Appendix I

Data requirements and format of the application dossier

Section 1

- Application form.
- General information of the medical device:
  - General description of the medical device, including the manufacturer's claim relating to the purpose of the incorporation of the ancillary medicinal substance, together with critical appraisal of results of the risk assessment;
  - Scientific explanation that the action of the medicinal substance incorporated in the medical device is only ancillary to that of the device.
- Signed declaration and CV from a qualified expert(s).

  When expert reports are used in Section 2 as critical summaries of the documentation, we request a signed declaration of ownership of the report. The expert shall have suitable technical or professional qualifications. A CV of the expert including brief information on their educational background, training and occupational experience shall be included. The professional relationship of the expert to the medical device manufacturer/notified body shall be declared.
- Report from the notified body verifying the usefulness of the incorporation of the ancillary medicinal substance.
- Labelling.

Section 2

- Module 2.3: quality overall summary (relevant parts) for the ancillary medicinal substance itself in accordance with the format of Volume 2B, CTD of the notice to applicants (EudraLex, The rules governing medicinal products in the European Union).
- Critical summaries (or expert reports) of the quality, non-clinical and clinical data provided for the ancillary medicinal substance incorporated in the medical device. (i.e. critical summaries (or expert reports)).

Section 3 - Quality Documentation

a) For the ancillary medicinal substance itself:

The supplier 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 two formats below:

1. Active Substance Master File (ASMF), structured according to Module 3.2.S of the CTD-format in accordance with the "Notice to Applicants" (Ref: "The rules governing medicinal products in the European Union", volume 2B).

   For a device containing more than one ancillary medicinal substance, the information requested for Module 3.2.S should be provided in its entirety for each drug substance.

   When the ancillary medicinal substance manufacturer uses an Active Substance Master File, he has to submit to AIFA its ASMF (close and open part), with the proof of payment of the required fees (https://www.aifa.gov.it/en/web/guest/tariffe)

For new applications the following documents should be included:

- Cover letter.
- Applicants Part (comprising relevant individual CTD documents - see below).
- Restricted Part (comprising relevant individual CTD documents - see below).
- Quality Overall Summary (comprising relevant individual CTD documents - see below).
- Letter of access.

For updates to ASMFs during the Consultation procedure, the documents above should be resubmitted in their updated form and an additional document with a table summarising the changes should be included.

2. Certificate of Suitability to the European Pharmacopoeia if available (Ref: EDQM website). Review of the application will be greatly facilitated in the case of medicinal substances supplied with a Ph. Eur. Certificate of Suitability, with the access declaration filled and signed.

Note 1: The guidelines "Summary of Requirements for Active Substances in the Quality Part of the Dossier" (CHMP/QWP/297/97 Rev 1 corr) and "Active Substance Master file Procedure" (CHMP/QWP/227/02 Rev 4 /Corr *) may be of assistance in deciding what information is required to address this section

Note 2: Reference to an Ph. Eur. monograph should be supplemented with relevant data on potential impurities arising from the particular route of synthesis, residual solvents, catalysts and also data on stability of the active substance to support the specified shelf-life.

Note 3: For active substances of animal origin, the risk of transfer of transmissible spongiform encephalopathies (TSE) to man should be addressed.

Note 4: A signed declaration should be provided that the active substance is manufactured in accordance with Good Manufacturing Practice (GMP) requirements for Active substances (see EMA/196292/2014 and EMA/CHMP/CVMP/QWP/696270/2010).

b) For the ancillary medicinal substance as incorporated in the medical device:

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

A chemical 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 AIFA 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.

Guideline on process validation for finished products - information and data to be provided in regulatory submissions (,EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1), Guideline on manufacture of the finished dosage form (EMA/CHMP/QWP/245074/2015) are useful to determine the supportive data required.

- **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. The routine test specification does not need to be the Ph. Eur. specification, but compliance with the Ph. Eur. monograph (where applicable) should be assured.

- **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” (ICH – Q2-R1) is useful to determine the supportive validation data required.

- **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” (CPMP/QWP/122/02, rev 1 corr) is useful to determine the data requirements.

Section 4

Non-clinical documentation for the ancillary medicinal substance incorporated in the medical device.

- **Non-clinical pharmacology**

This section should address the intended action of the ancillary medicinal substance in the context of its incorporation into a medical device.

- **Pharmacokinetics**

It is anticipated that pharmacokinetic studies will not be required in the majority of cases. 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 distribution and elimination (AUC and eventually metabolites, if relevant).

- **Toxicity**

Reference to the known toxicological profile of the medicinal substance may be provided. In the case of new active substances, the results of appropriate toxicity studies should be provided, taking into account relevant CHMP guidelines. 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).

- **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 results of medical device testing according to EN ISO 10993 should be provided, or, where appropriate, information from the scientific literature.

Section 5

- Clinical documentation for the ancillary medicinal substance incorporated in the medical device.

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.
The data should include:

- An explanation of why the medicinal substance is added to the device, identifying in particular patients who will benefit from the combination versus device alone.
- The mode of action of the components (device and medicinal substance) on their own and in the combination product.

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. It is expected that the data would provide adequate support to any claims without extrapolation.

Section 6
Details supplied by the manufacturers of the labeling and information to be provided with the medical device with regard to the ancillary medicinal substance, is to be supplied to the Competent Authority to assist in the understanding of the safety and usefulness of the ancillary medicinal substance together with the device.
The labeling should clearly indicate the presence of the ancillary medicinal substance and the Instructions for Use should contain sufficient information on the contra-indications and precautions for use to ensure safe use of the product.
Any claims made for the product should be supported by the data provided and where a claim is made on the basis of *in vitro* data only, this should be stated.

USEFUL GUIDELINES TO FULFIL THE DATA REQUIREMENTS

The following list of guidelines is not exhaustive and there may be other guidelines applicable.

1. General guidance

- Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices.
- MDCG 2022-5 April 2022 relating to the application of the Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices.
- Manual on borderline and classification for medical devices under Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on in vitro diagnostic medical devices, current version.
- EudraLex Notice to Applicants Volume 2B (Presentation and content of the dossier – CTD).
- Guideline on active substance Master File procedure (EMEA/CVMP/134/02 Rev 4; CPMP/QWP/227/02 Rev 4).

2. Guidance for new chemical entities

Quality

- Relevant CPMP/CHMP Guidelines published on the European Medicines Agency website (http://www.ema.europa.eu https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/clinical-efficacy-safety-guidelines)

Good manufacturing practice

- Relevant Annexes to the EU Guide to good manufacturing practice.

Non-clinical and clinical safety

- Relevant CPMP/CHMP guidance on new chemical entities from the Safety Working Party (SWP) and Efficacy Working Party (EWP) and CHMP temporary working parties (https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/non-clinical-guidelines) &

(http://www.ema.europa.eu - https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/clinical-efficacy-safety-guidelines)

- Guideline on the clinical and non clinical evaluation during the consultation procedure on medicinal substances contained in drug-eluting (medicinal substance-eluting) coronary stents (europa.eu) (EMEA/CHMP/EWP/110540/2007).