Agence nationale de sécurité du médicament et des produits de santé

Documentation requirements for an initial consultation

Language : French or English

Because of the wide range of medical devices which incorporate, as an integral part, an ancillary medicinal substance, a flexible approach to the data requirements is necessary. Nevertheless the information should be based in principle, to the extent relevant, on Annex I to Directive 2001/83/EC, as amended. It is envisaged that, where well-known medicinal substances for established purposes are the subject of the consultation, all aspects of safety and usefulness may not be required and many of the headings will be addressed by reference to literature, including standard textbooks, experience and other information generally available. Nonetheless all headings should be addressed; either with relevant data or justification for absence of data. The latter may be based on the manufacturer's risk assessment.
For new active substances and for known substances in a non-established purpose, comprehensive data is required to address the requirements of Annex I to Directive 2001/83/EC. The evaluation of such active substances would be performed in accordance with the principles of evaluation of new active substances.

part I Administrative information	1.1. Table of content 1.2. Submission letter from notified body and application form 1.3. Information about the experts (A declaration signed by the experts with brief information on their educational background, training and occupational experience. The professional relationship of the expert to the applicant shall be declared.) 1.4. Product information and labeling (At least, the product information relative to the combination will include the intended use, the claims, the method of use and the precaution for use.)

part II Summaries	2.1 Table of content 2.2 Application Form and appendix 2.3 The risk analysis of the integration of the ancillary medicinal substances to the medical device 2.4 Scientific Explanation for qualification Explanation of why the medicinal substance is added to the device, identifying in particular patients who will benefit from the combination versus device alone. Description of the mode of action of the components (device and medicinal substance) on their own and in the combination product. 2.5 Report from the notified body : Evaluation of the utility of the medicinal substance 2.6 Critical summaries (or expert reports) of the quality, non-clinical and clinical data provided

part III Quality	3.1Table of content 3.2 For the ancillary medicinal substance itself: The manufacturer of the ancillary medicinal substance should be stated and, where applicable, reference to the European Pharmacopoeia shall be made.

	Relevant information on the medicinal substance itself should be provided in one of the three formats below: Preferred • CTD-Module 3 in accordance with the format of the "Notice to Applicants" Ref : The rules governing medicinal products in the European Union", volume 2B, http://ec.europa.eu/health/documents/eudralex/index_en.htm Possible under conditions as those documents concerns only the active substance of the medicinal product, additional documents must be provided with them • In the form of an Active Substance Master File (ASMF), structured according to Module 3.2.s of the CTD-format (except for biological medicinal substance) • Certificate of Suitability to the European Pharmacopoeia if available Ref : EDQM website, http://www.edqm.eu/site/Legal_Status_Background-77.html Note1 : Review of the application will be greatly facilitated in the case of medicinal substances supplied with a PhEur Certificate of Suitability. Note 2 : The guidelines Summary of Requirements for Active Substances in the Quality Part of the Dossier and Active Substance Masterfile Procedure may be of assistance in deciding what information is required to address this section http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000081.jsp Note 3 : Reference to an EP monograph should be supplemented with relevant data on impurities, residual solvents, catalysts also stability of the active substance Note 4 : For biological medicinal substance, the certificate should be completed by relevant sections of CTD module 3 not covered by the certificate (e.g. description of manufacturing process and process control, controls of starting materials, manufacturing process development, process validation, characterization, reference materials, container closure system, stability…) Note 5 : For ancillary medicinal substance of animal or human origin, or manufactured using products of animal or human origin, information on the risk with respect to potential contamination with adventitious agents (viral and non-viral) should be provided according to CTD annex and the CHMP guidelines. In addition in the case of substances of animal origin, attention must be paid to the risk of transfert of transmissible spongiform encephalopathies (TSE) to humans. Note 6 : A statement should be provided that the active substance is manufactured in accordance with GMP requirements for Active substances.

Where the ancillary medicinal substance is further formulated, a manufacturing authorization and a GMP certificate should be provided.

3.3 For the ancillary medicinal substance as incorporated in the medical device:

- **Qualitative and quantitative particulars of the constituents**

A description of the substance and the amount of the medicinal substance incorporated into each medical device (specifying upper and lower limits based on production data and supported by reference to appropriate safety and efficacy studies).
If the substance is modified during its incorporation into the device, relevant information should be provided.
Other ingredients relevant to incorporation of the ancillary medicinal substance into the device, e.g. stabilisers, polymer excipients should also be described.

- **Description of method of manufacture**

An overall description will already form part of the application to the Notified Body; the section relevant to ANSM consultation should clearly define how the medicinal substance is incorporated into the device. If the medicinal substance is modified during its incorporation into the medical device, relevant information should be provided.

Submission of summary reports on process validation studies to demonstrate that the manufacturing method results in devices with controlled and consistent quantity of drug substance is encouraged.

- **Control of starting materials**

  The specification for the medicinal substance should be provided, along with sample Certificates of Analysis to demonstrate compliance with the specification.

- **Control tests carried out on intermediate stages of the manufacturing process of the medical device**

  This information is necessary if it is directly relevant to the quality of the medicinal substance as incorporated into the medical device.

- **Final Control tests of the ancillary medicinal substance in the medical device**

  Qualitative and quantitative tests carried out to control the ancillary medicinal substance in the medical device should be stated and justified. The test methods used should be fully described and supported by appropriate validation data. Analytical data on three batches, at least one of which is production scale, should be provided if available.

	Guideline: 'Validation of analytical procedures' is useful to determine the supportive validation data required. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002662.pdf • **Stability** Information defined to show the medicinal substance maintains its desired function throughout the shelf-life of the device, taking account of the manufacturer's recommended storage conditions, potential interactions with other materials, and potential degradation of the ancillary medicinal substance. The test methods should be described and shown to be stability indicating. Data on contents of ancillary medicinal product and degradation products measured during real-time as well as accelerated storage conditions are expected. Guideline: Stability Testing of Existing Active Ingredients and Related Finished Products is useful to determine the data requirements http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003466.pdf 3.4 Appendix

part IV Non clinical	4.1 Table of content 4.2 Non-clinical overview (or expert report) 4.3 Tabular summaries for non-clinical studies 4.4 Non-clinical documentation following the headings and data requirements of section c.3 of the MEDDEV 2.1/3 rev 3 4.4.1 Pharmacodynamics This section should address the intended action of the ancillary medicinal substance in the context of its incorporation into a medical device. 4.4.2Pharmacokinetics Some or all of the following areas may need to be addressed as appropriate: - Description of the pattern of local and systemic exposure to the ancillary medicinal substance, - Where the level of exposure fluctuates (AUC), the maximum level and duration of exposure should be considered, - Where it is considered possible that potential levels of systemic exposure may present a safety concern, maximum peak plasma concentration should be established, taking due consideration of individual variability, - New active substances will require information on the release from the medical device, and, if relevant, its subsequent absorption, distribution, metabolism and excretion (AUC and eventually metabolites, if relevant). 4.4.3 Toxicity (including single-dose toxicity, repeat-dose toxicity, geno-toxicity, carcino-genicity and reproductive and developmental toxicity, as applicable).

	Reference to the known toxicological profile of the ancillary medicinal substance. In the case of new active substances, the results of toxicity tests should be provided, taking into account relevant CHMP guidelines. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000083.jsp&jsenabled=true This may include information on toxicity and biocompatibility of the medical device which may be available from evaluation in accordance with the EN 10993 series of standards. All studies should be conducted in accordance with Good Laboratory Practice (GLP) 4.4.4 Local tolerance This is of particular relevance since the route of exposure to the ancillary medicinal substance may be different from its conventional application. The relevant results of medical device testing according to EN ISO 10993 should be provided or, where appropriate, information from the scientific literature. 4.5 Appendix

part V Clinical	5.1 Table of content 5.2 Explanation of why the medicinal substance is added to the device, identifying in particular patients who will benefit from the combination versus device alone. 5.3 Description of the mode of action of the components (device and medicinal substance) on their own and in the combination product. 5.4 Clinical overview (or expert report) 5.5 Tabular summaries for clinical studies application. 5.6 Clinical documentation 5.7 Appendix

Clinical evaluation remarks

Since these medical devices will be class III, clinical data will always be needed to form part of the information provided to the Notified Body under Annex II or III of the applicable Directive.

This section of data should verify the usefulness of the addition of the medicinal substance in the medical device.
Clinical data may comprise

- Critical evaluation of relevant scientific literature where equivalence to the device in question has been shown and the data demonstrate compliance with Essential Requirements
- Results of clinical investigations using the device
- A combination of the two above

Consequently the data might include, as appropriate, literature references, summaries of pre-clinical or clinical experience, results of clinical trials with the device alone, medicinal product alone or the device incorporating the medicinal substance.

An appropriate methodology for clinical investigations on medical devices is described in EN ISO14155-1:2003 – Clinical investigation of medical devices for human subjects – Part 1: General requirements and EN ISO14155-2:2003 – Clinical investigation of medical devices for human subjects – Part 2: Clinical investigation plans.

For certain types of products, e.g. antimicrobial wound dressings, *in vitro* data to demonstrate antimicrobial activity should be presented here.

The indications and claims made in the Instructions for Use leaflet should reflect the scope of the clinical data presented.

Where possible, all clinical data submitted by the manufacturer of the medical device to the Notified Body should be provided. Clinical data that is not directly relevant for supporting the medicinal substance's safety and usefulness can be included as an appendix

General Remarks	• If it is impossible to submit all the data requested, arguments should be presented for each section as to why this is not thought necessary. • As far as the chemical-pharmaceutical and biological data are concerned, the requirements for human medicinal products are set out in considerable detail in Directives, Regulations, Decrees and Guidelines. The data and format should comply with these documents as far as possible. • Only data relevant to the consultation should be submitted. • Reference to published literature should be accompanied by the full text of the published article/study
	ANSM may request information not listed below if deemed necessary

Documentation requirements for a modification of the ancillary medicinal substance for a class III rule 13 medical device already marked

Language : French or English

part I Administrative information	1.1 Table of content 1.2 Submission letter from notified body an application form 1.3 Information about the experts (A declaration signed by the experts with brief information on their educational background, training and occupational experience. The professional relationship of the expert to the applicant shall be declared.) 1.4 Updated product information and labeling (At least, the product information relative to the combination will include the intended use, the claims, the method of use and the precaution for use.)

part II Summaries	2.1 Table of content 2.2 Application Form and appendix 2.3 Summary and rational of the modifications to the ancillary substance, (tabulated format) 2.4 Updated Scientific Explanation for qualification 2.5 The updated risk analysis of the integration of the ancillary medicinal substances to the medical device 2.6 The updated critical summaries (or expert reports) of the quality, non-clinical and clinical data provided

part III Quality	3.1 Table of content 3.2 For the ancillary medicinal substance itself: The dossier must be structured as the initial dossier (see documentation requirements for an initial consultation). Section unchanged will only be completed with a statement that no change to initial dossier Section with modification must be completed with a complete explanation and justification of the modification and the corresponding updated documentation. 3.3 For the ancillary medicinal substance as incorporated in the medical device: The dossier must be structured as the initial dossier (see Documentation requirements for an initial consultation). Section unchanged will only be completed with a statement that no change to initial dossier Section with modification must be completed with a complete explanation and justification of the modifications and the corresponding updated documentation.

- **Qualitative and quantitative particulars of the constituent**

  A description of the substance and the amount of the medicinal substance incorporated into each medical device (specifying upper and lower limits based on production data and supported by reference to appropriate safety and efficacy studies). If the substance is modified during its incorporation into the device, relevant information should be provided. Other ingredients relevant to incorporation of the ancillary medicinal substance into the device, e.g. stabilizers, polymer excipients should also be described.

- **Description of method of manufacture**

  An overall description will already form part of the application to the Notified Body; the section relevant to ANSM consultation should clearly define how the medicinal substance is incorporated into the device. If the medicinal substance is modified during its incorporation into the medical device, relevant information should be provided.

  Submission of summary reports on process validation studies to demonstrate that the manufacturing method results in devices with controlled and consistent quantity of drug substance is encouraged.

- **Control of starting materials**

  The specification for the medicinal substance should be provided, along with sample Certificates of Analysis to demonstrate compliance with the specification.

- **Control tests carried out on intermediate stages of the manufacturing process of the medical device**

  This information is necessary if it is directly relevant to the quality of the medicinal substance as incorporated into the medical device.

- **Final Control tests of the ancillary medicinal substance in the medical device**

  Qualitative and quantitative tests carried out to control the ancillary medicinal substance in the medical device should be stated and justified. The test methods used should be fully described and supported by appropriate validation data. Analytical data on three batches, at least one of which is production scale, should be provided if available.

Guideline: 'Validation of analytical procedures' is useful to determine the supportive validation data required.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002662.pdf

	• **Stability** Information defined to show the medicinal substance maintains its desired function throughout the shelf-life of the device, taking account of the manufacturer's recommended storage conditions, potential interactions with other materials, and potential degradation of the ancillary medicinal substance. The test methods should be described and shown to be stability indicating. Data on levels of drug substance and degradation products measured during real-time as well as accelerated storage conditions are expected. Guideline: Stability Testing of Existing Active Ingredients and Related Finished Products is useful to determine the data requirements http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003466.pdf 3.4 Appendix

part IV Non clinical	The dossier must be structured as the initial dossier (see documentation requirements for an initial consultation). New studies will not be always necessary. Section unchanged will only be completed with a "no change statement" completed by a justification. 4.1 Table of content 4.2 Updated non-clinical overview (or expert report) 4.3 Tabular summaries for non-clinical studies 4.4 Updated Non-clinical documentation following the headings and data requirements of section c.3 of the MEDDEV 2.1/3 rev 3 4.4.1 Updated Pharmacodynamics This section should address the intended action of the ancillary medicinal substance in the context of its incorporation into a medical device. 4.4.2 Pharmacokinetics Some or all of the following areas may need to be addressed as appropriate: - Description of the pattern of local and systemic exposure to the ancillary medicinal substance, - Where the level of exposure fluctuates (AUC), the maximum level and duration of exposure should be considered, - Where it is considered possible that potential levels of systemic exposure may present a safety concern, maximum peak plasma concentration should be established, taking due consideration of individual variability, - New active substances will require information on the release from the medical device, and, if relevant, its subsequent absorption, distribution, metabolism and excretion (AUC and eventually metabolites, if relevant). 4.4.3 Toxicity (including single-dose toxicity, repeat-dose toxicity, geno-toxicity, carcino-genicity and reproductive and developmental toxicity, as applicable).

	Reference to the known toxicological profile of the ancillary medicinal substance. In the case of new active substances, the results of toxicity tests should be provided, taking into account relevant CHMP guidelines. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000083.jsp&jsenabled=true This may include information on toxicity and biocompatibility of the medical device which may be available from evaluation in accordance with the EN 10993 series of standards. All studies should be conducted in accordance with Good Laboratory Practice (GLP) 4.4.4 Local tolerance This is of particular relevance since the route of exposure to the ancillary medicinal substance may be different from its conventional application. The relevant results of medical device testing according to EN ISO 10993 should be provided or, where appropriate, information from the scientific literature. 4.5 Appendix

part V Clinical	The dossier must be structured as the initial dossier (see documentation requirements for an initial consultation). New studies will not be always necessary. Section unchanged will only be completed with a “no change statement” completed by a justification. 5.1 Table of content 5.2 Updated explanation of why the medicinal substance is added to the device, identifying in particular patients who will benefit from the combination versus device alone. 5.3 Updated description of the mode of action of the components (device and medicinal substance) on their own and in the combination product. 5.4 Updated clinical overview (or expert report) 5.5 Updated Tabular summaries for clinical studies application. 5.6 Updated clinical documentation 5.7 Appendix

General Remarks	• If it is impossible to submit all the data requested, arguments should be presented for each section as to why this is not thought necessary. • As far as the chemical-pharmaceutical and biological data are concerned, the requirements for human medicinal products are set out in considerable detail in Directives, Regulations, Decrees and Guidelines. The data and format should comply with these documents as far as possible. • In the case of substances of animal origin, attention must be paid to viral safety and the risk of transfer of transmissible spongiform encephalopathies (TSE) to humans. • Only data relevant to the consultation should be submitted. • Reference to published literature should be accompanied by the full text of the published article/study
	ANSM may request information not listed below if deemed necessary