individual who participates in a clinical trial, either as a recipient of an investigational medicinal product or as a control'.
  Use is made in the guidance of the term 'research participant' as an equivalent to 'subject', in order to avoid confusion with the aforementioned protected personal data (PPD) term 'data subject'.

- **Redaction Proposal Version:**

  This is the clinical report version containing the applicant's/MAH's proposed redactions on commercial confidential information (CCI) and personal data. These proposed redactions should be highlighted in a 'read-through' manner.

- **Redaction Proposal Document Package:**

  The "Redaction Proposal Document" package shall contain the redaction proposal versions of all clinical reports related to one single finalised regulatory procedure that falls under the scope of Policy 0070, along with a number of additional documents listed in the "External guidance on the procedural aspects related to the submission of clinical reports for the purpose of publication in accordance with EMA Policy 0070".

- **Final Redacted Version:**

  This is the clinical report version, submitted by the applicant/MAH for publication, which should reflect the EMA review outcome (accepted/rejected redactions).

- **Final Redacted Document Package:**

  A "Final Redacted Document" package shall contain the final redacted versions of all clinical reports related to one single finalised regulatory procedure that falls under the scope of Policy 0070.

4. Implementing Policy 0070

The publication of clinical reports in accordance with Policy 0070 is a new undertaking for EMA. Several new arrangements had to be developed to fully meet the purpose of Policy 0070. Taking into account the availability of limited resources and the anticipated high volume of work, EMA has aimed for the most cost-efficient approach in implementing Policy 0070, whilst respecting the objectives of Policy 0070. In order to achieve such objectives particular consideration had to be given to protecting personal data and protecting CCI.

In this guidance document detailed guidance is provided in the following fields:

- Procedural aspects related to the submission of clinical reports.
- Identification and redaction of CCI in clinical reports.
- Anonymisation of clinical reports.

Chapter 2

External guidance on the procedural aspects related to the submission of clinical reports for the purpose of publication in accordance with EMA Policy 0070

1. Introduction

This chapter provides guidance to applicants/MAHs in relation to procedural aspects on the submission of the clinical reports for publication by EMA under Policy 0070 as follows:

- Clinical report document types
- Process for the submission of clinical reports for publication
- Publication process

The guidance will be updated regarding post-authorisation procedures in relation to the effective date when these procedures come under Policy 0070.

2. Clinical report document types

2.1. Types of documents that fall within the scope of Policy 0070

Policy 0070 defines the clinical reports within its scope and which are subject to publication. This information is repeated in Chapter 1 (see section 2. Scope).

2.2. Types of documents or sections of documents considered to be in or out of scope of phase 1 of Policy 0070

In the Common Technical Document (CTD) sections falling within the scope of Policy 0070 there may be additional documents submitted by an applicant/MAH other than clinical overviews, clinical summaries and clinical study reports (CSRs). Therefore, EMA would like to clarify the types of documents that are subject to publication as well as whether there are any sections within the clinical reports that may be considered as out of scope of phase 1 of Policy 0070. Annex 1.12 of this guidance document contains a comprehensive list of which documents are subject to publication.

In addition to this comprehensive list EMA would like to further clarify the following points:

- The reports describing the safety and efficacy findings of the main period/phase of a clinical study are subject to publication. This position is taken regardless of the timing of submission of the results of the extension/follow-up of the same main study. More specifically, if the main part of the study (meaning the study preceding the extension/follow-up) is completed the study is not considered on-going. The status of the study (on-going or completed) is always evaluated at the time point of the publication. Where the study is on-going at the time of the regulatory submission but has been completed by the publication date, justifications stating “on-going study” will be disregarded. These completed (main parts) studies are considered in scope even if their follow-ups have not yet been completed by the time of the publication.
- Case narratives should not be removed nor redacted in full regardless of their location in the clinical reports (body of the report or listings). They should be, instead, anonymised. Regardless of the anonymisation technique used by the applicant/MAH, EMA cannot accept the redaction of the entire case narrative by default (as a rule). If, exceptionally, the entire case narrative needs to be redacted to ensure anonymisation, i.e. all identifiers (direct and indirect) need to be redacted, it has to be clearly justified in the anonymisation report.

- Likewise, patient level information referred to in the free-text should not be redacted in full but instead anonymised. Please refer to Chapter 3 “External guidance on the anonymisation of clinical reports for the purpose of publication in accordance with EMA Policy 0070”.

3. Process for the submission, review and publication of clinical reports

3.1. High level summary of the process

A high level workflow outlines the key components of the process from the submission by an applicant/MAH to the publication (please see Annex 1.9 for more details).

3.2. Notifications to Applicants

The applicant/MAH will receive notifications to submit a Redaction Proposal document package. In the case of initial marketing authorisation applications (initial MAAs), line extension applications and extension of indication applications, two notifications will be sent as follows: (i) the validation letter and (ii) the CHMP Opinion letter. The notification will be within the letter sent to the applicant/MAH for the relevant stage of the scientific review process. In the case of a withdrawal, the applicant/MAH will receive two notifications to submit a Redaction Proposal document package (i) in the validation letter (when the application was originally submitted) and (ii) in the acknowledgement letter of withdrawal to the applicant. A table outlining when each notification will be issued, for each application type, is provided below.

Application Type	First Notification	Second Notification
Initial MAA	Validation letter	CHMP Opinion letter or Acknowledgement letter of withdrawal
Line Extension		
Extension of Indication Application		

3.3. Detailed end-to end process

There are de facto four sub processes:

- Submission of Redaction Proposal document package.
- Consultation process.
- Submission of the Final Redacted document package.
- Publication process

The applicant/MAH is required to submit two packages to EMA:

- Redaction Proposal document package.
- Final Redacted document package.

3.3.1. Submission of the Redaction Proposal document package

3.3.1.1. Process to submit the Redaction Proposal document package

A workflow for the submission of the Redaction Proposal document package can be found in Annex 1.7 of this guidance document. This process requires the applicant/MAH to submit to EMA a redaction proposal version of the clinical reports for publication, in which proposed redactions are marked, in line with the CTD format of Modules 1, 2, and 5 or equivalent sections if the submission structure does not follow the ICH M4 guideline.

3.3.1.2. Timeline

The timeline for the submission of the Redaction Proposal document package by the applicant/MAH varies depending on the regulatory procedure.

For the Initial MAAs, and line extension applications, applicants/MAHs must submit their Redaction Proposal document package between day 181 and day 220 of the procedure (≤ 30 days pre-opinion and ≤ 10 days post-opinion).

For extension of indication applications, applicants/MAHs must submit their Redaction Proposal document package ≤ 30 days pre-opinion and ≤ 10 days post-opinion.

For withdrawn applications, applicants/MAHs must submit their Redaction Proposal document package ≤ 30 days post-receipt of the withdrawal letter by EMA. The notification to the applicant/MAH at CHMP opinion stage will state the specific deadline for the submission of the Redaction Proposal version for the medicinal product in question.

3.3.1.3. Content of the Redaction Proposal document package

An exhaustive list of the documents to be submitted within the Redaction Proposal document package is provided in Table 1 below, including the redaction proposal versions of all the listed clinical reports.

The required documents should be submitted within the relevant eCTD sections. For further reference please consult the eCTD Guidance Document (eSubmission) for the Centralized Procedure:

User Guidance for submissions via eSubmission Gatway

Harmonised Technical Guidance for eCTD Submissions in the EU

All documents including the cover letter with the required declaration of the Redaction Proposal document package must be uploaded via the gateway at the same time. Both, the proposed and the final redaction document packages should contain the same number of clinical reports. Therefore, even clinical reports where no CCI and/or PPD redactions are proposed and no justification table is required have to be submitted as part of both packages. The eCTD submission of the Redaction Proposal document package falls under the same eCTD life cycle of the initial MAA, line extension application or extension of indication application as applicable.

Table 1: Content of the Redaction Proposal document package, the corresponding eCTD location and the publication status

Redaction Proposal Document package	eCTD Module / Section within the eCTD	Documents published
Cover letter including the declaration confirming that the clinical reports submitted for scientific evaluation are the same as those submitted for publication, except for the proposed redactions/anonymisation. The cover letter templates are at Annex 1.4 and 1.5	1.0	Not published
A list of documents submitted, annexed to the cover letter. A template for this list is at Annex 1.3	1.0	Not published
clinical overview supplement/amendment/appendix	2.5	Not published
clinical summary supplement/amendment/appendix	2.7.1- 2.7.4	Not published
Clinical study report - body	5.3	Not published
Clinical study report - Appendices 16.1.1 (protocol and protocol amendments) 16.1.2 (sample case report form) 16.1.9 (documentation of statistical methods).	5.3	Not published
A complete set of justification tables (CCI redactions only) detailing all proposed redactions for each document. Links to downloadable templates are provided in Section 3.3.1.10 and a sample justification table is provided in Annex 1.10	Working document	Not published
Anonymisation Report, the report template is at Annex 1.2	1.9	Not published

If any of the parts of the Redaction Proposal document package, set out Table 1 above, including the required declaration in the cover letter is not submitted, the whole package will be rejected. In that case, a corrected complete package must be submitted. Individual parts cannot be submitted separately to correct submission deficiencies.

3.3.1.4. Anonymisation Report

One overall anonymisation report has to be submitted describing the methodology of the anonymisation applied in the submitted clinical reports. The report should also describe how the risk of re-identification has been measured and managed, or if the three criteria for anonymisation have been fulfilled. A template anonymisation report can be found at Annex 1.2 setting out its content and structure requirements.

3.3.1.5. Issues with hyperlinks, bookmarks or external links

The applicant/MAH is not expected to provide/ensure that hyperlinks between and within documents are functional. This also applies to bookmarks.

3.3.1.6. Leaf title naming in index XML of eCTD submission

For submission of the Redaction Proposal version and the Final Redacted version of the clinical reports, EMA requires the applicant/MAH to follow a predefined naming convention. During the submission the documents will have an XML leaf title as well as a filename (pdf). The naming convention applies to both the XML leaf title as well as the filename. Publishing the submission with recommended leaf titles and filenames as below will generate Best practice warnings (15.BP3, 15.BP5) during the eCTD technical validation, however this will not lead to validation failure or influence the acceptance of submission from a technical perspective.

The construction of the above naming conventions is based on the use of the following elements:

EMA requires the applicant/MAH to apply the following naming convention for the leaf titles in the index.xml:

<u>Module 2 documents</u>

TradeName[7]H/C/xxxxxx/xx/xxxx m25-clinical-overview-var

TradeName[7] H/C/xxxxxx/xx/xxxx m271-summary-biopharm-var

TradeName[7] H/C/xxxxxx/xx/xxxx m272-summary-clin-pharm-var

TradeName[7] H/C/xxxxxx/xx/xxxx m273-summary-clin-efficacy-var

TradeName[7] H/C/xxxxxx/xx/xxxx m274-summary-clin-safety-var

<u>Module 5 documents</u>

TradeName[7] H/C/xxxxxx/xx/xxxx m53xx-StudyReportNumber[8] P (for PIVOTAL) or S (for SUPPORTIVE) CSR body

[7] The trade name will be looked into on a case by case basis in case of a very long string of characters.
[8] For reports which present analysis of data collected from multiple studies, the applicant/MAH should include the report identification number (one identification number), instead of the study report numbers of each study from which the data was analysed (clinical trial or clinical study numbers). This information has to be included in the leaf titles and in the file names.

TradeName[7] H/C/xxxxxx/xx/xxxx m53xx-StudyReportNumber[8] P (for PIVOTAL) or S (for SUPPORTIVE) app1611 protocol

TradeName[7] H/C/xxxxxx/xx/xxxx m53xx-StudyReportNumber[8] P (for PIVOTAL) or S (for SUPPORTIVE) app1612 crf

TradeName[7] H/C/xxxxxx/xx/xxxx m53xx-StudyReportNumber[8] P (for PIVOTAL) or S (for SUPPORTIVE) app1619 sap

Where the applicant/MAH submits the body of the CSR together with the 3 Annexes (16.1.1, 16.1.2 and 16.1.9) as a single file, the leaf titles should follow the below naming convention:

TradeName[7] H/C/xxxxxx/xx/xxxx m53xx-StudyReportNumber[8] P CSR with app

TradeName[7] H/C/xxxxxx/xx/xxxx m53xx-StudyReportNumber[8] S CSR with app

In case the applicant/MAH has included US Integrated Summary of Safety (ISS) and US Integrated Summary of Efficacy (ISE), the leaf titles should follow the below naming convention:

TradeName[7] H/C/xxxxxx/xx/xxxx m274-ISS-var

TradeName[7] H/C/xxxxxx/xx/xxxx m273-ISE-var

TradeName[7] H/C/xxxxxx/xx/xxxx m53xx-ISS-var

TradeName[7] H/C/xxxxxx/xx/xxxx m53xx-ISE-var

3.3.1.7. Corresponding file names for the PDF documents

EMA requires the applicant/MAH to apply the following naming convention for the filenames of the PDF documents:

Module 2 documents

m25-clinical-overview-var.pdf

m271-summary-biopharm-var.pdf

m272-summary-clin-pharm-var.pdf

m273-summary-clin-efficacy-var.pdf

m274-summary-clin-safety-var.pdf

Module 5 documents

m53xx-StudyReportNumber[8]-p-csr-body.pdf

m53xx-StudyReportNumber[8]-s-csr-body.pdf

m53xx-StudyReportNumber[8]-p-app1611-protocol.pdf

m53xx-StudyReportNumber[8]-p-app1612-crf.pdf

m53xx-StudyReportNumber[8]-p-app1619-sap.pdf

Where the applicant/MAH submits the body of the CSR together with the 3 Annexes (16.1.1, 16.1.2 and 16.1.9) as a single file, the file names should follow the naming convention below:

m53xx-StudyReportNumber[8]-p-csr-with-app.pdf

m53xx-StudyReportNumber[8]-s-csr-with-app.pdf

In case the applicant/MAH has included US Integrated Summary of Safety (ISS) and US Integrated Summary of Efficacy (ISE), the File/document names should naming convention below:

m273-summary-clin-efficacy-ISE-var.pdf

m274-summary-clin-safety-ISS-var.pdf

m53xx-ISS-var

m53xx-ISE-var

In rare cases, or where more than one document is submitted in Module 2.5 or 2.7.1, 2.7.2, 2.7.3, 2.7.4 for the *same* indication/procedure, it should be indicated clearly in the var. part of the file name.

m25-clinical-overview-var.pdf

m271-summary-biopharm-var.pdf

m272-summary-clin-pharm-var.pdf

m273-summary-clin-efficacy-var.pdf

m274-summary-clin-safety-var.pdf

This var. part of the file name should *only* be inserted where more than one document is submitted for that particular indication/procedure. If for one submission there is only one 2.5, 2.7.1., 2.7.2, 2.7.3, and 2.7.4 var. should be excluded from the file name.

Regarding the technical requirements, please note that the PDF file names should be written in lower case and should not contain any special characters.

The construction of the above naming conventions is based on the use of the following elements:

1. Trade name: Product name
2. Procedure number: EMEA/H/C/xxxxxx/xx/xxxx
3. CTD Location

- Module 2.5
- Module 2.7.1
- Module 2.7.2
- Module 2.7.3
- Module 2.7.4
- Module 5.3.x.x

4. Type of document

- Clinical Overview
- Clinical Summary
- Study report number- P (for PIVOTAL) or S (for SUPPORTIVE) – CSR body
- Study report number– P (for PIVOTAL) or S (for SUPPORTIVE) Appendix 16.1.1 – protocol
- Study report number– P (for PIVOTAL) or S (for SUPPORTIVE) Appendix 16.1.2 – CRF
- Study report number– P (for PIVOTAL) or S (for SUPPORTIVE) Appendix 16.1.9 – SAP

Example 1 naming of the PDF:

For example, if the applicant/MAH has submitted a clinical overview for monotherapy and combination therapy for the same product in the initial MAA the example below should be followed:

a. If they are two *separate* documents, the file names should include the following:

m25-clinical-overview-monotherapy.pdf

m25-clinical-overview-combination.pdf

m271-summary-biopharm-monotherapy.pdf

m271-summary-biopharm-combination.pdf

m272-summary-clin-pharm-monotherapy.pdf

m272-summary-clin-pharm-combination.pdf

m273-summary-clin-efficacy-monotherapy.pdf

m273-summary-clin-efficacy-combination.pdf

m274-summary-clin-safety-monotherapy.pdf

m274-summary-clin-safety-combination.pdf

b. If the two forms of therapies (mono and combination) or indications are discussed in one document, the file naming should follow the original proposal, in particular:

m25-clinical-overview.pdf

m271-summary-biopharm.pdf

m272-summary-clin-pharm.pdf

m273-summary-clin-efficacy.pdf

m274-summary-clin-safety.pdf

The same problem should not occur in the naming of the module 5.3 files, as *the study number* will clearly indicate the correct study.

Example 2 naming of the PDF:

Another example is when during the scientific assessment additional information was included in the clinical overview or clinical summaries, which is reflected in a submission of an addendum. In this case the example below should be followed:

If an addendum was submitted *in addition* to the original document(s) the file names should include the following:

m25-clinical-overview.pdf

m25-clinical-overview-addendum.pdf

m271-summary-biopharm.pdf

m271-summary-biopharm-addendum.pdf

m272-summary-clin-pharm.pdf

m272-summary-clin-pharm-addendum.pdf

m273-summary-clin-efficacy.pdf

m273-summary-clin-efficacy-addendum.pdf

m274-summary-clin-safety.pdf

m274-summary-clin-safety-addendum.pdf

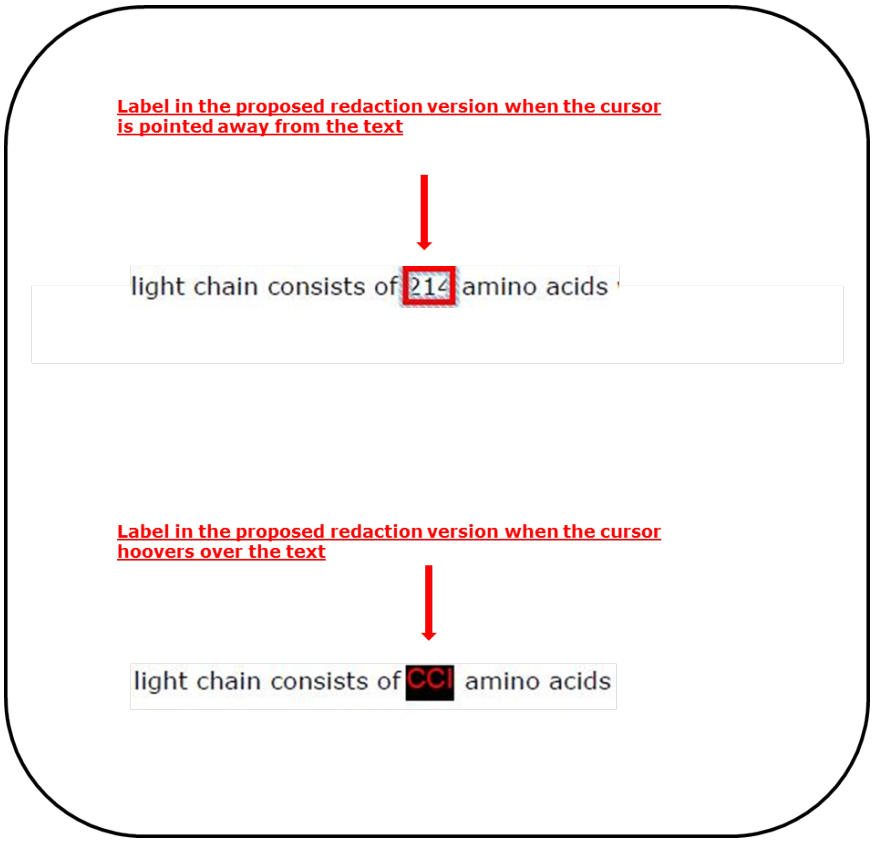
Anonymisation report

In the Redaction Proposal document package and in the Final Redacted document package the anonymisation report must be uploaded by applicants/MAHs in PDF format with the filename format of 'clinicaltrials-anonymisation_report-TradeName.pdf', where Trade Name is the name of the medicinal product.

3.3.1.8. Technical requirements for the preparation of the Redaction Proposal version of the clinical reports

Applicants/MAHs must prepare the Redaction Proposal version of their clinical reports in line with the following requirements. These are the minimum requirements that the redaction tool used should fulfil. With regards to format of the PDF documents submitted within the eCTD, the current eCTD specification applies. PDF versions 1.4-1.7 are currently accepted.

- The file format in which documents must be submitted is PDF format.
- The text proposed for redaction should be clearly identified as such (i.e. marked) and the text itself should be legible (read-through). Each proposed redaction of CCI and PPD should be labelled in the read-through documents using "CCI" or "PPD". For clarity please see below an example of CCI labelling:



- It should be possible to easily (with minimal intervention) render each of the proposed redactions permanent or to remove the proposed redaction.
- It should be possible to select one or more marked proposed redactions for comment, redaction or deletion. Editing individual proposed redactions should be possible for all parties. In order to view the history of the changes made, each change has to be visible in a comment list or audit trail.

Differences between format requirements for the preparation of the redaction proposal and final redacted version of the clinical reports are intentional as the Redaction Proposal version will not be watermarked and published. Some format limitations apply to the published documents only.

Although the choice of the redaction tool is a decision to be taken by each applicant/MAH, EMA will make available to Micro, Small and Medium sized Enterprises (SMEs) a license for a redaction tool for a period of 12 months. SMEs are advised to write to EMA five months prior to the CHMP opinion to apply for the redaction tool licence. The template of the letter to send to EMA is at Annex 1.1. SMEs will need to hold their SME status at the time of issuing the license for the product in question to qualify for the redaction tool licence.

EMA will assess the proposed CCI redactions. It is important that in the Redaction Proposal version of the submitted clinical reports the applicant/MAH clearly indicates each proposed CCI redaction. Therefore, all pieces of information proposed for CCI redaction should have a label, clearly indicating that the proposed redaction is requested on CCI grounds. Justification for each proposed CCI redaction should be included in the justification table. Please refer to Chapter 4 “External guidance on the identification and redaction of commercially confidential information in clinical reports submitted to EMA for the purpose of publication in accordance with EMA policy 0070” for further details.

EMA will review the anonymisation report to the effect that the applicant/MAH has followed the guidance and applied the chosen approach for anonymisation consistently in all clinical reports. For

further information on anonymisation please see Chapter 3 “External guidance on the anonymisation of clinical reports for the purpose of publication in accordance with EMA Policy 0070”.

Please note that for sections where per patient per visit IPD are identified in the clinical reports and the Agency agrees that they are out of the scope, these sections can be removed from the documents.

Where pages have been removed from the documents as out of scope the EMA requires the applicant/MAH to clearly indicate **which pages** and **what information** has been removed. The removed pages should be replaced by the following text in black contained on a white page:

1, removed page numbers (from-to) and the corresponding section title

2, statement *to reflect the above (“Out of Scope of phase I of Policy 0070 – <type of information/heading removed>”).*

For example in case there is per patient per visit data removed as out of scope of policy 0070, it should read:

“Out of Scope of phase I of Policy 0070 - Per patient/per visit line listings”.

The Agency considers per patient per visit data as those listings including values of the measured parameters (e.g. lab values) listed for **all** patients recruited and covering **all** study visits.

Therefore, for example, tables listing values of the measured parameters (e.g. HbA1C) or outcomes (protocol deviation, death, SAE, overall survival) at a certain **single** time point will not be considered per patient per visit line listing.

Also, the Agency does not consider per patient per visit line listings those tables where parameter or outcome values for **selected** patients and **selected** visits are presented.

3.3.1.9. Cover letter including declaration

The applicant/MAH should use the template cover letter text provided in Annex 1.4 or 1.5 when preparing the submission. In addition, the applicant/MAH should populate the formatted table template as published on EMA’s website (http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2011/05/WC500106371.doc). The completed formatted table template, the link to which is provided, should be embedded in the completed cover letter (Annex 1.4 or 1.5), for the Redaction Proposal document package. Below is an example illustrating the approach when working with the formatted table template:

The fields highlighted with yellow are specific for the sequences containing the documents submitted for the purpose of publication.

7 – Please select Clinical data for publication – Redaction Proposal

7.1 - Please select “initial”

7.2 – Please leave blank

7.3 – Please leave blank

10 – eCTD sequence: please insert the eCTD sequence of the procedure. For ‘related sequence’ field Same sequence number as stated in the EU Module 1 v3.0.1 specification. e.g. for Sequence 0010, related sequence field should be populated with value 0010.

7*	Submission Type (Please select)	Clinical data for publication – Redaction Proposal			
7.1*	Submission Unit Type	Initial			
7.2*	Grouping (more then one scope)	☐ Yes			
7.3*	Submission Description	Please select:			
10*	eCTD sequence	00xx		Related sequence	00xx

The applicant/MAH must confirm, in the formatted table, that the declaration has been included in the cover letter within the Redaction Proposal document package. If this declaration is omitted from the cover letter, the package will be rejected and a complete new package with the corrected cover letter must be submitted. The illustration below shows the section of the formatted table that should be checked by the applicant/MAH for this purpose.

16	Confirmation that the clinical reports submitted for scientific evaluation are the same as that submitted for publication, in the *Redaction Proposal* and *Final Redacted Versions,* except for the redactions	Included ☐ Yes

3.3.1.10. Justification table

For each of the clinical reports in the Redaction Proposal version in which CCI redactions are proposed, the applicant/MAH must complete a separate justification table in Word format. Should no CCI be identified in the document, a separate justification table is not required to be submitted. In such cases EMA will understand that there are no proposed CCI redactions, and therefore will not check the document(s).

If no CCI redactions are proposed in any of the clinical reports, the applicant/MAH should so indicate in the cover letter by including the following sentence:

<[NAME OF THE COMPANY] points out that no commercial confidential information has been identified in the entire ''Redaction Proposal Document'' package and therefore, justification tables are not submitted.>

If CCI has been identified in some but not all clinical reports, the applicant/MAH is asked to include the following statement in the cover letter:

<[NAME OF THE COMPANY] points out that commercially confidential information has only been identified in some documents for which [please insert the number of justification tables] justification tables were included in the "Redaction Proposal Document'' package and, confirms that in the documents for which with no corresponding justification table was submitted no CCI has been identified.>

Consequently, the corresponding Final Redacted version of the clinical reports will be published as provided by the applicant/MAH.

A sample justification table is available at Annex 1.10 and all templates can be downloaded from the following link:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001743.jsp&mid=WC0b01ac0580ae88cc. The justification table for each document should be individually named so that its electronic name matches the name of the corresponding clinical report. Please see the detailed guidance in Section 3.3.1.6 and 3.3.1.7 of this chapter on the naming conventions that must be followed for individual documents. As a general principle EMA expects that each of the justification tables corresponds to one submitted file. For example, if during the regulatory procedure a clinical overview addendum is submitted in addition to the initial clinical overview, EMA expects the applicant/MAH to prepare two separate justification tables since both documents are subject to publication.

For CSRs in Module 5 the applicant/MAH should submit the justification tables taking into consideration the following principle:

If the CSR and the appendices are submitted for publication purposes as **one standalone file**, then **one justification table** is expected to be prepared. This justification table will have separate subheadings for each of the parts of the document (body, 16.1.1, 16.1.2, 16.1.9). Such template is available for download from the following link http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001743.jsp&mid=WC0b01ac0580ae88cc.

If the CSR and the appendices are submitted for publication purposes as **separate files**, then **four justification tables** are expected to be submitted: one for each of the files, e.g. body, 16.1.1, 16.1.2, 16.1.9. Such template is available for download from the following link http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001743.jsp&mid=WC0b01ac0580ae88cc.

The justification tables should be submitted only to EMA with the Redaction Proposal document package, as part of a single ZIP package and outside the eCTD sequence structure in the separate folder named “Working Documents”. The Working Documents are submitted together with the eCTD sequence as part of one ZIP package through the Gateway. EMA requires that within the “Working Documents’’ folder the justification tables are placed in a separate folder entitled “Justification Tables”. Applicants/MAHs must ensure that the sequence number folder (e.g. 0000) is a root folder in the ZIP package within the same gateway transmission. This sequence number is required to ensure that the submission passes the technical validation.

3.3.1.11. Submitting the Redaction Proposal document package through the Gateway

Table 1 is set out to demonstrate where each document of the Redaction Proposal document package should be uploaded. The applicant/MAH must create a separate eCTD sequence with the relevant submission type (please refer to new EU Module 1 specifications), which will contain redacted/anonymised clinical reports as a separate data set (using eCTD operator ‘new’). The related sequence field in the eCTD sequence and the formatted table (cover letter) should always be the same sequence number as stated in the EU Module 1 v3.0.1 specification. e.g. for Sequence 0010, related sequence field should be populated with value 0010.

The clinical reports submitted in the Redaction Proposal document package must not be linked to any previously submitted documentation for the purpose of the scientific evaluation of a medicinal product. An applicant/MAH submitting multiple applications for the same medicinal product under different invented names is also required to provide a new sequence for the Redaction Proposal Document package for all of the products, unless the clinical reports are identical (with the exception of

references to the product names). In the latter case, the applicant/MAH makes a declaration in the cover letter that the clinical reports in the Redaction Proposal document package are identical.

3.3.1.12. Automated replies following acknowledgement and notification

The applicant/MAH will receive two automated replies following the eCTD sequence submission of their Redaction Proposal document package. An automated Gateway MDN (Message Delivery Notification) message will be sent to the applicant/MAH acknowledging receipt of the transmission. The MDN is equal to the signature upon delivery by the courier and only confirms that the package has been received by EMA. It does not confirm that a submission (eCTD) is technically valid, but only submission receipt. Users sending eCTD sequences containing the Redaction Proposal document package will also receive an acknowledgement confirming the receipt and pass/fail of the technical compliance check as per the current eCTD validation criteria for all submissions (the second automated reply). For failed submissions the error description can be found in the 'failure' acknowledgement (xml) and the submission has to be sent again.

3.3.1.13. Technical validation

Technical validation refers to the automated tool validation carried out on an eCTD submission by checking the document type definition (DTD) and technical components of the submission. Upon receiving the eCTD sequence EMA performs technical validation on the submitted eCTD sequence. On successful completion of this validation step, the applicant/MAH is informed.

Where an error is found during technical validation, the submission will not be loaded into the review system and a replacement sequence (sequence as appropriate) should be sent by the applicant/MAH by EMA.

For all submissions it is expected that following the recommended file naming conventions (in Sections 3.3.1.6 and 3.3.1.7) eCTD technical validation report will contain certain 'Best practice' warnings (15.BP3, 15.BP5), however this will not lead to rejection or influence the acceptance of submission from a technical perspective.

3.3.2. Consultation process

3.3.2.1. Redaction consultation process

On receipt of the Redaction Proposal document package, EMA initiates a redaction consultation process. A flowchart of the process is at Annex 1.11. This consultation process will allow EMA to thoroughly assess the validity of the proposed CCI redactions, and will enable the applicant/MAH to communicate clearly why, in their view, the information proposed for redaction is considered CCI. Following the assessment EMA will communicate its final conclusion to the company.

The redaction consultation consists of three different stages that are:

1. Internal receipt and distribution.
2. Validation.
3. Assessment of CCI.

3.3.2.1.1. Internal receipt and distribution stage

Upon receipt of the Redaction Proposal version of the clinical reports, together with the completed justification tables, a dedicated team in EMA will be assigned to coordinate the redaction consultation process. For each submitted package a contact person will be nominated.

3.3.2.1.2. Validation stage

Following internal receipt and distribution, EMA will first assess the validity of the justification comments. This stage will ensure that clear and valid justifications are assessed in the next stage of the consultation process. If the justifications provided are incomplete, not specific enough, or too general, EMA will contact the company for additional clarification. Further clarification will be required in cases such as:

- The text proposed for redaction is highlighted in the clinical report but missing from the justification table.
- All the proposed redactions are reflected in the justification table, but some columns/rows are incomplete.
- The same unspecific copy/paste justification is used throughout the entire justification table.

It is important to note here that this validation only covers the more practical aspects of the completion of the justification tables and not the content of each justification. The assessment of the content of the justification comments is the subject of the assessment phase of the redaction consultation process.

3.3.2.1.3. Assessment of CCI stage

Following a successful validation, EMA will start the assessment of the justifications submitted by the applicant/MAH. During the assessment EMA will take into account the extent to which the company has followed/adhered to the principles regarding redaction of CCI as described in the CCI guidance (Chapter 4) and as outlined in Annex 3 of Policy 0070. This assessment extends mainly to the content of the reasoning/justification behind why particular information is considered CCI by the applicant/MAH. Initially EMA will review the justifications and if further clarifications/more elaborate justifications are needed, the company will be contacted. Whenever clarification is requested, EMA will clearly indicate the instances directly in the justification table and send it to the applicant/MAH via Eudralink. Adequately clarified/revised justifications are expected to be sent back to EMA via Eudralink within 5-7 calendar days, depending on the volume of comments. If the applicant/MAH fails to submit the requested clarifications, EMA will consider the initial justifications irrelevant or insufficient and consequently reject the proposed redaction. A maximum of one round of consultation is permitted, which includes separate correspondence/exchanges between the applicant/MAH and EMA.

At the end of the assessment phase, EMA will inform the applicant/MAH of its conclusion for the entire set of the submitted clinical reports. The outcome of the assessment (rejection, acceptance, or partial rejection of the proposed CCI redactions) will be clearly communicated and documented in the appropriate columns of the justification tables.

The applicant/MAH then carries out the redactions using its redaction tool to create the Final Redacted version of each clinical report.

3.3.2.2. Review of the anonymisation report

EMA will review the anonymisation report to check whether the applicant/MAH followed the anonymisation guidance and applied it consistently throughout the documents. EMA will transmit its comments, if any, to the applicant/MAH but does not formally adopt the anonymisation report. If required, the applicant/MAH will send a revised anonymisation report and the anonymised, Final Redacted version of the clinical reports which will subsequently be published by EMA.

3.3.3. Submission of the Final Redacted document package

3.3.3.1. Process to submit the Final redacted document package

A workflow for the submission of the Final redacted document package can be found in Annex 1.8 of this guidance document. This process requires the applicant/MAH to submit to EMA a redaction proposal version of the clinical reports for publication.

3.3.3.2. Timeline

Within 7 calendar days following the issuance of the EMA redaction conclusion, applicants/MAHs must provide their written agreement to the redaction conclusion. The Final Redacted document package must then be provided ≤ 20 days following the receipt of this agreement. A workflow for the submission of the Final Redacted document package can be found at Annex 1.8 of this guidance document. If the applicant/MAH disagrees with the redaction conclusion, EMA will adopt a decision against which the applicant/MAH can file an application for annulment and related application for interim relief to the General Court of the European Union, in accordance with Article 263 of the Treaty of the European Union and the Rules of Procedure of the General Court. The related deadlines and time limits are set therein. Please see section 3.3.4 below for function details on this case.

3.3.3.3. Content of the Final Redacted document package

The applicant/MAH is required to prepare a separate sequence in eCTD format to submit the Final Redacted Document package. The eCTD submission of the final redacted document package falls under the same eCTD life-cycle of the initial MAA, line extension application or extension of indication application, as applicable. An exhaustive list of the documents to be submitted within the final redacted document package is provided in Table 2 below, including the final redacted versions of all the listed clinical reports.

The applicant/MAH is required to submit the package of documents listed in Table 2 as part of a single Final Redacted document package, all of which must be included in the same eCTD sequence. In respect of publication of multiple applications for the same medicinal product under different invented names where the clinical reports are identical (with the exception of references to the product names), EMA will provide a notice on its corporate website to cross reference the different invented names to the published final redacted version of the original medicinal product.

Table 2: Content of the Final Redacted document package, corresponding eCTD locations and the publication status

Final Redacted document package	eCTD Module / Section within eCTD	Document published
Cover letter, see the template at Annex 1.6, together with a list of documents submitted annexed to this letter	1.0	Not published
A list of documents submitted, annexed to the cover letter. A template for this list is at Annex 1.3	1.0	Not published
clinical overview supplement/amendment/appendix	2.5	Published
clinical summary supplement/amendment/appendix	2.7.1 - 2.7.4	Published
Clinical study report - body	5.3	Published
Clinical study report – Appendices 16.1.1 (protocol and protocol amendments) 16.1.2 (sample case report form) 16.1.9 (documentation of statistical methods).	5.3	Published
Anonymisation report, the report template is at Annex 1.2	1.9	Published

If any of the parts of the Final Redacted document package, set out Table 2 above, including the cover letter is not submitted, the whole package will be rejected. In that case, a corrected complete package must be submitted. Individual parts cannot be submitted separately to correct submission deficiencies.

Anonymisation report

The submitted anonymisation report has to describe the methodology of the anonymisation applied in each of the clinical reports in the Final Redacted version. The report should also describe how the risk of re-identification has been measured and managed, or if the three criteria for anonymisation have been fulfilled. A template anonymization report can be found at Annex 1.2 of this guidance, setting out the content and structure requirements.

The anonymisation report must be uploaded by applicant/MAH in PDF format with the filename format of 'clinicaltrials-anonymisation_report-TRADENAME.pdf' where Trade Name is the name of the medicinal product.

3.3.3.4. Technical requirements for the preparation of the final redacted version of clinical reports

The applicant/MAH must prepare a Final Redacted version of their clinical reports, as part of the Final Redacted document package, using a redaction tool. In order to support the watermarking and

publication process, the Final Redacted Version of the documents must fulfil technical requirements compared to the Redaction Proposal version. The Final Redacted version of the clinical reports must adhere to the requirements outlined below:

- With regards to PDF formats submitted within the eCTD, the current eCTD specification applies. PDF versions 1.4-1.7 are currently accepted.
- The size of the PDF files should not exceed 200 Mbyte each as a best practice rule.
- The PDF files must not be password protected, as EMA will add a watermark to every page.
- **The un-redacted text only** must be text-searchable. Redacted text and the blackened redaction box (that covers the redacted text) should neither be searchable nor subject to further editing.
- In order to distinguish between CCI and the PPD redactions, the following labelling and colour coding is expected in the ***Final Redaction Document Package*** (i.e. the documents to be published):

  for CCI: black background with red overlay text;

  for PPD: blue (pantone 291 C - corresponding to RGB colours 115, 203 and 235) background with black overlay text;

- Redactions must be clearly visible (typically using a black rectangle).
- Any (agreed) CCI or PPD redaction labels should be visible and irremovable together with the final redacted text.
- If the original clinical report contained text or figures in colour, the Final Redacted Version of documents in colour should also be in colour.

3.3.3.5. Cover letter

The applicant/MAH should submit the completed template cover letter provided in Annex 1.6, as a part of the Final Redacted document package. In addition, the applicant/MAH should populate the formatted table template (Please see the link: http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2011/05/WC500106371.doc) as published on EMA's website. This completed formatted table, should be attached to the completed cover letter from Annex 1.6, for the Final Redacted document package. Below is an example illustrating the approach when working with the formatted table template for complete and partial submissions.

The fields highlighted with yellow are specific for the sequences containing the documents submitted for the purpose of publication.

7 – Please select Clinical data for publication – Final version

7.1 - Please select "initial"

7.2 – Please leave blank

7.3 – Please leave blank.

10* - eCTD sequence: please insert the eCTD sequence of the procedure. For 'related sequence' field Same sequence number as stated in the EU Module 1 v3.0.1 specification. e.g. for Sequence 0010, related sequence field should be populated with value 0010.

7*	Submission Type (Please select)	Clinical data for publication – Final Version
7.1*	Submission Unit Type	Initial
7.2*	Grouping (more then one scope)	☐ Yes
7.3*	Submission Description	Please select:

10*	eCTD sequence	00xx	Related sequence	00xx

In the cover letter submitted to EMA for the Final Redacted Document package , an applicant/MAH should note that it provided a declaration in the cover letter with the Redaction Proposal Document package stating that the clinical reports submitted for publication are the same as those submitted for scientific review, with the exception of the agreed redactions and anonymisations.

3.3.3.6. Naming conventions for the clinical reports included in the Final Redacted Document package

The naming conventions of the clinical reports included in the Final Redacted document package must be the same as those used for the Redaction Proposal document package, see Sections 3.3.1.6 and 3.3.1.7.

3.3.3.7. Submitting the Final Redacted document package through the Gateway

The applicant/MAH is required to submit the Final Redacted Document package as a new sequence to EMA for publication. An applicant/MAH submitting multiple applications for the same medicinal product under different invented names is also required to provide a new sequence for the Final Redacted document package for all of the products.

This separate sequence must have the relevant submission type (please see new EU Module 1 specifications) and be separate (using eCTD operator 'new') to that created for the Redaction Proposal document package.

3.3.3.8. Automated replies following acknowledgement and notification

Applicants/MAHs will receive two automated replies following the eCTD sequence submission of their Final Redacted document package. An automated Gateway MDN (Message Delivery Notification) message will be sent to the applicant/MAH acknowledging receipt of the transmission. The MDN is equal to the signature upon delivery by the courier and only confirms that the package has been received by EMA. It does not confirm that a submission (eCTD) is technically valid, but only submission receipt. Users submitting eCTD sequences containing the Final Redacted document package will also receive an acknowledgement confirming the receipt and pass/fail of the technical compliance check as per the current eCTD validation criteria for all submissions (the second automated reply). For failed

submissions the error description can be found in the 'failure' acknowledgement (xml) and the submission has to be sent again.

3.3.3.9. Technical validation

Technical validation refers to the automated tool validation carried out on an eCTD submission by checking the document type definition (DTD) and technical components of the submission. If the technical validation is successful, the applicant/MAH is informed through an acknowledgement of receipt. Where an error is found during technical validation, the submission will not be loaded into the review system and a replacement sequence 0000 (or sequence as appropriate) should be requested from the applicant/MAH by EMA.

For all submissions it is expected that following the recommended file naming conventions (in Section 3.3.1.6 & 3.3.1.7) eCTD technical validation report will contain certain 'Best practice' warnings (15.BP3, 15.BP5), however this will not lead to rejection or influence the acceptance of submission from a technical perspective.

3.3.4. Publication process

Redacted/anonymised clinical reports will be published by EMA on its corporate website. Prior to publication EMA will watermark each page[9] of the clinical reports in the Final Redacted version submitted by the applicant/MAH. The timelines for the publication of redacted/anonymised clinical reports will vary depending on the regulatory procedure. For initial MAAs, line extension applications and extension of indication applications EMA will publish the redacted/anonymised clinical reports within 60 days of the issuance of the Commission decision. For withdrawn applications the publication of the redacted/anonymised clinical reports will take place within 150 days after the receipt of the withdrawal letter. The applicant/MAH will receive an automated confirmation from EMA once publication has taken place.

A situation may arise where an agreement between the applicant/MAH and EMA was not reached on the proposed redaction, and the applicant/MAH decided to apply for interim relief against an EMA decision to publish the documents without accepting the redactions which are still controversial. In this case, the applicant/MAH will submit a partial Final Redacted version package, whereby the clinical reports would be redacted according to the applicant/MAH's views. The applicant/MAH will confirm, in the text of the cover letter, which controversial redactions (page, line) have been made in the documents. Please note that applications for annulment of EMA decisions and the related application for interim relief are filed with the General Court of the European Union in accordance with Article 263 of the Treaty of the European Union and the Rules of Procedure of the General Court. The related deadlines and time limits are set therein.

In the event that interim relief is sought against the EMA decision, EMA will publish a partial Final Redacted Version of the clinical reports. When a final decision on the interim relief proceedings is issued, the applicant/MAH shall submit a Final Redacted Version in accordance with the indications from the Court of Justice of the European Union. EMA will withdraw from its corporate website the partial Final Redacted version previously published. EMA will then publish the Final Redacted version.

In an exceptional situation where an applicant/MAH does not submit a complete Redaction Proposal Document package or a complete Final Redacted document package, EMA will publish a non-compliance notice.

[9] The watermark text is:'www.ema.europa.eu
This document cannot be used to support any marketing authorisation application and any extensions or variations thereof'

4. Marketing authorisation transfers

In cases where a marketing authorisation holder (the Transferor) submits an application to transfer a marketing authorisation to another company (the Transferee), as of the date of notification of the amendment of the Commission decision in relation to the transfer of the marketing authorisation based on Regulation (EC) No 2141/96 (the transfer date), the Transferee becomes the new marketing authorisation holder and takes over all responsibilities pertaining to a marketing authorisation holder under EU pharmaceutical legislation.

Responsibilities under Policy 0070 are also transferred to the Transferee, and include responsibility for clinical reports that were redacted by the Transferor and published by the EMA before the transfer date. Should an MA transfer application be sent to the EMA during the Policy 0070 process, the process will continue on the basis of the agreements, submissions and declarations made by the Transferor. From the transfer date onwards, the EMA will liaise with the Transferee for all remaining aspects of the Policy 0070 process for the product subject to the transfer.

In some cases the transfer date may occur after the EMA conclusion is issued (to the Transferor) but before the final redacted document package is submitted. To remain compliant with Policy 0070 in these cases the Transferee must submit the final redacted document package in line with the EMA conclusion issued to the Transferor. The EMA strongly encourages that the Transferor and Transferee exchange information on the agreements, submissions or declarations made between the Transferor and EMA under the scope of the Policy 0070 publication process.

Chapter 3

External guidance on the anonymisation of clinical reports for the purpose of publication in accordance with EMA Policy 0070

1. Introduction

Policy 0070 states that adequate personal data protection needs to be ensured and that full compliance with applicable EU legislation needs to be achieved. Furthermore, the processing of personal data and its publication on the website by EMA is subject to the provisions of Regulation (EC) No 45/2001 and in particular is limited only to information that is adequate, relevant and not excessive for the purpose of transparency. It is important to recall that no personal data of trial participants[10] should be published.

The objective of this chapter is to provide information to the pharmaceutical industry on the anonymisation of clinical reports in the context of the implementation of phase 1 of EMA Policy 0070, i.e. publication of clinical reports on EMA's website. The information contained in this guidance document should be considered as EMA recommendations to MAHs/applicants on how best achieve anonymisation.

The current guidance provides information on some of the anonymisation techniques that are available to MAHs/applicants. The field of anonymisation, i.e. the techniques used by controllers of personal data to anonymise data, is a field of active research and rapidly evolving. This guidance is not intended to provide an exhaustive list of the techniques available or to mandate a specific methodology but rather to highlight to MAHs/applicants the anonymisation process to be followed to ensure that clinical reports submitted to EMA for publication are rendered anonymous prior to publication. The guideline will be updated in light of new developments.

This guidance document is without prejudice to the obligations of pharmaceutical companies as controllers of personal data under applicable national legislation on the protection of personal data.

2. Legal framework and available standards

This guidance has been developed based on the current available legislation in the EU as well as guidance and standards on the anonymisation of personal data (see below).

- Regulation (EC) No 45/2001 of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data, of 18 December 2000.
- Directive 95/46/EC of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data, of 24 October 1995.
- Opinion 05/2014 on anonymisation techniques of the Article 29 Data Protection Working Party.
- Opinion 06/2013 on open data and public sector information reuse of the Article 29 Data Protection Working Party.
- Information Commissioner's Office (ICO) Code of Practice. Anonymisation: managing data protection risk.
- Sharing clinical trial data: Maximizing benefits, minimizing risk. Institute of Medicine (IOM). 2015. Washington, DC: The National Academies Press.

[10] The term 'trial participant' in the current guidance relates to individuals on whom information has been collected related to the scientific objectives of the trial, e.g. patients and healthy volunteers.

- Pharmaceutical Users Software Exchange (PhUSE) de-identification standards for CDISC SDTM 3.2.
- Transcelerate BioPharma Inc.
  - Clinical Study Reports Approach to Protection of Personal Data.
  - Data De-identification and Anonymisation of Individual Patient Data in Clinical Studies– A Model Approach.
- White Paper on Anonymisation of Clinical Trial Data Sets. International Pharmaceutical Privacy Consortium (IPPC).
- Scientific literature (see References).

3. General considerations

A number of general aspects need to be considered when providing recommendations on how best achieve anonymisation. These relate to:

3.1. Context of data disclosure

The risk of re-identification can vary depending on the context of disclosure. In the case of public data release (publication to the world at large) the risk of re-identification needs to be very low since there are no controls that can be put in place. However, for non-public data-sharing a higher risk could be acceptable because robust governance arrangements (security, privacy, and contractual controls) can be established. It means that the same data can be adequately anonymised in different ways depending on the context of the data release. Therefore, it is necessary to take into consideration the context of the data release when deciding on the anonymisation process.

3.2. Concept of anonymisation

According to Article 2(a) of Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of **personal data** by the Community institutions and bodies and on the free movement of such data: *'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/her physical, physiological, mental, economic, cultural or social identity.*

Directive 95/46/EC refers to anonymisation in recital 26 and excludes anonymised data from the scope of data protection legislation. Hence, data protection law does not apply to data rendered anonymous in such a way that the data subject is no longer identifiable[11].

Anonymisation is the process of turning data into a form that does not identify individuals and where identification is not likely to take place. It allows for a much wider use of the information.

According to the Article 29 Data Protection Working Party (Art. 29 WP) data that have been altered using techniques to mitigate risks of re-identification of the individuals concerned, but have not attained the threshold required by Article 2(a) and recital 26 of Directive 95/46/EC are not considered anonymised data. Therefore, such approach is only appropriate for limited disclosure for re-use by screened parties but not for public disclosure and re-use under open licence. Recital 26 signifies that to

[11] ICO (UK Data Protection Agency) Code of Practice entitled "Anonymisation: managing data protection risk" https://ico.org.uk/media/for-organisations/documents/1061/anonymisation-code.pdf

anonymise any data, the data must be stripped of sufficient elements such that the data subject can no longer be identified. More precisely, the data must be processed in such a way that it can no longer be used to identify a natural person[12] by using "all the means likely reasonably to be used" by either the controller or a third party. It must be emphasised that recital 26 of Directive 95/46/EC sets a high threshold, as described in the Opinion of Art. 29 WP. Unless data can be anonymised to meet this threshold, data protection law continues to apply.[13]

The irreversibility of the anonymisation methodologies or techniques is also an important element as it can be used in order to differentiate from "pseudonymisation". Pseudonymisation consists of replacing one attribute (typically a unique attribute) in a record by another. When pseudonymisation is used alone, the natural person is still likely to be identified indirectly. Pseudonymisation reduces the linkability of a dataset with the original identity of a data subject but when used alone will not result in an anonymous dataset, therefore data protection rules still apply. It is, therefore, important to clarify that pseudonymisation is not an anonymisation method but a useful security measure. Consequently, additional measures should be considered in order to render the dataset anonymised, including removing and generalising attributes or deleting the original data or at least bringing them to a highly aggregated level.

3.2.1. Anonymisation criteria

According to the Opinion 05/2014 on anonymisation techniques of the Art. 29 WP, two options are available to establish if the data is anonymised. Either through the demonstration of effective anonymisation based on three criteria:

- Possibility to single out an individual.
- Possibility to link records relating to an individual**.**
- Whether information can be inferred concerning an individual.

or, whenever a proposal does not meet one of these criteria, through an evaluation of the identification risks.

An anonymisation solution preventing all three criteria is considered to be robust against identification performed by the most likely and reasonable means the data controller or any third party may employ, and will render the data anonymous.

3.2.2. Anonymisation techniques

There are several techniques that can be used in order to achieve anonymisation. Opinion 05/2014 on anonymisation techniques of the Art. 29 WP analyses the effectiveness and limits of existing anonymisation techniques against the EU legal background of data protection, and provides recommendations to handle these techniques by taking account of the residual risk of identification inherent in each of them[14].

[12] The definition of personal data as described in Article 2(a) of Regulation (EC) No 45/2001 relates to a 'natural person'. The Article 29 Working Party opinion 4/2007 on the concept of personal data further clarifies that information relating to dead individuals is therefore in principle not to be considered as personal data to the rules of the Directive, as dead are no longer natural persons in civil law. However, the opinion also points out that data on the deceased may still be personal information since it may refer to living persons, e.g. it may indicate family diseases relevant to living children or siblings. In addition, it might be difficult for the data controller to establish whether the person to whom the data relates is still alive.
[13] Opinion 05/2014 on anonymisation techniques and Opinion 06/2013 on open data and public sector information reuse of the Article 29 Data Protection Working Party .
[14] Opinion 05/2014 on anonymisation techniques of the Article 29 Data Protection Working Party.

3.3. Advances in technology

It is also important to take note of advances in technology (e.g. data mining) together with greater availability of data and the possibility of database linkage with the increased risk of re-identification. MAHs/applicants need to take into account (realistic) future developments in terms of availability of data and technologies that would allow identification. The Art. 29 WP Opinion 05/2014 on anonymisation techniques emphasises that even where a data controller believes it has successfully anonymised personal data, the data controller must continuously follow the developments in re-identification techniques, and if necessary reassess the risk of re-identification.

4. Applying these general considerations in the context of clinical reports for publication in accordance with EMA policy

4.1. Context of data disclosure

This guidance document comes within the context of public data release since EMA has defined a process for publication of clinical reports where clinical reports are available on-screen for any user, with a simple registration process, and are available for downloading to identified users. Both situations are governed by dedicated Terms of Use that clarify that users of the data shall not, in any case, attempt to re-identify trial participants or other individuals.

4.2. Concept of anonymisation

Clinical reports submitted to EMA for applications for marketing authorisation or post authorisation procedures mostly consist of pseudonymised aggregated data. They may contain individual patient information within, e.g. case narratives or tables of patient characteristics. Therefore, the reports cannot be considered anonymised and cannot be published as such. Applicants/MAHs, as data controllers of the personal information that might be contained in these documents, are required to submit clinical reports that have been rendered anonymous for the purpose of publication under Policy 0070. The anonymised clinical reports should be a copy of the clinical reports submitted in the context of the scientific evaluation procedure, stripped of sufficient elements such that the participants can no longer be identified. The data in the clinical reports must be processed in such a way that it can no longer be used to identify a natural person by using “all the means likely reasonably to be used” by either the controller or a third party, as described in Directive 95/46/EC.

4.3. Data utility

Different anonymisation techniques will lead to different levels of data utility in the anonymised reports. Applicants/MAHs should take into consideration the impact of the data transformations/redactions on the scientific usefulness of the data.

4.4. Advances in technology

As mentioned above, the Art. 29 WP Opinion 05/2014 on anonymisation techniques emphasises that the data controller must continuously follow the developments in re-identification techniques, and if necessary reassess the risk of re-identification. Applicants/MAHs, in accordance with national legislation on data protection, will need to take this aspect into consideration and to monitor continuously the development of technologies in this area in order to assess novel risks of re-identification for any future clinical reports published.

4.5. Rare diseases and small populations

EMA understands the complexity involved in the anonymisation of clinical reports in the case of rare diseases and small populations, due to the very low number of trial participants and of overall population. Therefore, careful consideration should be taken in the anonymisation of the clinical reports in these instances.

5. EMA recommendations to MAHs/applicants on how best to achieve anonymisation

5.1. Data utility

Taking into account the need to find the best balance between data utility and achieving an acceptably low risk of re-identification, what EMA ultimately would like to achieve is to retain a maximum of scientifically useful information on medicinal products for the benefit of the public while achieving adequate anonymisation. Therefore, the aim of this guidance is to assist pharmaceutical companies in achieving this objective by recommending methodologies and a process that could be applied to clinical reports.

The guidance is not intended to mandate any specific methodology but to highlight to applicants/MAHs the available techniques and those that EMA considers most relevant in the context of the anonymisation, to ensure that clinical reports submitted to EMA for publication are rendered anonymous prior to publication. However, the choice of anonymisation techniques to use, while retaining a maximum of scientifically useful information, is left up to the company.

It is up to the pharmaceutical company, taking due account of the ultimate purpose and use of the clinical reports, i.e. publication in EMA's website, and on the basis of the guidance made available to decide which option to use, i.e. demonstrate that after anonymisation all three criteria are fulfilled (singling out, linkability and inference) or to perform a risk assessment.

EMA understands that in an initial phase redaction techniques are likely to be used by applicants/MAHs, taking into account that for a certain period, pharmaceutical companies will have to anonymise their data retrospectively (reactive data anonymisation), i.e. after the clinical report has already been submitted for scientific review. Importantly, redaction alone is more likely to decrease the clinical utility of the data compared to other techniques.

Therefore, EMA is of the view that applicants/MAHs, after experience has been accumulated in the de-identification of clinical reports, should transition to other anonymisation techniques that are more favoured in order to optimise the clinical usefulness of the data published (proactive data anonymisation). Pharmaceutical companies are encouraged to use these anonymisation techniques as soon as possible, whilst ensuring data anonymisation is achieved.

5.2. Rare diseases, small populations and low frequency events

Clinical trials conducted on rare diseases and on small populations may have a high risk of re-identification. Therefore, specific attention should be given to these scenarios. Measuring the risk of re-identification and a thorough risk assessment should be performed in these cases and anonymisation of the data should be adapted to the identified risk. In addition, a quantitative approach to the measurement of the risk of re-identification should be favoured (see Section 5.4). This approach is also applicable to genetic information and low frequency events (e.g. rare events, extreme values, unusual treatments, pregnancy outcomes).

5.3. Specific recommendations to MAHs/applicants for the anonymisation of personal data of trial participants

The anonymisation techniques described in this guidance are applicable only to trial participants[15]. Personal data in relation to investigators, sponsors and applicants/MAHs should be redacted as described in section 6.

5.3.1. Anonymisation criteria

For clinical data, retaining the linkability of multiple records belonging to the same trial participant within the same document is important to understand the safety and efficacy profile of a medicinal product. In addition, inference is important in view of the scientific utility of the data, and emphasis should be made on the potential impact of inferred data on the trial participants. Therefore, since in order to achieve a maximum usefulness of the data published, it is unlikely that for clinical reports all three criteria can be fulfilled by any anonymisation solution, it is EMA's view that a thorough evaluation of the risk of re-identification needs to be performed (see section 5.4).

5.3.2. Anonymisation techniques

It should be noted that each anonymisation technique has its own strengths and weaknesses. The robustness of each anonymisation technique is based upon the aforementioned anonymisation criteria and will help identify the most suitable technique (or combination of different techniques) to establish an adequate anonymisation process for a given clinical report. Ultimately, the aim is to preserve data utility as much as possible whilst ensuring adequate anonymisation.

Not all anonymisation techniques described in Opinion 05/2014 of the Art. 29 WP may be suitable to anonymise personal data in clinical reports. The specificities of the clinical data should therefore be taken into consideration when selecting the most appropriate technique(s).

The simplest method of anonymisation is the removal of values for variables which allow direct or indirect identification of an individual from the data. This technique is sometimes called masking. Technically, it can be achieved by using a redaction tool which ensures that the redacted information is irreversibly blocked out. Masking of pre-specified variables can be done manually and/or may include the use of software that can help identifying pre-specified variables that need redaction. Masking of pre-specified variables is recommended. Removing entire sections of the report where masking is possible is not considered appropriate, and is, therefore, not recommended by EMA.

Apart from masking, the main anonymisation techniques are randomisation and generalisation.

Randomisation is a family of techniques that alters the veracity of the data in order to remove the strong link between the data and the individual. Recommended techniques include noise addition and permutation. Noise addition can consist of, for example, shifting dates randomly by a few days (forward or backwards), based on a uniform, or other type of, distribution. Permutation may have limitations as regards clinical utility as relationships between attributes can be destroyed. The differential privacy technique may not be applicable in the context of Policy 0070 since the same documents will be made available to all users.

The other main family of anonymisation techniques consists of generalising, or diluting the attributes of the data by modifying the respective scale or order of magnitude. An example would be a trial participant who suffers from asthma, born on 19 August 1978. This date of birth would be generalised

to 1978. Recommended generalisation techniques include aggregation and k-anonymity. L-diversity and t-closeness may not be recommended as they limit inferences significantly. Aggregation involves the replacement of a value by a range, e.g. a trial participant's age is replaced with an age range (age of 56 replaced with range of 50 to 60). K-anonymity goes a step further by preventing a trial participant from being singled out since it is grouped with, at least, *k* other trial participants in that range.

EMA follows closely the developments in techniques that can be used to anonymise clinical data through mathematical models together with metrics of re-identification. These techniques can be directly applied to the anonymisation of electronic datasets and allow the anonymisation of the copy of the CSR for publication using the underlying clinical data which has already been anonymised. This may facilitate the anonymisation process and maximise the information included in the copy of the CSR anonymised for publication. It does not mean that anonymisation will take place before the scientific review of the data for the purposes of the clinical trial and marketing authorisation assessment. None of these processes should undermine the submission of the full, pseudonymised clinical reports and underlying data. Most importantly, it needs to be demonstrated that these techniques can ensure that the risk of re-identification is acceptably low and in line with requirements for public disclosure and that the data transformation resulting from the applied anonymisation techniques will not lead to a different interpretation of the study results.

5.3.2.1. Anonymisation of Direct Identifiers

Direct identifiers are elements that permit direct recognition or communication with the corresponding individuals. Direct identifiers generally do not have data utility, with the exception of the patient ID.

Clinical reports submitted to EMA mostly consist of pseudonymised aggregated data and therefore it is unlikely that direct identifiers are present in the reports. Nonetheless, any direct identifiers still present should be redacted, e.g. name, email, phone number, signature and full address. Patient ID numbers (including randomization/treatment number or safety case ID) can be either redacted or recoded. Recoding or pseudonomysing direct identifiers have been demonstrated to reduce the risk of re-identification[16]. However, having a pseudonym means that information for the same individual can be linked which is likely to increase the risk of re-identification. On the other hand, the value of the data is significantly reduced where the ability to follow a patient across visits and events is broken. The risk of linking the information for the same individual can be measured and net effect on risk can be determined. A decision on whether to redact or recode patient ID should be made on a case-by-case basis based on the impact on the risk. Moreover, it should also be considered that for any extension to the initial marketing authorisation application study, the same patients will be recoded differently from the initial marketing authorisation study. EMA recognises that in such situations data utility may be suboptimal since this creates a problem of linkability between the initial study and the extension study.

5.3.2.2. Anonymisation of Quasi Identifiers

Quasi identifiers are variables representing an individual's background information that can indirectly identify individuals. Unlike direct identifiers, information from quasi identifiers increases the scientific usefulness of the information published. Geographical location is an important variable since clinical practice can vary from country to country and this can impact on the outcome. Relative dates relating to individual patients are also important due to the potential impact on the outcome of the trial. Patient

[16] David Carrell, Bradley Malin, John Aberdeen, et al. "Hiding in plain sight: use of realistic surrogates to reduce exposure of protected health information in clinical text". J Am Med Inform Assoc 2013;20:342–348.

level demographic information such as sex, age, race, ethnicity, height and weight can be confounders and therefore of critical scientific utility.

In order to render the clinical reports anonymised it is not always necessary to redact all quasi identifiers. The need to redact quasi identifiers will depend on the following aspects:

- Number of quasi identifiers per trial participant
- Frequency of trial participants with same category/value on a set of the quasi identifiers (group size)
- Size of population

It is up to the applicant/MAH to decide which quasi identifiers need to be redacted and which could remain in the reports. The rationale for the decision should be included in the risk assessment section of the anonymisation report to be provided to EMA (see section 5.5).

The factors having the most impact on data de-identification are geographical location and dates leading to a higher risk of re-identification. A feature of anonymisation is that it is only partially determined by the data to be protected. The ability to identify a trial participant depends on both these data and the state of knowledge of the observer concerning the trial participants in the data. For these reasons, location and dates are important. They may not be the most specific identifiers of a trial participant but they are often the most easily obtainable from other sources. Therefore, clinical data containing information on geographical location and dates should be carefully anonymised (see sections 5.3.2.2.1 and 5.3.2.2.2).

5.3.2.2.1. Dates

There are various dates that can be included in clinical reports, e.g. date of birth of trial participants, date of trial participant visits, dates of adverse events and study dates. Date of birth of trial participant should be redacted (month and day) with the exception of the year. Other dates such as event or assessment dates can be offset as described below.

The most commonly used method to de-identify dates is to offset the dates. In this method, dates are replaced with a new date generated using a random offset for each participant and this offset is applied to all dates in the study for that participant. By using one offset for all dates for a participant, the relative distance between a participant's dates is maintained from their original dates to their de-identified dates.

It is not advisable to use only one random offset for an entire study, i.e. the same offset for all the trial participants since if the offset is identified for one participant, it is therefore identified for all participants in that study. For this reason, an algorithm that assigns different random offsets to each participant in a study is considered a stronger approach when using this method.

A date offset algorithm should be applied to offset dates. It can use the starting day of the trial as an anchor date and it must be ensured that the offset dates are within the range of dates for e.g. findings, events collected during the trial. The difference between the anchor date and the first event/finding will be set as the offset which will vary from trial participant to trial participant.

In case of partial dates the offset dates must also be partial. Partial dates after offsetting are less reliable in terms of date sequencing with a consequent negative impact on data utility. Special consideration should be made to adaptive design trials, e.g. if a new arm is added during the course of the trial.

An alternative to the method described above is to derive the relative study day method. If a variable containing Relative Study Day is not already present in the data provider's datasets, it is calculated for each observation as the number of days relative to a reference date, e.g. date of study entry or date of randomization. The same algorithm is applied to all dates across the study in order to maintain the relationship between events for each participant (e.g. their visit schedule). All date variables are then removed from or set to blank in the de-identified datasets.

It is preferable, from a data utility perspective, to keep both types of dates, i.e. absolute (actual date) and relative.[17]

5.3.2.2.2. Geographical location

The geographical location is an important element that can lead to re-identification of patients. It might be necessary to aggregate or generalise from country to region or continent unless this information is critical to the analysis. The need to aggregate or generalise should be considered when performing the risk assessment. The link between individual patient data and the identity of the site should be removed since a frequency analysis can most likely reveal the most recruiting site in a country, which will in turn include many of the trial participants. However, it may not be the case where the recruitment is uniform across all sites.

5.4. Anonymisation process

In order to facilitate the applicant/MAH approach to anonymisation EMA recommends to follow the anonymisation process described below[18]:

1. *Determination of direct identifiers and quasi-identifiers*

   A person's identity can be disclosed from either direct identifiers or indirect/quasi identifiers. Direct identifiers are elements that permit direct recognition or communication with the corresponding individuals, such as personal names, email addresses, telephone numbers, and national insurance numbers. Direct identifiers are not often useful for data analysis.

   Quasi identifiers are variables representing an individual's background information that can indirectly identify individuals, such as their date of birth, death, or clinic visit, residence postal code, sex and ethnicity. Quasi identifiers also include demographics and socioeconomic information. Both types of variables must be addressed during anonymisation. In recent cases of re-identification, attackers used quasi identifiers to successfully determine the identity of individuals[19]. It is therefore important to protect the quasi identifiers as well as the direct identifiers.

   Classification of variables into categories of personal data

   There are three conditions for a variable to be considered an identifier (direct or quasi), i.e. replicability (the variable values must be sufficiently stable over time so that the values will occur consistently in relation to the data subject), distinguishability (the variable must have sufficient variability to distinguish among individuals in the data) and knowability (an adversary must know the identifiers about the data subject in order to re-identify them). If a variable is not knowable by an adversary, it cannot be used to launch a re-identification attack on the data (see below for further details on adversaries and attacks).

[17] PhUSE De-Identification Working Group, "De-Identification Standards for CDISC SDTM 3.2," 2015.
[18] Institute of Medicine (IOM). 2015. Sharing clinical trial data: Maximizing benefits, minimizing risk. Washington, DC: The National Academies Press. Appendix B.
[19] BMJ 2015; 350: h1139 Anonymising and sharing individual patient data.

Once a variable has been determined to be an identifier it is necessary to establish whether it should be classified as a direct identifier or a quasi-identifier. This is important because the techniques used to protect direct identifiers are different from those used for quasi identifiers.

PhUSE has defined a set of rules developed to facilitate the assessment of direct and quasi identifiers in the data. These rules help pharmaceutical companies to establish the various categories of personal data that can be found in the clinical reports.

2. *Identification of possible adversaries and plausible attacks on the data*

For public data release, adversaries are most likely interested in showing that an attack is possible (demonstration attack). The following potential scenarios of re-identification can be conceived in the context of the publication of clinical trial data:

- An organisation sees a financial interest in finding out who are the trial participants in the clinical trial. Usually it would require some strategy to identify accurately a fair number of trial participants
- One trial participant is of particular public interest and is focussed on by the press or other body
- A group or individual, possibly for academic reasons, in order to embarrass the data controller, or to undermine the public support for release of data, wishes to identify just one trial participant without regard to which trial participant it might be
- A random event in which an individual happens to examine a report including data on a trial participant with whom they are well acquainted to the extent that they can accurately guess that certain information relates to that trial participant.

Each of the scenarios described above reflect possible adversaries and plausible attacks, having different risk implications. Applicants/MAHs should identify possible adversaries and plausible attacks on the data and evaluate the impact on the risk of re-identification.

3. *Data utility considerations*

This is an important requirement that MAHs/applicants need to consider carefully when selecting the anonymisation methodology. If anonymisation of the data results in clinical reports that are no longer useful for their intended secondary purposes, data utility is compromised. Furthermore, anonymisation of clinical reports results in the data being perturbed in some way. Ensuring that the analysis results produced after anonymisation are similar to the results that would be obtained from the original clinical reports is critical. Therefore, the amount of distortion should be minimised. Ultimately, a balance must be reached in order to obtain an acceptably low probability of re-identification and a high utility data.[20]

4. *Determining the risk of re-identification threshold and evaluation of the actual risk of re-identification*

Measuring the risk of re-identification involves selecting an appropriate risk metric, a suitable threshold and the actual measurement of the risk in the clinical data information to be disclosed. The choice of a metric depends on the context of data release. For public release it is advisable to use the maximum risk.

Setting an acceptable threshold encompasses evaluation of the existing mitigation controls (none in the context of public disclosure), the extent to which a particular disclosure would be an invasion of privacy to the trial participant and the motives and the capacity of the attacker to re-identify the

[20]K. El Emam, Kald Abdallah. “De-identifying Clinical Trials Data”. Applied Clinical Trials, Mar 20, 2015.

data. Once a threshold has been determined, the actual probability of re-identification can be measured. If the probability is higher than the threshold, anonymisation of the data needs to be performed. Otherwise, the data can be considered to have a very small risk of re-identification and to be fully anonymised.

Based on the recommendations made in the IOM report and the available precedents for public release of health data, EMA believes that it is advisable to set the threshold to a conservative level of 0.09. However, it is up to the applicant/MAH to decide on the most appropriate threshold for public disclosure of the clinical reports at stake, and if a different threshold is selected a justification shall be provided.

The most appropriate way to measure the risk of re-identification for an entire dataset, in the context of public disclosure, is through the maximum risk, which corresponds to the maximum probability of re-identification across all records.

Further information about the methodology to calculate the risk of re-identification is available in the literature, such as for instance that the probability of re-identification of a record in a data set is 1 divided by the frequency of trial participants with same category/value of a set of the quasi identifiers (group size).

It is acknowledged that initially anonymisation will involve reactive data anonymisation where the assessment of risk of re-identification may be mostly qualitative. The approach to be taken in the case of a qualitative risk assessment is very similar to that of a quantitative approach, the difference being that rather than having a probability and measure of the risk as numerical values there is instead a qualitative scale (e.g. high, medium, low risk).

Applicants/MAH are encouraged to use quantitative methods to measure the risk of re-identification as soon as they are in a position to do so.

Applicants/MAH may not follow, in an initial phase, an analytical approach, and therefore it will not be necessary to calculate the risk of re-identification. In such cases step 4 of the anonymisation process could be omitted.

5. *Anonymisation methodology*

Applicants/MAH should identify the most suitable technique (or combination of different techniques) to establish an adequate anonymisation process and should describe how they reduce the risk of re-identification. In addition, justification should be provided for the data that is altered and the choice of anonymisation techniques used.

6. *Documenting the anonymisation methodology and process*

   Documenting the methodology used is an important step as it provides information not only on the techniques that have been used to anonymise the data but also the rationale for using them. It should also be described how the clinical reports have been rendered anonymous either by measuring and managing the risk of re-identification, or by demonstrating that the three criteria for anonymisation have been fulfilled.

5.5. Reporting on the anonymisation process

The anonymisation methodology used by applicants/MAHs must include a way of demonstrating adequate anonymisation of the reports and have a repeatable process to follow. The methods and outcome of the anonymisation process must be documented.

Applicants/MAHs should therefore describe the anonymisation process followed in an anonymisation report. In addition, the report should describe how the risk of re-identification has been measured and managed, or if the three criteria for anonymisation have been fulfilled.

As recommended by the Art. 29 WP, data controllers should disclose the anonymisation technique(s) being implemented in the case of public release of the anonymised data. Therefore, the anonymisation report will be published by EMA, together with the clinical reports.

6. Redaction of personal data of investigators, sponsor staff and applicant/MAH staff

Personal data of individuals other than patients, i.e. investigators, sponsor staff and applicant/MAH staff will not be published with the following exceptions:

- The sponsor and coordinating investigator signatories of the clinical study report and the identities of the investigator(s) who conducted the trial and their sites.

However, their contact details and signature should be redacted. Personal data relating to all other clinical study personnel should also be redacted. Data pertaining to the above exceptions in other parts of the CSR will be redacted as they may give away geographical information (e.g. site number, site address, investigator names) that could be linked to patients and hence may enable their identification.

Chapter 4

External guidance on the identification and redaction of commercially confidential information in clinical reports submitted to EMA for the purpose of publication in accordance with EMA Policy 0070

1. Introduction

The guidance provided in this chapter has been developed as a working tool and a reference document for pharmaceutical companies preparing their justifications of CCI in documents that fall under the scope of Policy 0070.

Generally, the majority of the clinical information contained in clinical reports which fall under the scope of Policy 0070 should not be considered CCI.

However, EMA acknowledges that in limited circumstances clinical reports may contain CCI, and could, therefore, be subject to redaction prior to publication. Whenever redaction of CCI is proposed by the applicant/MAH, consultation with the party in question will be undertaken. The justification for the redaction of CCI will be scrutinised by EMA in order to assess whether the definition of CCI applies. Consequently, Annex 3 "Redaction principles" to Policy 0070 identifies certain types of information that **potentially** may be considered CCI.

Please note that, as described in this document, the list of elements and pieces of information that would not be considered CCI by EMA is not exhaustive and provides only examples. Each individual redaction proposed by the applicant/MAH will be assessed by EMA on its own merit.

It is anticipated that the preparation and publication of the documents covered by Policy 0070 will raise some practical questions, such as on how to apply the aforementioned redaction principles, and on the presentation and justification of the proposed redactions.

This guidance will enable the public to obtain a better understanding of the level and nature of redactions that are typically accepted within the published documents as well as a comprehensive overview on how the redaction of CCI is handled within the context of Policy 0070. The guidance will focus on:

- How to identify and flag/highlight in the clinical reports pieces of text (proposed redactions) that may potentially constitute CCI.
- The minimum level of detail expected in the justification that will allow EMA to perform an adequate and informed evaluation of the proposed redactions.
- Establishing a better defined approach of the identification of CCI when applying the redaction principles laid out in policy 0070.

The ultimate goals of this guidance are:

- To ensure a common understanding of what may potentially be or cannot be considered CCI within clinical reports.
- To increase consistency in the proposed and accepted redactions across the range of clinical reports relating to various human medicinal products and regulatory procedures falling under Policy 0070.
- To ensure a good quality of the justifications for the proposed redactions, hereby reducing the administrative burden for all parties involved in the preparation and publication of the documents falling under Policy 0070.

2. Existing guidance documents

While Policy 0070 applies without prejudice to EMA's activities conducted in accordance with Regulation (EC) No 1049/2001, EMA strives to ensure consistency between the approach for the redaction of documents published in accordance with Policy 0070 and similar documents released in response to requests for access to documents in accordance with Regulation (EC) No 1049/2001. This document should therefore be read in conjunction with the following policies and guidance documents which have been released in the past and provide relevant background:

- European Medicines Agency policy on publication of clinical data for medicinal products for human use (Policy 0070).
- European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use)[21] (Policy 0043) – adopted on 30 November 2010. Policy 0043 should be read in conjunction with the Output of the European Medicines Agency policy on access to documents related to medicinal products for human and veterinary use[22] – adopted on 30 November 2010.

Over the past few years, EMA has worked in partnership with National Competent Authorities in establishing guidance which has contributed to a harmonised approach for access to documents across EU Member States. As a result several documents were prepared, all finding their legal basis in the above-mentioned Regulation (EC) No 1049/2001. Released over time, they established sets of principles and recommendations covering both redactions of CCI and personal data regardless of the nature of the information (quality, non-clinical and clinical):

- HMA/EMEA recommendations on transparency – recommendations on the handling of requests for access to Periodic Safety Update Reports (PSURs)[23] – adopted on 23 November 2009.
- HMA/EMA guidance document on the identification of commercially confidential information and personal data within the structure of the marketing authorisation (MA) application – release of information after the granting of a marketing authorisation[24] – adopted on 09 March 2012.
- Principles to be applied for the implementation of the HMA/EMA Guidance on the identification of CCI and PPD in MA Applications[25] – adopted on 09 March 2012.

3. Points to be taken into account for the preparation of the redaction proposal version of a clinical report

For the purpose of this guidance, CCI shall mean any information contained in the clinical reports submitted to EMA by the applicant/MAH which is not in the public domain or publicly available, and where disclosure may undermine the legitimate economic interest of the applicant/MAH.

Prior to proposing any redactions, the applicant/MAH should be aware of the level of information already available in the public domain concerning their product's development (e.g. study design and results), scientific knowledge and advancements within the relevant (for the particular product)

[21] European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use)
[22] Output of the European Medicines Agency policy on access to documents related to medicinal products for human and veterinary use
[23] HMA/EMEA recommendations on transparency – recommendations on the handling of requests for access to Periodic Safety Update Reports (PSURs)
[24] HMA/EMA guidance document on the identification of commercially confidential information and personal data within the structure of the marketing authorisation (MA) application – release of information after the granting of a marketing authorisation
[25] Principles to be applied for the implementation of the HMA/EMA Guidance on the identification of CCI and PPD in MA Applications

therapeutic area(s). Such preparatory work by the applicant/MAH is essential and will enable an expedited consultation process, thereby reducing the number of instances in which EMA will have to reject proposed redactions because the information is already in the public domain.

3.1. How to read and apply the redaction principles laid out in Policy 0070

EMA has identified in Policy 0070 (Annex 3 – Redaction principles) certain types of information that may **potentially** be considered CCI. These principles should not be perceived by the applicant/MAH as an open and unconditional invitation to propose, on a regular basis, the redaction of information falling within the types of information described in the aforementioned Annex 3. In other words, the applicant/MAH should not consider by default such types of information as being CCI. The redaction proposals based on grounds of CCI must be backed up by the applicant/MAH with a specific and clear justification which is subject to EMA's review.

If the applicant/MAH identifies a piece of information such as a word or figure, part of a sentence, part of a paragraph that they wish to include amongst the proposed redactions, the applicant/MAH has to ensure that the information in question:

- DOES NOT fall under any of the data elements and types of information described in Section 3.2 of this guidance document.
- DOES fall under the types of information that may **potentially** be considered CCI according to Policy 0070 Annex 3.

Moreover, the applicant/MAH should ensure that a specific, pertinent, relevant, not overstated, and appropriate justification is included in the justification table corresponding to the piece of information that is proposed for redaction.

The applicant/MAH is advised to limit the extent of the proposed redactions to the word(s), figure, and pieces of text that, in their view, can be considered CCI. The applicant/MAH is discouraged from proposing the redaction of entire pages, sub-sections of a report or full tables, especially when, in their view, only some sentences within the text or some specific figures within the tables fall under the types of information described in Annex 3 and are considered CCI.

3.2. Information that EMA does not consider CCI

In order to achieve a high level of consistency in the redaction of CCI in the final redacted documents (and to decrease the administrative burden) EMA has grouped the types of information that EMA does not consider CCI. Should the information proposed to be redacted be in the public domain or bear no innovative features, EMA will not accept its redaction. In addition, if the applicant/MAH fails to provide sufficient and relevant justification, the proposed redactions will be rejected. Finally, section 3.2.3 describes some additional examples of types of information which will not be accepted to be redacted as CCI. These examples reflect the most common redactions proposed by applicants/MAHs which are usually rejected by EMA in the framework of Access to Documents in accordance with Regulation (EC) No 1049/2001. The information covered by the above examples pertains to quality, non-clinical and clinical data which, in EMA's view, is necessary for the understanding of the rest of the clinical report, and therefore its disclosure is in the public interest. EMA foresees the use of 5 rejection codes that would mirror the above considerations. At the end of the redaction consultation process, these codes will be included in the justification table, reflecting EMA's final position.

3.2.1. Information that is already in the public domain or publicly available – Rejection code 01

EMA recommends that the applicant/MAH compiles a list of the most common websites/locations where information regarding their own medicinal product is usually made available. Applicants/MAHs should create and maintain their own specific list detailing the level of public information concerning their product(s). Based on EMA experience gained through handling Access to Documents Requests, EMA suggests that the following sources of information be included in the list (as a minimum):

- Applicants'/MAHs' own web-site(s).
- EMA web-site (product EPAR, scientific guidelines).
- Clinical trials registries (such as EU Clinical Trials Register, ClinicalTrials.gov).
- Web-sites of other regulatory authorities within the EU and outside the EU (such as FDA, PMDA, TGA, Health Canada) especially when the product (or another product containing the same active substance) is approved in those specific jurisdictions.
- Scientific literature and articles (such as Textbooks, PubMed, Medline).

The information sources suggested above by EMA are not intended to constitute an exhaustive list, but rather to serve as a starting point for the applicant/MAH in the creation of their own (more exhaustive, customized) list. Should the company compile such list, the above mentioned examples should be considered as the minimum number of information sources to be scrutinized by the applicant/MAH in order to reach a basic level of awareness on publicly available information related to the product concerned. As this list is not required as per Policy 0070, EMA only recommends it to be prepared for the company's internal use.

Should EMA deem that any of the proposed redactions concern information which is already in the public domain the following rejection code will be used in the justification table:

CCI - Rejection 01 – Information already available in the public domain or publicly available

This code reads as follows:

"*The information proposed to be redacted is already available in the public domain.*

In addition, EMA considers that it has not been demonstrated how the disclosure of this publicly available information would undermine your economic interest or competitive position.

EMA therefore adopts the position that the information proposed to be redacted does not constitute commercially confidential information and it is not accepted by EMA as a valid redaction proposal. "

In addition, EMA will add the reference to the publicly available information source.

3.2.2. Information that does not bear any innovative features – Rejection code 02

Information which has already been revealed to some extent, can be inferred from information available in the public domain, or has the content of textbooks or scientific guidelines as its scientific backbone, should not be included in the proposed redactions.

The fact that certain pieces of information are not in the public domain as such, (word for word) does not necessarily mean that they should be considered by default to be CCI. The applicant/MAH is expected to duly justify why the piece of information in question should be considered CCI by EMA.

In many instances, particular pieces of text contained in clinical reports describe how the applicant/MAH complied with regulatory and scientific guidelines and how they applied the scientific knowledge available at that time to their own development programme. In essence, these pieces of text do not reveal any novel elements (of any regulatory or scientific nature) as the approaches described in the text are built upon logic and common sense in line with the content of publicly available documents such as:

- Scientific literature and articles (Textbooks, PubMed, Medline).
- Scientific and regulatory guidelines and guidance documents.
- Treatment/clinical practice/disease management guidelines.

Should EMA deem that any of the proposed redactions fall within the scope of the information described above, the following rejection code will be used in the justification table:

CCI - Rejection 02 – Common knowledge

This code reads as follows:

"*The information proposed to be redacted reflects approaches or decisions that were/are based on widely known practices/regulatory and scientific information.*

In addition, EMA considers that its innovative features have not been pointed out and it has not been demonstrated how its disclosure would undermine your economic interest or competitive position.

EMA therefore adopts the position that the information proposed to be redacted does not constitute commercially confidential information and it is not accepted by EMA as a valid redaction proposal. "

In addition, EMA will add the reference to the publicly available source of information that would suggest that the information in question can be considered common knowledge.

3.2.3. Additional information the disclosure of which would be in the public interest – Rejection code 03

It is EMA's view that some data elements should not be redacted from clinical reports due to the fact that they are relevant for the understanding of the documents published in accordance with Policy 0070. Some of these elements are presented below in Sections 3.2.3.1 to 3.2.3.4. The list is not intended to be exhaustive but details the most frequent data elements, considered CCI by applicants/MAHs during the Access to Documents consultation process, and which are rejected by EMA.

The vast majority of information contained in clinical reports is of a clinical nature. However, these clinical reports may also contain information of a quality, non-clinical and general or administrative nature, some of which may potentially be considered CCI. Therefore, EMA has grouped the elements which are not considered CCI into four categories as follows:

3.2.3.1. General or administrative information

- Unit measurements, in such cases only the actual value may be considered CCI. [e.g.]2.5mL/kg → [redacted] mL/kg.
- Study identification number(s) (e.g. EudraCT, ClinicalTrials.gov Identifier (NCT…), sponsor's internal study number).
- Names and addresses of investigator sites and the names of the principal investigators at each study site (unless it is mentioned in the context of individual patient data/case narratives and is

deemed to constitute personal data – see "External guidance on the anonymisation of clinical reports for the purpose of publication in accordance with EMA policy 0070").

- Names of the countries where the clinical study is/was conducted (unless it is mentioned in the context of individual patient data/case narratives and is deemed to constitute personal data – see "External guidance on the anonymisation of clinical reports for the purpose of publication in accordance with EMA policy 0070").
- Number (how many) of study sites/research facilities were involved in the research.
- Name of the applicant's/MAH's own research facility(ies) where clinical studies were conducted (e.g. phase I studies).
- Name of the trial sponsor or the legal entity (CRO) that acted as the clinical trial (CT) applicant on behalf of the sponsor.
- Names of all CROs and vendors involved in trial-related duties and functions (e.g. central laboratories, IVRS provider, image reading centres, conduct of assays).
- Standard Operating Procedure (SOP) numbers and titles.

3.2.3.2. Quality-related information

- Structural formula of active metabolite(s) and metabolic pathway(s).
- Lot/batch numbers of the investigational products understood as either test product, active comparator or placebo (excluding manufacturing site(s) IDs).
- Excipient names which usually constitute publicly available information detailed in SmPCs.
- Function of excipients as such information is widely available in the public domain.
- Excipient batch numbers.
- Even if a method of measurement is selected from several available methods, the name of the method or the combination of methods and their general description is not CCI.
- High level safety-related information such as a virus inactivation process, ultrafiltration (removal of pyrogen), and the name of a purification process or the operation of a specific material.
- The name of a cell line or strain with genetic recombination, when it is in commercial use or already published (e.g. CHO cell, *E. Coli* K-12).
- Standard storage and shipping conditions of blood or tissue samples such as storage temperature or duration, which are described in related scientific guidelines (e.g. bioanalytical methods).
- Temperature, humidity parameters, and storage duration as applied in stability tests.

3.2.3.3. Non-Clinical-related information

- Information concerning a generally-used/well-known immunohistochemistry method (e.g. ELISA/LC-MS).
- Drug concentration measurements including results.
- The quantification range (lower and upper quantification limits) of pharmacokinetic and pharmacology tests/methods.

- The name and high level description of test methods should not be redacted where a test is conducted based on a standard dissolution test/method referred to in scientific guidelines.
- Information on radio-labelled molecules including information on the tagging site (unless it constitutes a novelty feature of the method developed by a company, as its disclosure would undermine the applicant's/MAH's legitimate economic interest).
- Information on scientific advice received from any Regulatory Agency during the development of the product related to the approved indication. It includes but it is not limited to information on the design and conduct of completed studies for which the results were submitted within the marketing authorisation application, the timing of requesting/obtaining the scientific advice and the names of the Agencies that issued those scientific advice.

3.2.3.4. Clinical-related information

- Primary and secondary endpoints (including biomarkers and exploratory endpoints).
- The justification of planned sample size.
- Protocol and protocol amendments (including and not limited to: treatment arms, inclusion/exclusion criteria, allowed concomitant medication(s), reasons for withdrawal and reasons for protocol amendments).
- Statistical methods (including imputation methods used for missing data).
- Information on clinical data management (such as query resolution).
- Information on the purpose and outcome of audits and inspections carried out during the conduct of clinical trials, including the audit plans.
- Literature reviews, meta-analyses and pooled data analyses supporting certain study design elements or certain safety and efficacy claims.
- Bioanalytical methods: name of the methods and the general description together with the validation parameters.
- The fact that the formulation was changed during the development programme including the description of any relationships between the different formulations used in the various development programme phases, as well as the timing of such changes and the results of equivalence tests.
- Safety-related information such as adverse reactions (presented in various forms such as aggregated data or within case narratives) regardless of whether they are reflected in the approved product information or whether they were observed in clinical trials or reported after authorisation (unless certain elements/adverse reactions are deemed to constitute personal data – see the "External guidance on the anonymisation of clinical reports for the purpose of publication in accordance with EMA policy 0070").
- Safety-related information/case narratives, even where the described case is related to "off label use" or reported from clinical studies conducted in other indications not yet applied for or approved.
- Plasma drug concentration values and pharmacokinetic and pharmacodynamic parameters.
- General information on PK/PD models, parameters and the results of the PK/PD model simulations.

- Information on scientific advice received from any Regulatory Agency during the development of the product related to the approved indication. It includes but it is not limited to information on the design and conduct of completed studies for which the results were submitted within the marketing authorisation application, timing of requesting/obtaining the scientific advice and the names of the Agencies that issued those scientific advices.

Should EMA deem that any of the proposed redactions fall under the scope of the information described above the following rejection code would be used in the justification table:

CCI - Rejection 03 – Disclosure due to public interest

This code reads as follows:

"*The information proposed to be redacted is relevant for the understanding of:*

- *the conduct of the clinical studies;*
- *the reliability and validity of the data/research findings (data submitted for evaluation;)*
- *the safety and efficacy profile of the product;*
- *the reasoning underpinning the company claims and the opinion adopted by the CHMP and the subsequent decision of the European Commission, if applicable.*

EMA therefore adopts the position that there is a genuine public interest in the disclosure of this information and consequently it should be released."

3.2.4. Information lacking sufficient or relevant justification – Rejection code 04 and 05

The justification wording has to refer clearly to the information proposed to be redacted. It has to highlight the innovative features of the information in the context of the common knowledge within the specific scientific area. It has to indicate explicitly to which on-going development programme the proposed redaction relates. It also has to explain how the disclosure of the information concerned would undermine the applicant's/MAH's legitimate economic interest. If EMA considers that the level of justification is not sufficiently detailed, additional clarifications will be requested on an ad-hoc basis, whether formally or informally, e.g. via a telephone call. Failure to provide the requested clarifications within a reasonable time frame would render the available justification insufficient, as detailed below.

Whenever EMA considers that the level of justification provided by the applicant/MAH is not sufficiently specific or too vague, the following rejection code will be used in the justification table:

CCI – Rejection 04 – Insufficient justification

This code reads as follows:

"*EMA has concluded that the justification is not satisfactory as it does not clearly demonstrate how the disclosure of this particular information would undermine the economic interest or competitive position of your company*."

Whenever the justification provided by the applicant/MAH does not correspond to/match the (type of) information proposed for redaction, i.e. is not relevant to the information proposed to be redacted, the following rejection code will be used in the justification table:

CCI - Rejection 05 – Irrelevant justification

This code reads as follows:

"*EMA considers that the justification provided is not related to the information proposed to be redacted. Therefore, in the absence of an adequate justification EMA is unable to recognise how the disclosure of this particular information would undermine your economic interest or competitive position.*

EMA therefore adopts the position that the information proposed to be redacted does not constitute commercially confidential information and that is not accepted by EMA as a valid redaction proposal. "

The following section of the guidance presents some examples of justifications that are considered by EMA to be insufficient.

EXAMPLE 1

"Unpublished data - These study results have not been published in any peered-reviewed [*sic*] publication."

EXAMPLE 2

"Company confidential information - Disclosure of these elements will harm [the company]'s commercial interests because it may enable third party access to business-critical information."

EXAMPLE 3

"This information can be interpreted out of context. Such interpretation could lead to a misleading image of the safety profile of the product."

EXAMPLE 4

"Detailed Statistical/Analytical Method : See Article 4.2 1st indent of Regulation (EC) The institutions shall refuse access to a document where disclosure would undermine the protection of commercial interests of a natural or legal person, including intellectual property."

EXAMPLE 5

"The deleted text is detailed information for the active substance which is considered as confidential information."

EXAMPLE 6

"Regulatory interaction – approaches and interactions which could give competitors substantial advantages."

EXAMPLE 7

"The analytical methods are [the company]'s intellectual property, which [the company] developed by expending a significant amount of time, and human, financial and commercial resources."

EXAMPLE 8

"Information is commercially confidential, competitively sensitive information and includes intellectual property including trade secret information."

EXAMPLE 9

"Information on the safety profile of the product not reflected in the SmPC."

EXAMPLE 10

"Information is commercially confidential, competitively sensitive information and includes intellectual property including trade secret information."

EXAMPLE 11

"The text proposed to be redacted reveals purpose and timing of discussions with health authorities, this is considered sensitive information that is not consolidated in this way within the public domain, and indeed we cannot find this information in public forum.

4. How to prepare justifications in support of proposed redactions

4.1. The content of the justification table and its use

The purpose of the justification table is to enable targeted comments on the proposed CCI redactions for use by both EMA and the applicant/MAH. The justification table is essentially a living document and will be used as a communication tool throughout the redaction consultation process. It will contain the justifications from the applicant/MAH on the proposed CCI to redact and EMA's assessment. At the end of the redaction consultation process this table will be sent to the applicant/MAH as part of EMA's conclusion. The justification tables should contain justifications for all pieces of text considered CCI and proposed to be redacted. All the proposed redactions listed in the justification table should correspond to the text highlighted for redaction in the redaction proposal version of the corresponding clinical report. Should the company highlight a piece of text proposed for redaction in the document, but fails to explain its redaction in the justification table, the proposal will be considered invalid and will be sent back for clarification. For further details on the redaction consultation process see the "External guidance on the procedural aspects related to the submission of clinical reports for the purpose of publication in accordance with EMA policy 0070".

4.2. Completing the justification table

For the Redaction Proposal Version of each of the clinical reports in which CCI redactions are proposed, applicants/MAHs must complete a separate justification table in Word format. Should there be no CCI identified in the document, a separate justification table is not required to be submitted. In such cases EMA will understand that there are no proposed CCI redactions and therefore will not check the document. Consequently, the corresponding Final Redacted Version will be published as provided by the applicants/MAH. Accordingly, the applicant/MAH is expected to indicate clearly which justification table corresponds to which clinical report. In addition, the justification tables should be individually named so that the electronic name of each table matches the name of the corresponding clinical report. A detailed naming convention to be used for both the clinical reports and the justification tables is provided is section 3.3.1.7 of the "External guidance on the procedural aspects related to the submission of clinical reports for the purpose of publication in accordance with EMA policy 0070" .

Please see a sample justification table below (Figure 1) and all templates can be downloaded from the following link http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp&mid=WC0b01ac0580999a9d. As a general principle, EMA expects that each of the justification tables corresponds to one submitted file. For example, if during the regulatory procedure a clinical overview addendum is submitted in addition to the initial clinical overview, EMA expects the

applicant/MAH to prepare two separate justification tables since both documents are subject to publication.

For CSRs in Module 5 the applicant/MAH should submit the justification tables taking into consideration the following principle:

If the CSR and the appendices are submitted for publication purposes as **one standalone file**, then **one justification table** is expected to be prepared. This justification table will have separate subheadings for each of the parts of the document (body, 16.1.1, 16.1.2, 16.1.9). Such template is available for download from the following link http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp&mid=WC0b01ac0580999a9d. If the CSR and the appendices are submitted for publication purposes as **separate files**, then **four justification tables** are expected to be submitted: one for each of the files, e.g. body, 16.1.1, 16.1.2, 16.1.9. Such template is available for download from the following link http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp&mid=WC0b01ac0580999a9d.

Fig.1 Sample Justification table for CCI redactions

Justification Table: Invented Product name (INN) – procedure number

Applicant/MAH Consultation on <**Module 5.3.1** (Reports of Biopharmaceutical Studies), **Module 5.3.2** (Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials), **Module 5.3.3** (Reports of human pharmacokinetic (PK) studies), **Module 5.3.4** (Reports of human pharmacodynamic (PD) studies), **Module 5.3.5** (Reports of efficacy and safety studies), **Module 2.5** (Clinical Overview), **Module 2.7.1** (Summary of Biopharmaceutical Studies and Associated Analytical Methods), **Module 2.7.2** (Summary of Clinical Pharmacology Studies), **Module 2.7.3** (Summary of Clinical Efficacy), **Module 2.7.4** (Summary of Clinical Safety) - <Name of the document as per naming convention><Name of the Applicant consulted>

By submitting this justification table, you confirm that you have checked that the information you wish to redact is **NOT** in the public domain. Please ensure that the proposed redactions are in line with Annex 3 of POLICY/0070 and the Guidance on identification and redaction of commercially confidential information in clinical reports submitted to the European Medicines Agency for the purpose of publication.

Page number(s)	Title of Section(s)	Text proposed for redaction by the Applicant/MAH	Applicant/MAH to reference the section(s) of the Annex 3 of Policy 0070 on which the redaction is based. (If not obvious please explain how the proposed redacted text falls under this/these particular section(s) of Policy 0070 and is/are relevant for.)	Applicant/MAH to provide justification of CCI (Please explain how the release of this information will damage your company's commercial interest or competitive position)	Agency Assessment of the proposed redaction: Rejected/ Partially Accepted/ Accepted	Agency's rationale/redaction code

As already explained before, the applicant/MAH is also not expected to propose information to be redacted that is already available in the public domain. Therefore, when completing the justification table, the applicant/MAH should confirm that all the necessary searches have been performed (see section 3.2.1 of this chapter) and the information proposed to be redacted as CCI is not in the public domain or publicly available, by ticking/checking the box at the top of the justification table. More details can be found in section 3.2 of this chapter on what EMA considers is NOT CCI.

The individual columns should contain the following information:

Column 1 (Page number(s)):

In column 1 the applicant/MAH should indicate the page number of the relevant clinical report, where the information that the applicant/MAH proposes to redact is located. If exactly the same information can be found throughout the document and the company has the same justification for the redaction of

this information, EMA would advise the company to indicate all the page numbers in one row, instead of filling in a new line for each page.

Column 2 (Title of Section(s)):

In column 2, EMA expects the applicant/MAH to indicate the appropriate section of the document where the proposed redaction can be found. If exactly the same information can be found throughout the document and the company has the same justification for the redaction of this information, EMA would advise the company to indicate all relevant sections in one row, instead of filling in a new line for each page and section.

Column 3: (Text proposed for redaction by the applicant/MAH):

This column should include the exact proposed CCI redactions verbatim (to the extent that is feasible) from the clinical report. In case entire tables and figures are among the proposed redactions EMA would advise the applicants/MAHs to clearly identify in this column the table/figure number and its title. If for practical reasons the proposed redactions cannot be reflected verbatim in this column this should be pointed out in an understandable manner. Regardless of whether the proposed redactions are reflected verbatim in this column, the applicants/MAHs are reminded that in all cases these proposed redactions should be highlighted and easily identifiable in the corresponding clinical report.

Column 4: (Reference to the section(s) of the Annex 3 of Policy 0070 based on which the redaction is requested):

In this column the applicant/MAH should indicate the corresponding categories of clinical data as highlighted in Annex 3 of Policy 0070. As mentioned in Policy 0070 "*The same rules regarding CCI and the redaction principles will apply to the same information presented in other formats or other sections in the documents submitted by the applicant/MAH to the Agency",* certain categories of clinical data can be found in different parts of the clinical CTD modules, even within the same documents. Therefore to avoid misinterpretation/miscommunication when justifying a proposed redaction, EMA requires the use of the following categories of clinical data to be referenced in this column:

- Product Development Rationale.
- Biopharmaceutics - Detailed information on bioassays and analytical methods.
- Clinical Pharmacology - PK/PD determination.
- Benefits and Risks Conclusions.
- Information on protocol development.
- Study Objectives (including Exploratory Endpoints and Efficacy and Safety Variables).
- Determination of Sample Size – background considerations.

If the reference to the section of the Annex 3 is not obvious, EMA expects the applicant/MAH to provide an explanation of how the specific part of the information proposed for redaction falls within one of the categories in Annex 3.

Column 5 (Justification of CCI):

In column 5 the applicant/MAH should describe in detail the reasons why it considers the information proposed to be redacted to be commercially confidential.

For example, if the applicant/MAH has proposed information for redaction which falls within the scope of Annex 3 section 'Biopharmaceutics - Detailed information on bioassays and analytical methods' (it

will be in column 4 of the justification table) it is not sufficient to say that this section includes information about specifications on company assays and immunogenicity assays. Instead, details of which assay(s), and more importantly which part of the assay(s), the company considers CCI must be specified.

Another example is when the applicant/MAH proposes to redact information related to a future or an ongoing development programme for a new indication. In this case, the Product Development Rationale' section should be listed in column 4 as the relevant section from Annex 3. In column 5 the applicant/MAH has to give details of this ongoing development programme and explain how it is related to the text proposed for redaction. From this explanation it should be clear to EMA which part of the text proposed for redaction is directly relevant and what the link is/how that particular piece of information would give insight to/inform the reader about a possible new indication.

In this column, EMA expects to see clear explanations as to how the release of the specific information proposed for redaction will damage the company's legitimate commercial interest. It is important to note that simply declaring that the information is considered CCI by a company because upon release it will damage their legitimate commercial interest is not sufficiently specific for EMA to reach an informed conclusion. Therefore such unspecific, vague justifications will be rejected by EMA.

Finally, should any of the clinical reports contain data (results) pertaining to indications not applied for or not evaluated yet, it should be clearly explained in column 5. In this case the relevant section of Annex 3 that has to be indicated in column 4 is Product Development Rationale. The applicants/MAHs are expected to justify every element proposed to be redacted. A justification based on the fact that the applicant/MAH has not yet applied for that particular indication would be deemed by EMA as insufficient. The applicant/MAH has to bear in mind that information related to future development plans is very likely to be available on their own web-sites and information related to on-going clinical trials is very likely to be available on clinical trials registries (see section 3.2.1 for further details).

Columns 6 and 7 (EMA's review):

The last two columns will capture the conclusion of EMA's review and the rationale behind it. To the extent that the information proposed to be redacted falls within the scope of the information described in this guidance document (see section 3.2), EMA will include under the EMA rationale column the corresponding CCI codes (**CCI - Rejection 01 – Information already available in the public domain or publicly available, CCI - Rejection 02 – Common knowledge**, **CCI - Rejection 03 – Disclosure due to public interest, CCI - Rejection 04 – Insufficient justification and CCI - Rejection 05 – Irrelevant justification.**)

The justification tables containing the outcome of EMA's review will be sent to the applicant/MAH once EMA has reached its conclusion.

Chapter 5

Annexes

1. Annexes

1.1. Redaction tool application letter for SMEs

SME Request for Redaction Tool License

European Medicines Agency

30 Churchill Place

Canary Wharf

London

E14 5EU

Dear ,

RE: EMEA/X/X/XXXXXX/XXXX

[Product Invented Name; INN, Company Name, Company SME Registration number, EMA-SME number]

Request for Redaction Tool License

[Company name] is writing to request a redaction tool license for the purpose of creating the Redaction Proposal Version and Final Redacted Version of the clinical reports for the [withdrawn] initial marketing authorisation application/line extension application/extension of indication application (delete as appropriate) for [product INN].

The Redaction Proposal version and Final Redacted Version of the clinical reports will be submitted in line with the European Medicines Agency's policy on the publication of clinical data for medicinal products for human use, Policy 0070. [Company name] confirms eligibility for the redaction tool license, on the grounds of its awarded Small and Medium Sized Enterprise (SME) status. SME qualification by EMA (<EMA SME number>) expires on XX XX XXXX. It is understood that SME status will be checked by EMA at time of issuing the licence, with disclaimers to access rights to be removed if the SME status has expired at that time or in cases of merger/out licensing.

In addition, [Company name] undertakes not to transfer, redistribute, sublicense or otherwise make available the redaction tool license, as provided to [Company name] by EMA, to any third party, including to other EMA designated SMEs. [Company name] also confirms that by accepting a redaction tool license [company name] also accepts the licence terms of use related to the redaction tool and all related liability for noncompliance or breach thereof. [Company name] acknowledges and agrees that EMA will not be liable or responsible in any way for any non-compliance with or breaches of these terms on behalf of [Company name].

Redaction Tool Application – SME

Please complete this form in capitals

Company name: ______________________________

EMA-SME Number: ______________ Expiry: ______________

Product Invented Name: ______________________________

INN: ______________________________

EMA number: EMEA/H/C/______________________________

Contact person for interaction purpose with EMA

Name: ______________________________

Position within the SME: ______________________________

Address: ______________________________

Post Code: | | | | | | | | | | |

Country: ______________________________

Telephone

Country Code: __________ Area Code: __________ Number: __________

Email Address: | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | | | | |

Email address specifically for software licence purposes. This email address will be used for all subscription purposes with the supporting company. This email address will be your company's identification reference with the supplier.

Identification

E-mail Address: | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | | | |

Name (in Capitals): ______________________________

Signed ______________________________ Date: ______________

1.2. Anonymisation report - Template

Product name:

Active substance:

Procedure number:

Applicant/MAH:

The aim of the anonymisation report is to provide an overview of the anonymisation process followed, the methodology used, the rationale for data transformations/redactions required for the adequate anonymisation of the data and the impact on data utility. The information presented in the anonymisation report should not in itself lead to an increased risk of re-identification. The report can be divided in subsections, one for each of the clinical study reports submitted for publication.

This document is without prejudice to the obligations of pharmaceutical companies as controllers of personal data under applicable EU and national legislation on the protection of personal data.

This template should be used in conjunction with the External guidance on the anonymisation of clinical reports for the purpose of publication in accordance with EMA Policy 0070.

1.2.1. Anonymisation methodology

Applicants/MAHs should provide information on the approach chosen to protect personal information:

- *Non-analytical*
- *Analytics* – these methods analyse the data itself to measure the risk and to how best de-identify the data. Some of the open source software tools available are listed below.
  - Tools available for unstructured text data

    http://idash-nlp.ucsd.edu/nlp-tools-new.php
  - Tools for structured microdata

    http://arx.deidentifier.org/

    http://arx.deidentifier.org/overview/related-software/

1.2.2. Identification of data variables (direct and quasi identifiers)

There are several sections with data results in clinical reports that may contain personal data of trial participants: these include disposition of trial participants, protocol deviations, demographics, other baseline characteristics, treatment compliance, pharmacodynamics, pharmacokinetics, efficacy and safety (adverse events, laboratory findings, and vital signs).

In general, clinical overviews and clinical summaries do not contain personal data related to trial participants. An exception is section 2.7.4.2.2 (Narratives) of the Summary of Clinical Safety as described in ICH M4E (R1) which states that "Narratives should not be included here, unless an abbreviated narrative of particular events is considered critical to the summary assessment of the drug." In addition, some of the tables included in the clinical overviews and clinical summaries may also contain personal data. Following the structure of the CSR as described in ICH Topic E3, sections 2 (synopsis) and sections 10 to 14 (study patients, efficacy, safety, conclusions, tables-figures-graphs) of the CSRs are likely to contain personal data of trial participants. However, it does not exclude the

possibility of personal data also being included in other sections or appendices of the clinical reports. Appendices of the clinical study report that are in scope of the Policy 0070 (protocol, protocol amendments, sample case report form, and documentation of statistical methods) generally do not contain personal data.

- **Describe direct and quasi identifiers in the clinical reports [26]**
  - Direct identifiers, e.g. patient ID
  - Indirect identifiers, e.g. age
- **De-identification**

  Direct identifiers
  - Provide information on the redaction of direct identifiers, e.g. patient name, address if present in the reports
  - Regarding patient ID, provide information on whether it has been redacted or recoded and the resulting impact on the risk of re-identification

  Quasi (indirect) identifiers
  - For quasi-identifiers, provide information on the anonymisation techniques used and the rationale for using them.

1.2.2.1. Assessment of anonymisation

As described in section 3 of the "External guidance on the anonymisation of clinical reports for the purpose of publication in accordance with EMA Policy 0070", according to the Opinion 05/2014 on anonymisation techniques of the Article 29 Data Protection Working Party, two options are available to establish if the data is anonymised.

One option relates to the anonymisation based on three criteria (see below Section 1.2.2.1.1); the second option refers to the anonymisation based on the evaluation of the re-identification risk (see below Section 1.2.2.1.2). Only one of the options should be followed for each clinical report, i.e. only section 1.2.2.1.1 or section 1.2.2.1.2 is to be completed.

1.2.2.1.1. Fulfilment of the criteria for anonymisation[27]

The applicant/MAH confirms/demonstrates that after anonymisation of the clinical reports the three criteria described below have been fulfilled.

a. No possibility to single out an individual

Data presented in an aggregated manner does not usually lead to the possibility of singling out an individual. However, in the case of small studies with few patients it might be more likely to single out individuals and therefore this criterion may not be fulfilled. Individual patient data in the clinical reports can also allow singling out an individual, but if adequately anonymised it can be demonstrated that the possibility to single out an individual is remote.

[26] PhUSE has listed direct and quasi identifiers that can be found in clinical data. This can facilitate the identification of variables in clinical reports (http://www.phuse.eu/Data_Transparency_download.aspx)

[27] According to Opinion 05/2014 on anonymisation techniques of the Article 29 Data Protection Working Party

b. No possibility to link records relating to an individual

If the patient ID is redacted from the clinical reports it is less likely to link information relating to an individual. A combination of quasi identifiers reported in several sections of the report could also lead to linking information relating to one individual.

c. Information cannot be inferred concerning an individual

The value of an additional variable concerning an individual can be inferred from a narrative that has not been suitably anonymised.

[If this section has been completed and the three criteria have been met, there is no need to complete the next section on the risk assessment]

1.2.2.1.2. Risk assessment

The aim of the risk assessment is to determine how much de-identification/anonymisation is required in order to reduce the risk of re-identification to an acceptable level.

- Identification of possible adversaries and plausible attacks on the data - for public data release, adversaries are most likely interested in showing that an attack is possible (demonstration attack).
- Evaluate the risk of re-identification
  - Choose qualitative or quantitative approach and provide justification
  - Set threshold
    - ✓ qualitative: low; justify the selected level
    - ✓ quantitative: numerical value; justify the selected threshold
  - List variables that will be used for the risk calculation
  - Calculate risk
    - ✓ qualitative: calculate the level of risk (e.g. high, medium, low) based on the characteristics of the source data (e.g. prevalence of the disease, trial sample size, number of sites)
    - ✓ quantitative: calculate the probability of uniquely identifying an individual
  - Check that the re-identification risk is lower than the pre-defined threshold
  - De-identify data until the risk of re-identification is lower than the set threshold. De-identification can be an iterative process until anonymisation of the data is reached.

[If the applicant/MAH decides to perform a risk assessment, there is no need to complete section 1.2.2.1.1]

1.2.3. Data utility considerations

A balance must be reached in order to obtain an acceptably low risk of re-identification and high utility data, taking into consideration that the protection of personal data is of paramount importance.

Applicants/MAHs should state that they have carefully considered the impact of the anonymisation methodology used on data utility.

1.2.4. Conclusion

On the basis of the information provide above, there should be evidence that the re-identification risk, after the data has been anonymised, is below the pre-defined threshold, or that the three criteria listed under 1.2.2.1.1 have been fulfilled.

[NAME OF THE COMPANY] declares the anonymisation report has been prepared following the guidance made available by EMA, and the anonymisation techniques have been applied consistently in the preparation of the documents comprising the Redaction Proposal Version.

1.3. Template for list of documents submitted

Module 2.5

- document 1
- doucment2

Module 2.7

- document 1
- document 2

Module 5

- document 1 – [*CSR1*] body
- document 2 – [*CSR1*] Appendix 16.1.1
- document 3 – [*CSR1*] Appendix 16.1.2
- document 4 – [*CSR1*] Appendix 16.1.9
- document 5

1.4. Template cover letter text: "Redaction Proposal Document" package

For applications for which a CHMP opinion has been adopted

European Medicines Agency

30 Churchill Place

Canary Wharf

London

E14 5EU

XX XXXX XXXX

Dear ,

RE: EMEA/X/X/XXXXXX/XXXX

[Product INN, Company Name]

Redaction Proposal Document package

Please find enclosed the "Redaction Proposal Document" package submitted at procedural Day xxx of the initial marketing authorisation application/line extension application/extension of indication application (delete as appropriate) for [product INN]. The "Redaction Proposal Document" package is submitted in line with the European Medicines Agency policy on the publication of clinical data for medicinal products for human use, Policy 0070. Comprising the "Redaction Proposal Document" package submitted to EMA are the following, with their respective locations in the eCTD:

- Cover letter [with annexed list of documents covering the entire Redaction Proposal sequence] (Module 1.0)
- Clinical Overviews (Module 2.5)
- Clinical Summaries (Module 2.7, Sections 2.7.1 – 2.7.4)
- Clinical Study Reports – body and appendices 16.1.1, 16.1.2 and 16.1.9 (Module 5.0, Section 5.3)
- Justification table for each document (uploaded as a 'working document')
- Anonymisation Report (Module 1.9)

<[NAME OF THE COMPANY] points out that no commercial confidential information has been identified in the entire "Redaction Proposal Document'' package and, therefore, justification tables are not submitted.> [Optional text as applicable]

<[NAME OF THE COMPANY] points out that commercially confidential information has only been identified in *some documents for which* [*please insert the number of justification tables*] justification tables were included in the "Redaction Proposal Document'' package and, confirms that in the

documents for which with no corresponding justification table was submitted no CCI has been identified and therefore no redactions are proposed.> [Optional text as applicable]

<[NAME OF THE COMPANY] declares the clinical reports are identical to those filed by <[NAME OF MAH] for the duplicate medicinal product "INVENTED NAME" [Optional text as applicable]

<[NAME OF THE COMPANY] declares the anonymisation report has been prepared in accordance with the guidance made available by EMA and applied consistently in the preparation of the Redaction Proposal Version.

In addition, [NAME OF THE COMPANY] hereby declares that the documents submitted ("Original Submission") in accordance with European Medicines Agency's ("EMA") Policy on publication of clinical data for medicinal products for human use ("POLICY/0070") are true and complete copies of the final version of [MODULES XX, XX, XX] submitted by the company in support of [DESCRIPTION OF THE APPLICATION] ("Clinical Reports Documentation") with the exception of (i) omission of documents, or elements thereof, falling out of the scope of POLICY/0070; and (ii) proposed redactions of commercially confidential information and any amendment aimed at ensuring anonymisation of the Clinical Reports Documentation. The proposed redactions of commercially confidential information and amendments pursuing anonymisation shall fully reflect the requirements of this POLICY/0070.

[NAME OF THE COMPANY] further declares that any subsequent submissions ("Subsequent Submissions") to the Original Submission during the consultation process, in accordance with POLICY/0070, will contain at all times true and complete copies of the Original Submission with the exception of the proposed redactions of commercially confidential information subject to this consultation. This shall apply to the submission of the final set of documents with the redactions agreed between [NAME OF THE COMPANY] and EMA ("Final Submission") for the purposes of proactive publication in accordance with POLICY/0070.

In addition, [NAME OF THE COMPANY] also declares that (i) the Subsequent Submissions do not contain any redactions of commercially confidential information that were not present in the Original Submission; and (b) the Final Submission does not contain any redactions of commercially confidential information that were not explicitly agreed in writing by EMA.

Finally, [FULL NAME AND POSITION] declares that [HE/SHE] is duly authorized to take this action and make this binding undertaking on behalf of [NAME OF THE COMPANY].

Yours sincerely,

1.5. Template cover letter text: "Redaction Proposal Document" package

In case of withdrawal of applications

European Medicines Agency

30 Churchill Place

Canary Wharf

London

E14 5EU

XX XXXX XXXX

Dear ,

RE: EMEA/X/X/XXXXXX/XXXX

[Product INN, Company Name]

Redaction Proposal Document package

Further to [Company name]'s written notification on [insert date] of the withdrawal of the initial marketing authorisation application/line extension application/extension of indication application (delete as appropriate) for [product INN], please find enclosed the "Redaction Proposal Document" package. The "Redaction Proposal Document" package is submitted in line with the European Medicines Agency policy on the publication of clinical data for medicinal products for human use, Policy 0070. Comprising the "Redaction Proposal Document" package submitted to EMA are the following, with their respective locations in the eCTD:

Cover letter [with annexed list of documents covering the whole Redaction Proposal sequence] (Module 1.0)

Clinical Overviews (Module 2.5)

Clinical Summaries (Module 2.7, Sections 2.7.1 – 2.7.4)

Clinical Study Reports – body and appendices 16.1.1, 16.1.2 and 16.1.9 (Module 5.0, Section 5.3)

Justification table for each document (uploaded as a 'working document')

Anonymisation Report (Module 1.9)

<[NAME OF THE COMPANY] points out that no commercial confidential information has been identified in the entire ''Redaction Proposal Document'' package and therefore, justification tables are not submitted.> [Optional text as applicable]

<[NAME OF THE COMPANY] declares the clinical reports are identical, with the exception of references to the product names, to the original medicinal product. [Optional text as applicable]

<[NAME OF THE COMPANY] declares the anonymisation report has been prepared in accordance with the guidance made available by EMA and applied consistently in the preparation of the document comprising the Redaction Proposal Version.

In addition, [NAME OF THE COMPANY] hereby declares that the documents submitted ("Original Submission") in accordance with European Medicines Agency's ("EMA") Policy on publication of clinical data for medicinal products for human use ("POLICY/0070") are true and complete copies of the final version of [MODULES XX, XX, XX] submitted by the company in support of [DESCRIPTION OF THE APPLICATION] ("Clinical Reports Documentation") with the exception of of (i) omission of documents, or elements thereof, falling out of the scope of POLICY/0070; and (ii) proposed redactions and any other intervention needed to ensure anonymisation of the Clinical Reports Documentation. These redactions and any intervention needed to ensure anonymisation of trial participants shall fully reflect the provisions and requirements of this POLICY/0070 and [REFERENCE TO THE RELATED GUIDANCE DOCUMENT(S)].

[NAME OF THE COMPANY] further declares that any subsequent submissions ("Subsequent Submissions") to the Original Submission during the consultation process, in accordance with POLICY/0070 and [REFERENCE TO THE RELATED GUIDANCE DOCUMENT(S)], will contain at all times true and complete copies of the Original Submission with the exception of the redactions subject to this consultation. This shall apply to the submission of the final set of documents with the redactions agreed between [NAME OF THE COMPANY] and EMA ("Final Submission") for the purposes of proactive publication in accordance with POLICY/0070.

In addition, [NAME OF THE COMPANY] also declares that (i) the Subsequent Submissions do not contain any redactions that were not present in the Original Submission; and (b) the Final Submission does not contain any redactions that were not explicitly agreed in writing by EMA.

Finally, [FULL NAME AND POSITION] declares that [HE/SHE] is duly authorized to take this action and make this binding undertaking on behalf of [NAME OF THE COMPANY].

Yours sincerely,

1.6. Template cover letter text: "Final Redacted Document" package

For all applications covered by the policy

European Medicines Agency

30 Churchill Place

Canary Wharf

London

E14 5EU

XX XXXX XXXX

Dear ,

RE: EMEA/X/X/XXXXXX/XXXX

[Product INN, Company Name]

Final Redacted Document package

Further to the "Redaction Proposal Document" package submitted to EMA on XX XXXX XXXX and the written correspondence of XX XXXX XXXX confirming [company name]'s [partial/full] agreement with EMA's redaction conclusion of XX XXXX XXXX, please find enclosed the "Final Redacted Document" package for the [withdrawn] initial marketing authorisation application/line extension application/extension of indication application (delete as appropriate) for [product INN].

The "Final Redacted Document" package is submitted for the purpose of the European Medicines Agency policy on the publication of clinical data for medicinal products for human use, Policy 0070.

A declaration is provided in the cover letter submitted with the "Redaction Proposal Document" package that the clinical reports submitted for publication are the same as those submitted for scientific review, with the exception of anonymisations and redactions.

In case of full agreement:

The "Final Redacted Document" package is submitted in line with the EMA redaction conclusion and to the extent these were agreed both by the Agency and [company name].

In case of partial agreement:

The "Final Redacted Document" package is submitted in line with the EMA redaction conclusion with the exception of those parts that are subject to interim relief proceedings.

[Company name] disagrees with the EMA's position concerning the rejection of the following redactions and these redactions were maintained in the "Final Redacted Document" package, contrary to EMA's redaction conclusion of XX XXXX XXXX:

- [The applicant/MAH will state which redactions (page, line) that were rejected in the EMA conclusion have been maintained in the Final Redaction version of the clinical reports to be published.]

The undisputed parts are in line with EMA's conclusion.

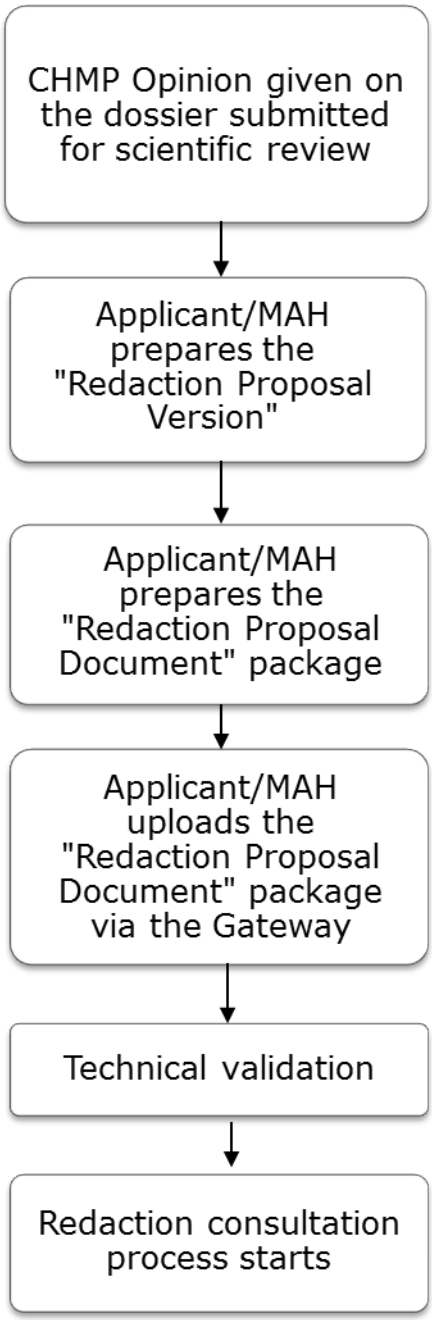
Comprising the "Final Redacted Document" package submitted to EMA are the following documents, with their respective locations in the eCTD:

- Cover letter [with annexed list of documents covering the whole Final Redaction package of documents] (Module 1.0)
- Clinical Overviews (Module 2.5)
- Clinical Summaries (Module 2.7, Sections 2.7.1 – 2.7.4)
- Clinical Study Reports – body and appendices 16.1.1, 16.1.2 and 16.1.9 (Module 5.0, Section 5.3)
- Anonymisation Report (Module 1.9)

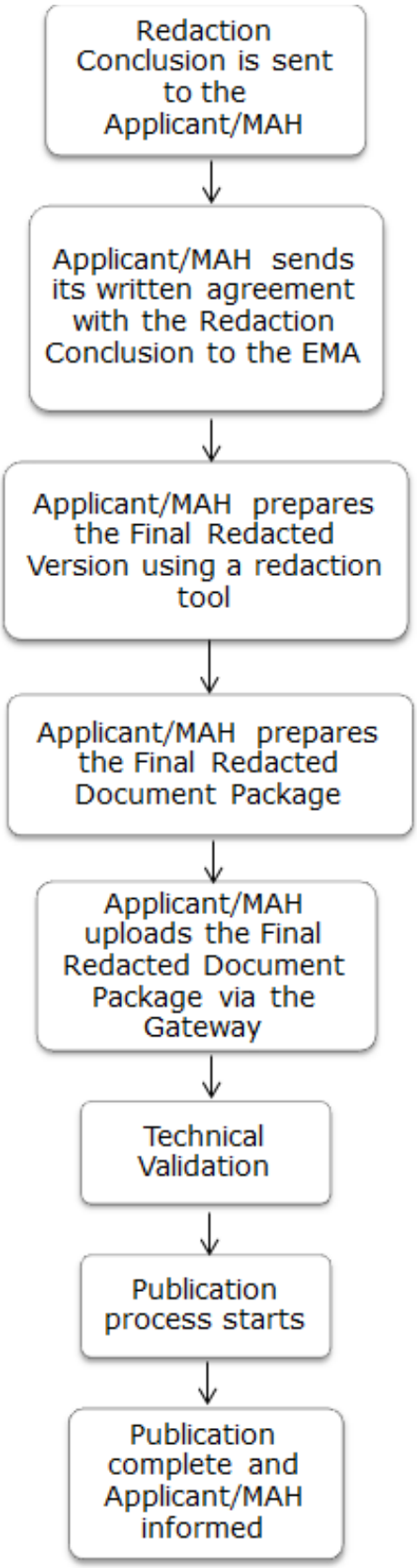
We look forward to the publication of the redacted clinical reports by EMA and to being notified by EMA of their publication.

Yours sincerely,

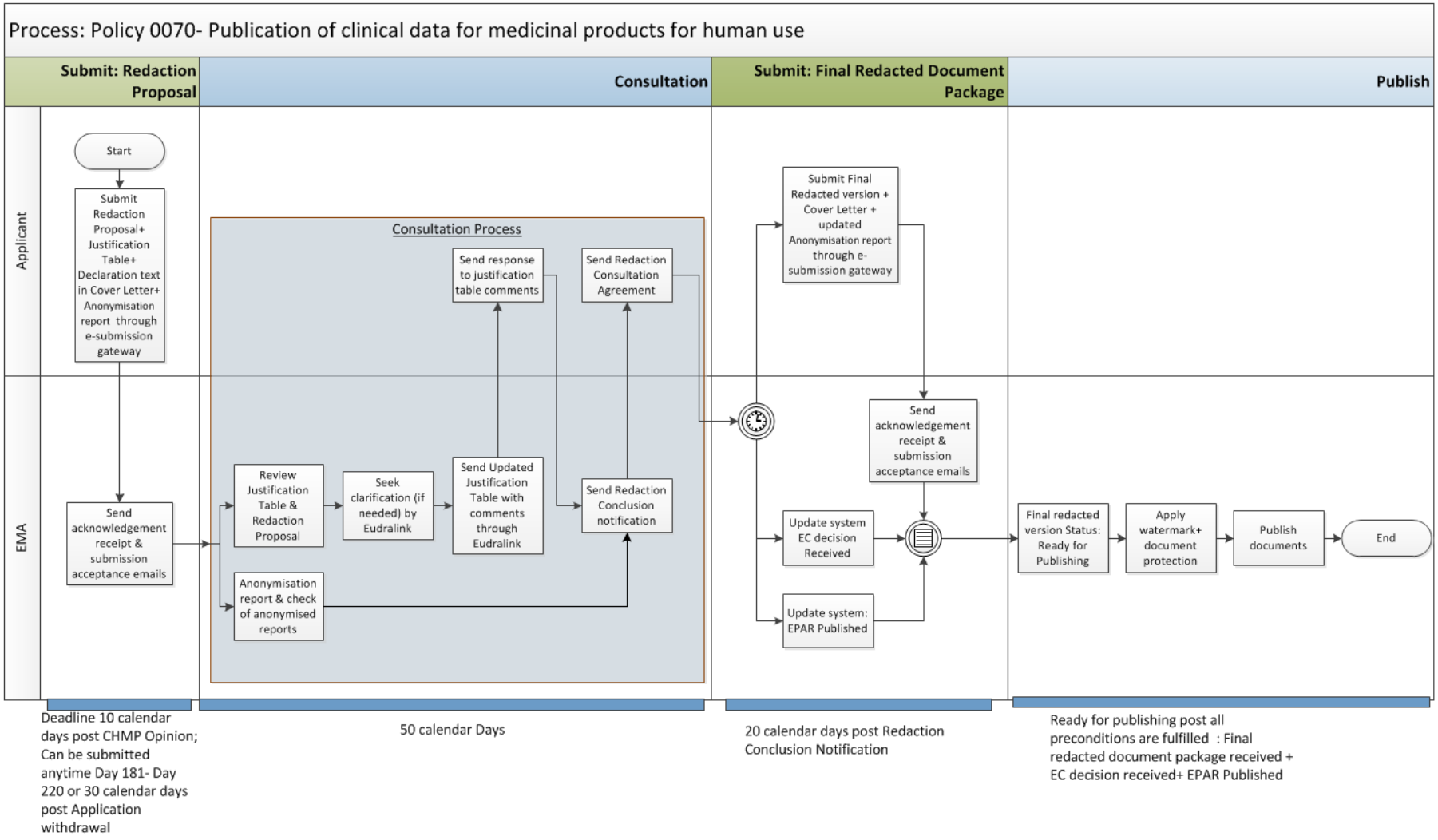
1.7. "Redaction Proposal Version" process flowchart



1.8. "Final Redacted Version" process flowchart



1.9. Workflow for the submission of clinical reports for publication



1.10. Sample of Justification table for CCI redactions

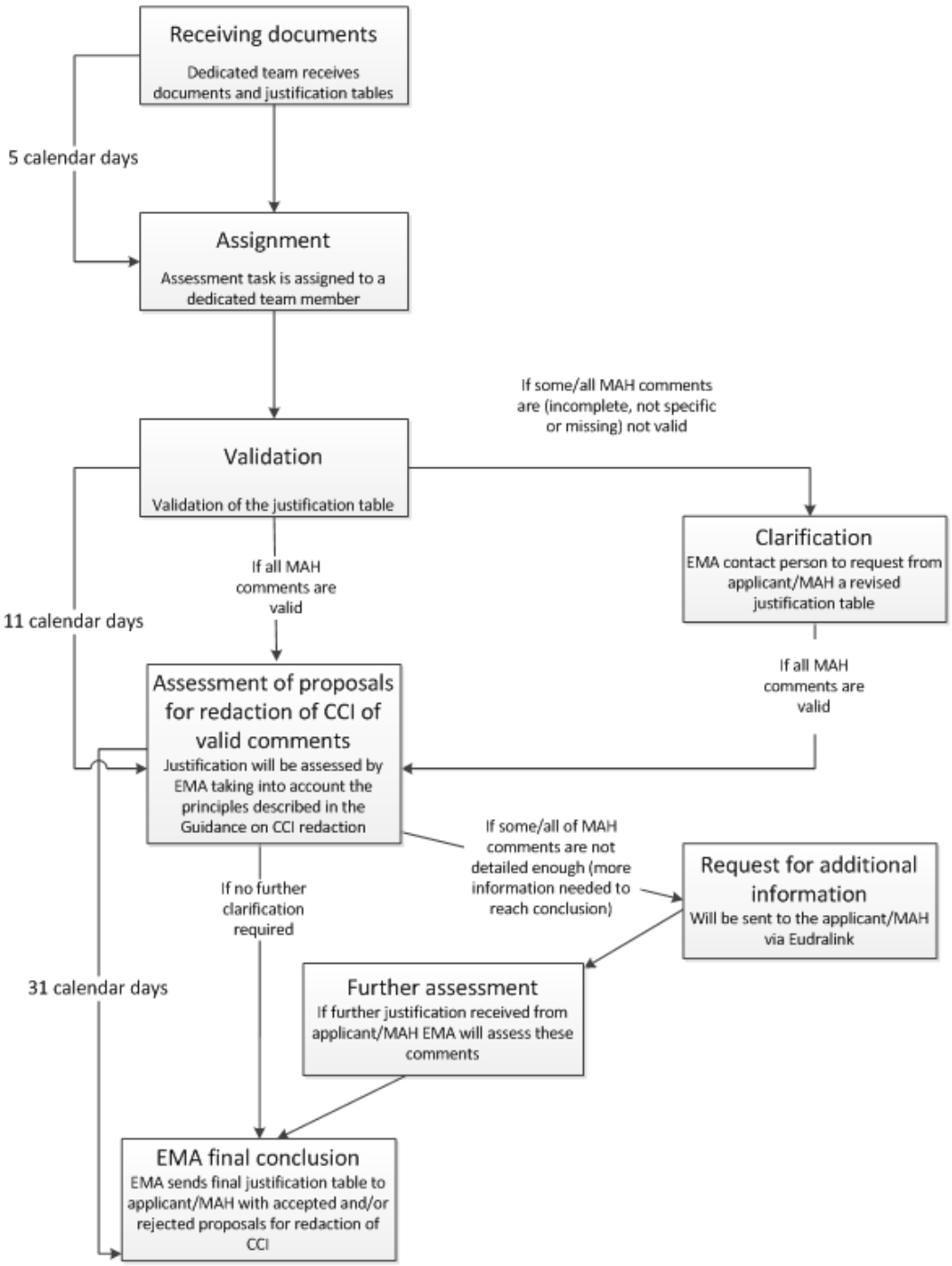
Justification Table: Invented Product name (INN) – procedure number

Applicant/MAH Consultation on <**Module 5.3.1** (Reports of Biopharmaceutical Studies), **Module 5.3.2** (Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials), **Module 5.3.3** (Reports of human pharmacokinetic (PK) studies), **Module 5.3.4** (Reports of human pharmacodynamic (PD) studies), **Module 5.3.5** (Reports of efficacy and safety studies), **Module 2.5** (Clinical Overview), **Module 2.7.1** (Summary of Biopharmaceutical Studies and Associated Analytical Methods), **Module 2.7.2** (Summary of Clinical Pharmacology Studies), **Module 2.7.3** (Summary of Clinical Efficacy), **Module 2.7.4** (Summary of Clinical Safety) - <Name of the document as per naming convention><Name of the Applicant consulted>

By submitting this justification table, you confirm that you have checked that the information you wish to redact is NOT in the public domain. Please ensure that the proposed redactions are in line with Annex 3 of POLICY/0070 and the Guidance on identification and redaction of commercially confidential information in clinical reports submitted to the European Medicines Agency for the purpose of publication.

Page number(s)	Title of Section(s)	Text proposed for redaction by the Applicant/MAH	Applicant/MAH to reference the section(s) of the Annex 3 of Policy 0070 on which the redaction is based. (If not obvious please explain how the proposed redacted text falls under this/these particular section(s) of Policy 0070 and is/are relevant for.)	Applicant/MAH to provide justification of CCI (Please explain how the release of this information will damage your company's commercial interest or competitive position)	Agency Assessment of the proposed redaction: Rejected/ Partially Accepted/ Accepted	Agency's rationale/redaction code

1.11. Redaction consultation process flowchart



1.12. In and Out of scope of phase 1 of Policy 0070

- **Common Technical Document (CTD) structure**

CTD Module / Section	Document	Scope	Explanation / Clarification
2.5 Clinical Overview			
2.5	Clinical Overview	In	All sections of the "**Clinical overview**" regardless whether they are submitted as separate standalone documents or all together in a single document are subject to publication. All documents included in CTD Module 2.5 such as "**Clinical overview supplement / amendment / appendix**" which were submitted during the evaluation procedure are subject to publication. However, EMA notes that, the appendixes to clinical overviews(Module 2.5), appendixes to clinical summaries (Modules 2.7.1 to 2.7.4) and CSR bodies may contain individual patient data listings (referred to further below as "per patient/per visit line listings"). For example, these per patient/per visit line listings may be contained in CSR section 14.3.4 Abnormal Laboratory Value Listing (Per Patient/per Visit). EMA considers that such **per patient / per visit line listings** fall outside the scope of phase 1 of the Policy and, therefore, it is acceptable to have them removed from the clinical reports prepared for publication at this stage of the implementation. All these per patient/per visit line listings will be falling in the scope of phase 2 of the Policy. Please note that for sections where per patient per visit IPD are identified in the clinical reports and the Agency agrees that they are out of the scope, these sections can be removed from the documents. However the pages/sections considered out of scope and therefore removed
2.5.1	Product Development Rationale	In	
2.5.2	Overview of Biopharmaceutics	In	
2.5.3	Overview of Clinical Pharmacology	In	
2.5.4	Overview of Efficacy	In	
2.5.5	Overview of Safety	In	
2.5.6	Benefits and Risks Conclusions	In	
2.5.7	Literature References	In	
2.5	Any other documents (not explicitly mentioned in ICH M4)	In	

CTD Module / Section	Document	Scope	Explanation / Clarification
			have to be replaced by a blank page containing the following: 1, removed page numbers (from-to) and the corresponding section title 2, statement that it is per patient per visit data removed as out of scope of policy 0070, reading: "**Out of Scope of phase I of Policy 0070- Per patient / per visit line listings**". The Agency considers per patient per visit data as those listings including values of the measured parameters (eg. lab values) listed for **all** patients recruited and covering **all** study visits. Therefore, for example, tables listing values of the measured parameters (eg. HbA1C) or outcomes (protocol deviation, death, SAE, overall survival) at a certain **single** time point will not be considered per patient per visit line listing. Also, the Agency does not consider per patient per visit line listings those tables where parameter or outcome values for **selected** patients and **selected** visits are presented. Please note that only the **list of references** is subject to publication. If actual scientific papers and articles are included in CTD section 2.5.7 these documents are NOT subject to publication.

2.7 Clinical Summary			
2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods			
2.7.1	Summary of Biopharmaceutic Studies and Associated Analytical Methods	In	All sections of the "**Summary of Biopharmaceutic Studies and Associated Analytical Methods**" regardless whether they are submitted as separate single documents or all together in a standalone document are subject to publication. All documents included in CTD section 2.7.1 such as "**Clinical summary supplement/amendment/appendix**"" which were submitted during the evaluation procedure are subject to publication. However, EMA notes that, the appendixes to clinical overviews (Module 2.5), appendixes to clinical summaries (Modules 2.7.1 to 2.7.4) and CSR bodies may contain individual patient data listings (referred to further below as "per patient/per visit line listings"). For example, these per patient/per visit line listings may be contained in CSR section 14.3.4 Abnormal Laboratory Value Listing (Per Patient/per Visit). EMA considers that such **per patient/per visit line listings** fall outside the scope of phase 1 of the Policy and, therefore, it is acceptable to have them removed from the clinical reports prepared for publication at this stage of the implementation. All these per patient/per visit line listings will be falling in the scope of phase 2 of the Policy. Please note that for sections where per patient per visit IPD are identified in the clinical reports and the Agency agrees that they are out of the scope, these sections can be removed from the documents. However the pages/sections considered out of scope and therefore removed have to be replaced by a blank page containing the following: 1, removed page numbers (from-to) and the corresponding section title 2, statement that it is per patient per visit data removed as out of scope of policy 0070,
2.7.1.1	Background and Overview	In	
2.7.1.2	Summary of Results of Individual Studies	In	
2.7.1.3	Comparison and Analyses of Results Across Studies	In	
2.7.1.4	Appendix	In	
2.7.1	Any other documents (not explicitly mentioned in ICH M4)	In	

			reading: "**Out of Scope of phase I of Policy 0070- Per patient/per visit line listings**". The Agency considers per patient per visit data as those listings including values of the measured parameters (eg. lab values) listed for **all** patients recruited and covering **all** study visits. Therefore, for example, tables listing values of the measured parameters (eg. HbA1C) or outcomes (protocol deviation, death, SAE, overall survival) at a certain **single** time point will not be considered per patient per visit line listing. Also, the Agency does not consider per patient per visit line listings those tables where parameter or outcome values for **selected** patients and **selected** visits are presented.

2.7.2 Summary of Clinical Pharmacology Studies			
2.7.2	Summary of Clinical Pharmacology Studies	In	All sections of the "**Summary of Clinical Pharmacology Studies**" regardless whether they are submitted as separate standalone documents or all together in a single document are subject to publication. All documents included in CTD section 2.7.2 such as "**Clinical summary supplement/amendment/appendix**" which were submitted during the evaluation procedure are subject to publication. However, EMA notes that, the appendixes to clinical overviews(Module 2.5), appendixes to clinical summaries (Modules 2.7.1 to 2.7.4) and CSR bodies may contain individual patient data listings (referred to further below as "per patient/per visit line listings"). For example, these per patient/per visit line listings may be contained in CSR section 14.3.4 Abnormal Laboratory Value Listing (Per Patient/per Visit). EMA considers that such **per patient/per visit line listings** fall outside the scope of phase 1 of the Policy and, therefore, it is acceptable to have them removed from the clinical reports prepared for publication at this stage of the implementation. All these per patient/per visit line listings will be falling in the scope of phase 2 of the Policy. Please note that for sections where per patient per visit IPD are identified in the clinical reports and the Agency agrees that they are out of the scope, these sections can be removed from the documents. However the pages/sections considered out of scope and therefore removed have to be replaced by a blank page containing the following: 1, removed page numbers (from-to) and the corresponding section title 2, statement that it is per patient per visit data removed as out of scope of policy
2.7.2.1	Background and Overview	In	
2.7.2.2	Summary of Results of Individual Studies	In	
2.7.2.3	Comparison and Analyses of Results Across Studies	In	
2.7.2.4	Special Studies	In	
2.7.2.5	Appendix	In	
2.7.2	Any other documents (not explicitly mentioned in ICH M4)	In	

			0070, reading: "**Out of Scope of phase I of Policy 0070- Per patient/per visit line listings**". The Agency considers per patient per visit data as those listings including values of the measured parameters (eg. lab values) listed for **all** patients recruited and covering **all** study visits. Therefore, for example, tables listing values of the measured parameters (eg. HbA1C) or outcomes (protocol deviation, death, SAE, overall survival) at a certain **single** time point will not be considered per patient per visit line listing. Also, the Agency does not consider per patient per visit line listings those tables where parameter or outcome values for **selected** patients and **selected** visits are presented.
2.7.3 Summary of Clinical Efficacy			
2.7.3	Summary of Clinical Efficacy	In	All sections of the "**Summary of Clinical Efficacy**" regardless whether they are submitted as separate standalone documents or all together in a single document are subject to publication. All documents included in CTD section 2.7.3 such as "**Clinical summary supplement/amendment/appendix**" or **"Integrated Summary of Efficacy (ISE)"** which were submitted during the evaluation procedure are subject to publication. However, EMA notes that, the appendixes to clinical overviews(Module 2.5), appendixes to clinical summaries (Modules 2.7.1 to 2.7.4) and CSR bodies may contain individual patient data listings (referred to further below as "per patient/per visit line listings"). For example, these per patient/per visit line listings may be
2.7.3.1	Background and Overview of Clinical Efficacy	In	
2.7.3.2	Summary of Results of Individual Studies	In	
2.7.3.3	Comparison and Analyses of Results Across Studies	In	
2.7.3.4	Analysis of Clinical Information Relevant to Dosing Recommendations	In	
2.7.3.5	Persistence of Efficacy and/or Tolerance Effects	In	
2.7.3.6	Appendix	In	

2.7.3	Any other documents (not explicitly mentioned in ICH M4)	In	contained in CSR section 14.3.4 Abnormal Laboratory Value Listing (Per Patient/per Visit). EMA considers that such **per patient/per visit line listings** fall outside the scope of phase 1 of the Policy and, therefore, it is acceptable to have them removed from the clinical reports prepared for publication at this stage of the implementation. All these per patient/per visit line listings will be falling in the scope of phase 2 of the Policy. Please note that for sections where per patient per visit IPD are identified in the clinical reports and the Agency agrees that they are out of the scope, these sections can be removed from the documents. However the pages/sections considered out of scope and therefore removed have to be replaced by a blank page containing the following: 1, removed page numbers (from-to) and the corresponding section title 2, statement that it is per patient per visit data removed as out of scope of policy 0070, reading: "**Out of Scope of phase I of Policy 0070- Per patient/per visit line listings**". The Agency considers per patient per visit data as those listings including values of the measured parameters (eg. lab values) listed for **all** patients recruited and covering **all** study visits. Therefore, for example, tables listing values of the measured parameters (eg. HbA1C) or outcomes (protocol deviation, death, SAE, overall survival) at a certain **single** time point will not be considered per patient per visit line listing. Also, the Agency does not consider per patient per visit line listings those tables where parameter or outcome values for **selected** patients and **selected** visits are presented.

2.7.4 Summary of Clinical Safety			
2.7.4	Summary of Clinical Safety	In	All sections of the "**Summary of Clinical Safety**" regardless whether they are submitted as separate standalone documents or all together in a single document are subject to publication. All additional documents included in CTD section 2.7.4 such as "**Clinical summary supplement/amendment/appendix**" or "**Integrated Summary of Safety (ISS)"** which were submitted during the evaluation procedure are subject to publication. However, EMA notes that, the appendixes to clinical overviews(Module 2.5), appendixes to clinical summaries (Modules 2.7.1 to 2.7.4) and CSR bodies may contain individual patient data listings (referred to further below as "per patient/per visit line listings"). For example, these per patient/per visit line listings may be contained in CSR section 14.3.4 Abnormal Laboratory Value Listing (Per Patient/per Visit). EMA considers that such **per patient/per visit line listings** fall outside the scope of phase 1 of the Policy and, therefore, it is acceptable to have them removed from the clinical reports prepared for publication at this stage of the implementation. All these per patient/per visit line listings will be falling in the scope of phase 2 of the Policy. Please note that for sections where per patient per visit IPD are identified in the clinical reports and the Agency agrees that they are out of the scope, these sections can be removed from the documents. However the pages/sections considered out of scope and therefore removed have to be replaced by a blank page containing the following: 1, removed page numbers (from-to) and the corresponding section title
2.7.4.1	Exposure to the Drug	In	
2.7.4.2	Adverse Events	In	
2.7.4.3	Clinical Laboratory Evaluations	In	
2.7.4.4	Vital Signs, Physical Findings, and Other Observations Related to Safety	In	
2.7.4.5	Safety in Special Groups and Situations	In	
2.7.4.6	Post-marketing Data	In	
2.7.4.7	Appendix	In	
2.7.4	Any other documents (not explicitly mentioned in ICH M4)	In	

			2, statement that it is per patient per visit data removed as out of scope of policy 0070, reading: "**Out of Scope of phase I of Policy 0070- Per patient/per visit line listings**". The Agency considers per patient per visit data as those listings including values of the measured parameters (eg. lab values) listed for **all** patients recruited and covering **all** study visits. Therefore, for example, tables listing values of the measured parameters (eg. HbA1C) or outcomes (protocol deviation, death, SAE, overall survival) at a certain **single** time point will not be considered per patient per visit line listing. Also, the Agency does not consider per patient per visit line listings those tables where parameter or outcome values for **selected** patients and **selected** visits are presented.
2.7.5 References			
2.7.5	(All) References	Out	These documents (the list of references or the literature references themselves) **are not clinical summaries** therefore are not subject to publication
2.7.6 Synopsis of Individual Studies			
2.7.6	(All) Synopsis of Individual Studies	Out	These documents **are not clinical summaries** therefore are not subject to publication
5 Clinical Study Reports			
5.1 Table of Contents of Module 5			
5.1	Table of Contents of Module 5	Out	This document **is not a clinical study report (CSR)** therefore is not subject to publication
5.2 Tabular Listing of All Clinical Studies			
5.2	Tabular Listing of All Clinical Studies	Out	This document **is not a clinical study report (CSR)** therefore is not subject to publication

5.3 Clinical Study Reports			
5.3.1 Reports of Biopharmaceutic Studies			
5.3.1.1 Bioavailability (BA) Study Reports			
5.3.1.1	(All) Bioavailability (BA) Study Reports	In	
5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports			
5.3.1.2	(All) Comparative BA and Bioequivalence (BE) Study Reports	In	
5.3.1.3 In vitro - In vivo Correlation Study Reports			
5.3.1.3	(All) In vitro - In vivo Correlation Study Reports	Out	These study reports contain information on predictive mathematical models describing the relationship between an in vitro property and a relevant in vivo response. These reports **are not expected to contain safety and efficacy results**. Therefore, EMA considers that these study reports are not subject to publication.
5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies			
5.3.1.4	(All) Reports of Bioanalytical and Analytical Methods for Human Studies	Out	These study reports contain information on the assays validation and analytical methods employed during the conduct of the clinical trials. These reports **are not expected to contain safety and efficacy results**. Therefore, EMA considers that these study reports are not subject to publication.
5.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials			
5.3.2.1 Plasma Protein Binding Study Reports			
5.3.2.1	(All) Plasma Protein Binding Study Reports	In	

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies			
5.3.2.2	(All) Reports of Hepatic Metabolism and Drug Interaction Studies	In	
5.3.2.3 Reports of Studies Using Other Human Biomaterials			
5.3.2.3	(All) Reports of Studies Using Other Human Biomaterials	In	
5.3.3 Reports of Human Pharmacokinetic (PK) Studies			
5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports			
5.3.3.1	(All) Healthy Subject PK and Initial Tolerability Study Reports	In	
5.3.3.2 Patient PK and Initial Tolerability Study Reports			
5.3.3.2	(All) Patient PK and Initial Tolerability Study Reports	In	
5.3.3.3 Intrinsic Factor PK Study Reports			
5.3.3.3	(All) Intrinsic Factor PK Study Reports	In	
5.3.3.4 Extrinsic Factor PK Study Reports			
5.3.3.4	(All) Extrinsic Factor PK Study Reports	In	
5.3.3.5 Population PK Study Reports			
5.3.3.5	(All) Population PK Study Reports	In	
5.3.4 Reports of Human Pharmacodynamic (PD) Studies			
5.3.4.1 Healthy Subject PD and PK/PD Study Reports			
5.3.4.1	(All) Healthy Subject PD and PK/PD Study Reports	In	
5.3.4.2 Patient PD and PK/PD Study Reports			

5.3.4.2	(All) Patient PD and PK/PD Study Reports	In	
5.3.5 Reports of Efficacy and Safety Studies			
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication			
5.3.1.1	(All) Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication	In	
5.3.5.2 Study Reports of Uncontrolled Clinical Studies			
5.3.5.2	(All) Study Reports of Uncontrolled Clinical Studies	In	
5.3.5.3 Reports of Analyses of Data from More than One Study			
5.3.5.3	(All) Reports of Analyses of Data from More than One Study	In	All reports included in CTD section 5.3.5.3 including "**Integrated Summary of Safety (ISS)"** or **"Integrated Summary of Efficacy (ISE)"** which present the results of analyses of safety and efficacy data collected from more than one clinical study, and which were submitted during the evaluation procedure, are subject to publication. To be noted that for all reports presenting results of analyses of data from more than one study (e.g. meta-analyses and pooled analyses) the statistical plans are expected to be published. They are considered the equivalent of CSR section 16.1.9.
5.3.5.4 Other Study Reports			
5.3.5.4	(All) Other Study Reports	In	This CTD section may contain reports of **controlled or uncontrolled studies not related to the claimed indication**. EMA would like to confirm that these reports are subject to publication. To the extent that for example only the safety findings reported in these documents were taken into account during the scientific review (e.g. included in the safety database) EMA foresees that the efficacy sections of the published reports would contain redactions. However, the applicants/MAHs are expected to justify these redactions and not to only provide as a justification that they have not yet applied for a particular indication.
5.3.6 Reports of Post-Marketing Experience			

5.3.6	(All) Reports of Post-Marketing Experience	Out	These reports (e.g. PSURs/PBERs) **are not Clinical Study Reports (CSRs)** therefore they are not subject to publication.
5.3.7 Case Report Forms and Individual Patient Listings			
5.3.7	(All) Case Report Forms and Individual Patient Listings	Out	These reports **are not Clinical Study Reports (CSRs)** therefore they are not subject to publication.
5.4 Literature References			
5.4	(All) Literature References	Out	These documents **are not clinical reports (understood as clinical overviews, clinical summaries or clinical study reports)** therefore are not subject to publication

- ## Clinical Study Report (CSR) structure

Clinical Study Report (CSR) components	Clinical Study Report (CSR) sections	Scope	Explanation/Clarification
A. CSR body			
1. TITLE PAGE		In	If ICH E3 format is not followed for a particular CSR, the corresponding information/sections (1-15) and annexes (16.1.1, 16.1.2 and 16.1.9) will be subject to publication. All sections of the body of the CSR (sections 1 to 15 as per ICH E3) are subject to publication. However, EMA notes that under ICH E3, the CSRs may contain individual patient data listings (referred to further in the document as "per patient/per visit line listings") even within the body of the report. For example, these per
2. SYNOPSIS		In	
3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT		In	
4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS		In	
5. ETHICS		In	
6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE		In	
7. INTRODUCTION		In	
8. STUDY OBJECTIVES		In	

Clinical Study Report (CSR) components	Clinical Study Report (CSR) sections	Scope	Explanation / Clarification
9. INVESTIGATIONAL PLAN		In	patient/per visit line listings may be contained in CSR section **14.3.4 Abnormal Laboratory Value Listing (Per Patient / per Visit)**, as well as elsewhere in the CSR body or in the appendixes of the clinical overviews (Module 2.5) or clinical summaries (Modules 2.7.1 to 2.7.4). EMA considers that such per patient/per visit line listings fall outside the scope of phase 1 of the Policy and, therefore, it is acceptable to have them removed from the clinical reports prepared for publication at this stage of the implementation. All these per patient/per visit line listings will be falling in the scope of phase 2 of the Policy. It is extremely important to note that the exclusion of the per patient/per visit line listings DOES NOT apply to any other listings such as listings presenting data in an aggregated format or listings of case narratives. As an example on how this statement should be interpreted, EMA would like to emphasize that CSR sections: - 14.3.1 Displays of Adverse Events - 14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events - 14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events DO FALL in the scope of the policy and SHOULD NOT BE REMOVED from the CSRs that are prepared for publication. Please note that for sections where per patient per visit IPD are identified in the clinical reports and the Agency agrees that they are out of the scope, these sections can be removed from the documents. However the pages/sections considered out of scope and therefore removed
10. STUDY PATIENTS		In	
11. EFFICACY EVALUATION		In	
12. SAFETY EVALUATION		In	
13. DISCUSSION AND OVERALL CONCLUSIONS		In	
14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT		In	
14.3.1 Displays of Adverse Events		In	
14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events		In	
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events		In	
14.3.4 Abnormal Laboratory Value Listing (Each Patient)		Out	
15. REFERENCE LIST		In	

Clinical Study Report (CSR) components	Clinical Study Report (CSR) sections	Scope	Explanation / Clarification
			have to be replaced by a blank page containing the following: 1, removed page numbers (from-to) and the corresponding section title 2, statement that it is per patient per visit data removed as out of scope of policy 0070, reading: "**Out of Scope of phase I of Policy 0070- Per patient / per visit line listings**". The Agency considers per patient per visit data as those listings including values of the measured parameters (eg. lab values) listed for **all** patients recruited and covering **all** study visits. Therefore, for example, tables listing values of the measured parameters (eg. HbA1C) or outcomes (protocol deviation, death, SAE, overall survival) at a certain **single** time point will not be considered per patient per visit line listing. Also, the Agency does not consider per patient per visit line listings those tables where parameter or outcome values for **selected** patients and **selected** visits are presented. To be noted that the same CCI, PPD and publication principles will apply to EU as well as non-EU studies in the context of Policy 0070.
B. CSR Appendices			
16.1 STUDY INFORMATION			
16.1.1 Protocol and protocol amendments		In	The following CSR appendices ONLY are subject to publication: 16.1.1 Protocol and protocol amendments
16.1.2 Sample case report form (unique pages only)		In	

Clinical Study Report (CSR) components	Clinical Study Report (CSR) sections	Scope	Explanation / Clarification
			16.1.2 Sample case report form (unique pages only) 16.1.9 Documentation of statistical methods If for a particular CSR the ICH E3 format is not followed, the corresponding information/sections (1-15) and annexes (16.1.1, 16.1.2, 16.1.9) will be subject to publication.
16.1.3 List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - Representative written information for patient and sample consent forms		Out	
16.1.4 List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study		Out	
16.1.5 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement		Out	
16.1.6 Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used		Out	
16.1.7 Randomisation scheme and codes (patient identification and treatment assigned)		Out	
16.1.8 Audit certificates (if available) (see Annex IVa and IVb of the guideline)		Out	
16.1.9 Documentation of statistical methods		In	
16.1.10 Documentation of inter-laboratory standardisation methods and quality assurance procedures if used		Out	
16.1.11 Publications based on the study		Out	

Clinical Study Report (CSR) components	Clinical Study Report (CSR) sections	Scope	Explanation / Clarification
16.1.12 Important publications referenced in the report		Out	
16.2. PATIENT DATA LISTINGS			
All appendices located under **16.2. PATIENT DATA LISTINGS**		Out	
16.3 CASE REPORT FORMS			
All appendices located under **16.3 CASE REPORT FORMS**		Out	
16.4. INDIVIDUAL PATIENT DATA LISTINGS (US ARCHIVAL LISTINGS)			
All appendices located under **16.4. INDIVIDUAL PATIENT DATA LISTINGS (US ARCHIVAL LISTINGS)**		Out	

Chapter 6

References

1. References

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David Carrell, Bradley Malin, John Aberdeen, et al. “Hiding in plain sight: use of realistic surrogates to reduce exposure of protected health information in *clinical text”. J Am Med Inform Assoc 2013;20:342–348.*

European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use)

Output of the European Medicines Agency policy on access to documents related to medicinal products for human and veterinary use

HMA/EMEA recommendations on transparency – recommendations on the handling of requests for access to Periodic Safety Update Reports (PSURs);

HMA/EMA guidance document on the identification of commercially confidential information and personal data within the structure of the marketing authorisation (MA) application – release of information after the granting of a marketing authorisation;

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