



## Guidance for Notified Bodies

### Devices which incorporate an ancillary medicinal substance

Consulting the MHRA with respect to the ancillary medicinal substance

# Guidance for notified bodies: devices which incorporate an ancillary medicinal substance

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Visit: [CESP website](http://www.cesp.eu)

## PREFACE

This Guidance is for Notified Bodies and their client companies wishing to consult the Medicines and Healthcare products Regulatory Agency (MHRA) with regard to the ancillary medicinal substance incorporated in a medical device.

The requirements for consultation in accordance with the Medical Devices Directive 93/42/EEC are clearly explained in MEDDEV 2.1/3: 'EC Guidance document on "Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative"'. See European Commission Website Link: [Guidelines relating to medical devices directives](#)

This MHRA guidance note explains the information required by the Agency for the Consultation and the format in which it should be supplied.

It is hoped that this guidance will be helpful to Notified Bodies and to manufacturers intending to submit consultation applications for medical devices incorporating ancillary medicinal substances. In addition, if consultations are made in a common format, the MHRA will be better able to process consultations effectively and expeditiously.

We shall be glad to provide advice on individual queries and products. Please see the list of contact points on the first page.

The information is current but may be further updated in light of any amendments to the EC Medical Devices Directive the Medical Device Regulation EU 2017/745 or European guidelines relating to Medicines. Please refer to the current version of Guidance Note 31 available on the MHRA GOV.UK website Link: [Devices incorporating an ancillary medicinal substance](#)

This Guidance Note should not be taken as a complete or definitive statement of the law. It is not intended as a substitute for legal or other professional advice. The MHRA accepts no liability for any loss or damage caused, arising directly, or indirectly, in connection with reliance on the contents of this guidance note.

GUIDANCE FOR NOTIFIED BODIES:  
DEVICES WHICH INCORPORATE AN ANCILLARY MEDICINAL SUBSTANCE

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## 1 WHAT DOES THE DIRECTIVE REQUIRE?

Under the terms of the EC Medical Devices Directive 93/42/EEC (the MDD), products which combine a medicinal substance with a medical device are regulated in one of the follow ways:

- **Drug-delivery products presented as an integral combination with a medicinal product are regulated as medicinal products**  
e.g. pre-filled syringes
- **Drug-delivery products presented separately from the medicinal product are regulated as medical devices**  
e.g. drug delivery pump
- **Medical devices incorporating, as an integral part, an ancillary medicinal substance**  
e.g. catheters coated with heparin or an antibiotic agent; drug-eluting stents; wound dressings with antibacterial agent

This last category of products is subject to devices control but the ancillary medicinal substance must be verified by analogy with data requirements in medicines legislation, and a medicines competent authority must be consulted. For products incorporating a human blood product derivative, the European Medicines Agency must be consulted.

*This guidance relates to the last of the above three categories, i.e. medical devices incorporating a medicinal substance where the action of the substance is ancillary to that of the device.*

More detailed guidance on the borderline between drugs and devices, and between the above categories, giving specific examples of each, is provided in the EC Guidance Document MEDDEV 2.1/3 and manual of decisions.

Also, see MHRA Website page Link: [Medical Devices Directive/Borderline with medicines](#). For specific advice, please see contact details on the first page.

### 1.1 Purpose of the consultation

For devices incorporating, as an integral part, an ancillary medicinal substance, the notified body shall, having verified the usefulness of the substance as part of the medical device and taking account of the intended purpose of the device, seek a scientific opinion from one of the Competent Authorities designated by the Member States on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the substance into the device.

The term 'Competent Authority' (CA) is used in this document to represent such a competent body within the meaning of Directive 2001/83/EC, as amended, and indicates the authority responsible for the evaluation of applications for medicinal products being placed on the market.

The aspect of "usefulness" relates to the rationale for using the medicinal substance in relation to the specific intended purpose of the device. It refers to the suitability of the medicinal substance to achieve its intended action, and whether the potential

inherent risks (aspect of “safety”) due to the medicinal substance are justified in relation to the benefit to be obtained within the intended purpose of the device.

The role of the medicines CA is to review the data available on the medicinal substance – the quality, safety and clinical benefit/risk profile of the substances as incorporated into the device. The consultation will only take into account information relevant to the medicinal substance, but this will include data to demonstrate:

- Quality, consistency, uniformity and stability of the substance in the device,
- Safety of the substance in the intended use (which may be very different from intended use and route of administration in authorised medicinal products)
- Clinical benefit vs potential risks in the proposed uses(s)

By means of the consultation process the CA may make available relevant information concerning risks related to the use of the substance (e.g. resulting from pharmacovigilance). The CA will inform the Notified Body (NB) of its opinion, taking into account the manufacturing process and the data related to usefulness of incorporation of the ancillary medicinal substance.

The NB should take into account the opinion of the CA and use its judgement to either approve the drug/device combination, after consideration of all aspects of risk/benefit in the intended or expected use of the product, or alternatively to reject the product.

## 1.2 The consultation process

In accordance with MEDDEV 2.1/3, Section C, the Notified Body should ensure that data supplied by the manufacturer in relation to the device and its intended use includes a specific segment regarding the medicinal substance being incorporated with ancillary purpose. **Presentation of the data in line with eCTD principles and the format set out in Section 2.4 of this Guidance note will facilitate efficient review by the MHRA.**

Before consulting MHRA the Notified Body should have come to a preliminary opinion regarding the suitability of the device incorporating the ancillary medicinal substance. A requirement introduced by Directive 2007/47/EC with effect from March 2010 is for the Notified Body to prepare an assessment of the usefulness of the medicinal substance as incorporated into the device, prior to submission of the consultation application to the Competent Authority. A copy of this assessment should be included with the submission or may be submitted as supplementary data within one month of the Consultation submission date.

It is at the discretion of the Notified Body to choose the Competent Authority with whom he consults. The European Medicines Agency (EMA) may be consulted, where the substance involved has been included in a medicinal product which has been authorised through the Centralised Procedure. The EMA must be consulted for all medical devices incorporating ancillary human blood derivatives.

The Notified Body may consider it of benefit to utilise, for the consultation, a Competent Authority previously responsible for a marketing authorisation for a medicinal product which incorporates the medicinal substance involved in the consultation process.

## 2 HOW TO CONSULT THE MHRA

### 2.1 Pre-submission meetings and notification

To facilitate allocation of the consultation to assessors in the relevant therapeutic assessment team, when a submission date is identified, it is helpful to send a pre-submission notification e-mail to the contacts on the first page.

In cases where there is a potential classification query (i.e. where there may be differences in opinion about whether the device or medicinal substance contributes the principal mode of action) it is strongly advised that confirmation is sought prior to submission, to prevent delays to the assessment process. Similarly, where there are different presentation/strengths of the product, or the first time a consultation has been submitted by a notified body or for a particular type of combination, prior discussion of submission strategy and data requirements is recommended.

Meetings associated with an imminent or ongoing Consultation may be arranged as part of the Consultation procedure. A scientific advice meeting to discuss the Consultation at an early stage may also be arranged if required, as for medicinal product licence applicants. The scientific advice meetings are chargeable – please see MHRA GOV.UK website for details and costs (Fees for Drug/Device meetings). Link: [Scientific advice meetings](#)

### 2.2 The consultation application form (NBA 201)

The consultation form NBA 201 should be completed by the Notified Body and submitted electronically as indicated below. Normally a separate form should be completed for each device. However, a single form may cover a group of similar products for which the medicinal substance is identical (e.g. a series of catheters in different sizes, but with an identical medicinal component at the same concentration). A copy of the consultation form NBA 201 is attached to this Guidance.

#### 2.2.2 NB Consultation reference number

Before completing the consultation form a Notified Body will need:

- a **company number** (i.e. a number unique to the Notified Body)
- a **product number** (i.e. a number to identify each consultation)

These numbers are combined to produce a unique reference number for each consultation: e.g. **NB 01234/ 0001** (where 01234 is the company number and 0001 the product number). The reference number is obtained from the MHRA Information Processing Unit: [Area0-PLNumberAllocation@mhra.gov.uk](mailto:Area0-PLNumberAllocation@mhra.gov.uk) (State in the subject line 'NB Consultation number allocation'). Insert this reference number on the consultation form and please include it in the subject line on all correspondence regarding the Consultation.

#### 2.2.2 Fees

Consultation is subject to payment of the appropriate fee. Details of the current fees can be found on the MHRA GOV.UK website Link: [Fees for Drug-Device Combination products](#). (No fee is payable in respect of a product moving from

medicines to devices control which holds a current marketing authorisation as a medicine in the UK, so long as the product remains unchanged in all respects, including claims and product information.)

The Notified Body will be invoiced for the appropriate fee, from April 2017 there is no need to pay this in advance. The fee may be paid directly by the device manufacturer if the **remittance advice sent in with payment clearly states the reference number referred to above**, to ensure that the money is allocated to the correct account.

Details on how to pay the fees can be found on the MHRA website Link: [MHRA Bank account details](#). For help with payment of fees, contact: [cashiers@mhra.gov.uk](mailto:cashiers@mhra.gov.uk).

### 2.3 Information on the ancillary medicinal substance

Data supporting use of the medicinal substance should be sent with the application form. The information required is set out at **Annex A**. This is based on the MEDDEV guidance 2.1/3 rev 3, and supplemented with guidance of EudraLex Notice to Applicants Volume 2B (Presentation and content of the dossier – CTD). The Common Technical Document (CTD) format is used for medicinal product Marketing Authorisation applications

### 2.4 Submission instructions

Notified Body Consultation submissions are now made through the Common European Submission Portal (CESP)

Please see **Annex B** for detailed submission information.  
The following should be included in the submission:

- **Application form with attachments**
- **Information relating to the**
  - **ancillary medicinal substance itself**
  - **ancillary medicinal substance as incorporated into the device**

following the headings and data requirements of Section C.3 of MEDDEV guidance 2.1/3 rev 3 and relevant sections of the CTD format.

**Responses** should be submitted using the submission procedure as detailed above, with the NB reference number stated on all communication, with clear reference to the fact that the contents are responses.

## 3 WHAT HAPPENS NEXT?

### 3.1 Subsequent amendments to the consultation

If any changes occur to the information on the consultation form before the MHRA provides its report, please notify us (see contact details on the first page).

### 3.2 The assessment process



The data provided will be used to set up a Case Folder on the MHRA electronic case management system.

The data will then be accessed by a Pharmaceutical Assessor to review the Quality aspects (data on active substance alone and section 2b); a Non-Clinical Assessor for review of Non-clinical aspects (section 3) and a Clinical Assessor from the relevant Therapeutic Group to review the NB report on usefulness, clinical data provided by the Applicant and to assess the benefit/risk profile taking into account relevant pharmacovigilance data where necessary.

Each Assessor will provide individual reports which are combined to form the final Decision Notification report issued to the Notified Body. In cases where one report is completed before the others and further information is to be requested, questions may be sent informally via the Notified Body to enable the Applicant to start preparing responses before the full report is available.

### 3.3 The MHRA's report to the Notified Body

After considering the submission, the MHRA will send its report to the Notified Body on the safety, quality and usefulness of the medicinal substance in relation to the intended purpose of the device.

For devices incorporating a known ancillary medicinal substance the target assessment time for issuing the first assessment report will normally be within 100 days from validation. For all other cases, such as a new medicinal substance or a new clinical use is claimed, then target time for assessment is 150 days from validation. In all cases, the overall assessment time should not exceed the 210 day limit as stated in the directive and the guidance in MEDDEV 2.1/3, produced by the European Commission.

In many cases, further information is required before MHRA is able to verify the quality, safety and acceptable clinical benefit/risk profile of the medicinal substance as used in the proposed device. If it is considered that the information requested should be readily available or obtainable within a reasonable time period (e.g. 90 days), a Request for Further Information (RFI) letter will be sent along with first assessment report on one or more parts of the consultation. If however, the additional information required is deemed to necessitate major data gathering work, the consultation will receive a negative opinion and recommendations will be given to explain the additional data that would be needed to gain approval. In this case, a supplementary consultation should then be submitted.

When a RFI letter is sent out, review will be suspended ('clock stop') until a complete response document is received. If any further points for clarification are raised, these will be communicated as soon as possible (within 30 days), with the aim of providing the complete MHRA report within the 210 day net review time (i.e. whilst all data requested is with MHRA). **For these time lines to be met, it is requested that the submission format outlined in Annexes A and B is complied with. Data that is not presented in accordance with the requirements, e.g. in folders, files > 25 MB, incorrectly named files, irrelevant data and non-bookmarked pdf. files can cause difficulty in uploading and accessing the necessary information.**

**Responses** should be submitted using the submission procedure as detailed above.

### 3.4 Informing the MHRA of the decision of the Notified Body

Following receipt of the final Decision Notification report from the MHRA, the Notified Body is required to give due consideration to the report when making its decision, and then to communicate its decision to the MHRA using Form NB 202 (see attached; Word document available from the website). Where a Notified Body receives a negative opinion from the medicines Competent Authority they should consult with the device Competent Authority before issuing a certificate.

### 3.5 Further consultations on the same device (Variations)

If there is any change in the design or manufacture of the device which could influence the quality, safety or usefulness of the drug substance in the device or in respect of amended or additional data, a new consultation form should be completed with a new reference number (**Supplementary Consultation**).

Examples of amendments that may require a Supplementary Consultation include:

- Change to the supplier of the ancillary medicinal substance or intermediate processor
- Change to the formulation or grade of the medicinal substance or an intermediate
- Significant change to the manufacturing process or change to the specification of the medicinal substance as notified by the substance manufacturer
- Changes to quality control tests relevant to the active substance during manufacture
- Change of manufacturing process for the incorporation of the medicinal substance into the device
- Change of packaging
- Change in the method of sterilisation
- Extension of shelf life (unless stated in the initial dossier that an extension to shelf-life is planned and in the MHRA assessment report that the planned increase to shelf-life would not require a supplementary consultation providing all data are within specification)
- Changes to the intended use of the device
- Some changes in the design of the device which may impact on the availability or release of the medicinal substance (e.g. device size increase if the quantity of the medicinal substance per device is increased, change in device surface area)

This list is intended for guidance and is not prescriptive or exhaustive. It is the responsibility of the Notified Body to decide if a Supplementary Consultation is required, based on information provided by the manufacturer.

The **Supplementary Consultation** should be submitted in a similar way to the original consultation, however a reduced fee is applicable (see [fees guidance](#) – additional report) and only data that are relevant to the change are required, supported by a summary report and updated risk assessment if applicable. The reference number of the original consultation should also be quoted on the form to facilitate linking of Case Folders within the MHRA.

The target time for first assessment of these applications is 60 days from validation, but will vary depending on the complexity of the consultation. If required a Request for Further information (RFI) will be raised at the first assessment and the clock will be turned-off. The net target time for completion of supplementary consultation is 90 days from validation.

Changes to the qualitative or quantitative composition relating to the active substance(s), or indications for use etc. would normally be subject to a new, full consultation. Examples include:

*quantitative change to, addition or deletion of one or more active substances;*  
- replacement of the active substance by another salt/ester complex/derivative;  
- incorporation of an additional medicinal substance

*variations relating to the use of the medical device*  
- addition of an indication in another therapeutic area;  
- addition of or change to the route of administration;

### **3.6 Renewal of CE Certification**

**In the Notified Body Operations Group NBOG Guidance 2014-1, regarding Renewals, section 5.2 states:**

In case of devices containing medicinal products, devices utilising materials of animal origin or devices assisted by human blood derivatives (covered by Directive 2001/83/EC or by Commission Regulation (EU) No 722/2012) the Notified Body has to consult the Competent Authority previously involved (or, if previously involved or exclusively responsible the EMA) to verify if new aspects will result in deviating opinions. The view of MHRA is that this requirement can be met by submitting a supplementary consultation. A summary of changes to the medical device since the initial consultation should be provided, along with an opinion by the Notified Body as to whether those changes are likely to affect the safety and performance of the device, based on the initial Decision Notification report of the MHRA. MHRA will review this summary and opinion and advise whether further information is required in support of the renewal. The target timeframe for the request for renewal and assessment of supplementary information will be same as that for supplementary consultation 60 days for first assessment and total target assessment time of 90 days (taking into account clock-off time whilst any further data requested are awaited).

### **3.7 Change of Notified Body**

It is recognised that manufacturers may have reasons to change notified body following initial consultation and this may also result in a change to the medicines CA that is consulted. It is expected that the new Notified Body will contact the previous NB to obtain the original CA opinion on the ancillary medicinal substance. If the Notified Body is unsure whether the original CA opinion is sufficiently detailed for the new NB to satisfy themselves regarding the quality, safety and clinical benefit/risk profile of the ancillary medicinal substance, the NB may contact MHRA to discuss whether a new consultation is required.

## Annex A

### INFORMATION ON THE ANCILLARY MEDICINAL SUBSTANCE

#### General

1. Information addressing the safety, quality and usefulness of the medicinal substance should be prepared by the manufacturer, submitted to the Notified Body, and then forwarded by the Notified Body to the MHRA. In addition, a report on the usefulness of the medicinal substance should be prepared by the Notified Body and attached to the NBA 201 Application form, or supplied within one month of the date of submission.

2. 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 relevant extent on Annex 1 to Directive 2001/83/EC, as amended, elaborated in Sections 1) to 4) below.

It is envisaged that where well-known medicinal substances for established purposes are involved, original data on all aspects of safety and usefulness may not be required and many of the headings will be addressed by reference to the 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.

This principle also applies to the Usefulness report – for novel combination products or products used in new indications or routes of administration, it will be expected that the usefulness report will be a more detailed, critical analysis, utilising appropriate expertise, than for a product that is considered to be equivalent to an already marketed product.

3. For new active substances and for known medicinal substances for a non-established purpose, comprehensive data is required to address the requirements of Annex 1 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.

4. There are a number of useful European guidelines relating to the quality, safety and efficacy of medicinal substances as used in medicinal products. Some of the more pertinent guidelines are mentioned below. Whilst it is not intended that the guidelines will be strictly adhered to, justification for the use of different approaches will be expected. Hyperlinks to the European Medicines Agency (EMA) website are included below, which may change in future. Please consult the EMA webpage '[Scientific guidelines for human medicinal products](#)' for current documents.

**Please note: It is important for efficient review of the consultation that only data relevant to the ancillary medicinal substance under the headings below are provided to MHRA.** Please use the submission format detailed in section 2.4 Submission Instructions and **Annex B**.

## DOCUMENTATION TO BE PROVIDED TO MHRA

- **Application form with attachments**
- **Information relating to the**
  - **ancillary medicinal substance itself**
  - **ancillary medicinal substance as incorporated into the device**addressing the headings below:

### 1) **General information**

A 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. It is useful to include illustrations of the medical device and how the medicinal substance is incorporated, since medicines assessors may not be familiar with the proposed device. Also, explanation about marketing history and any classification discussions can be helpful.

### 2) **Quality Documentation**

#### a) **For the ancillary medicinal substance:**

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 three formats below:

- 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](#) – relevant sections reproduced in **Annex C**).
- in the form of an Active Substance Master File (ASMF), structured according to Module 3.2.S of the CTD-format.
- Certificate of Suitability to the European Pharmacopoeia if available (Ref: [EDQM website](#)) **Note:** Review of the application will be greatly facilitated in the case of medicinal substances supplied with a Ph.Eur. Certificate of Suitability.

**Note 1:** 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

**Note 2:** If an EP monograph exists for a medicinal substance, this should be complied with. Reference to an EP monograph should be supplemented with relevant data on potential impurities arising from the particular route of synthesis, residual solvents, catalysts and data on stability of the active substance to support the specified shelf-life. Such data should be provided whether or not there is an EP monograph.

**Note 3:** For applications with a CEP, it will be expected that the Declaration of Access is suitably completed and analytical data should be provided to demonstrate

that the active substance routinely meets the requirements of the CEP, including any additional tests mentioned. In addition, unless a shelf-life is stated in the CE, stability data should be provided to support a specified shelf-life.

**Note 4:** For active substances of animal origin, the risk of transfer of transmissible spongiform encephalopathies (TSE) to man should be addressed.

**Note 5:** A signed declaration should be provided that the active substance is manufactured in accordance with Good Manufacturing Practice (GMP) requirements for Active substances.

**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 should be stated. To ensure a consistent product is manufactured, it is expected that upper and lower limits will be specified, based on production data and supported by reference to appropriate safety and usefulness studies. If the substance is modified during its incorporation into the device, relevant information should be provided. All other ingredients (excipients) relevant to incorporation of the ancillary medicinal substance into the device, or release of the substance from the device, e.g. stabilisers, polymer excipients should also be described and control specifications provided. Wherever possible, reference to Pharmacopoeial standards should be provided.

- **Description of method of manufacture**

An overall description will already form part of the application to the Notified Body; the section relevant to MHRA 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 and will facilitate review. In some cases, where original validation reports are provided, this can delay assessment due to searching for the data relevant to support consistent incorporation and homogenous distribution of the medicinal substance.

- **Control of starting materials**

The specification for the medicinal substance should be provided, along with exemplar Certificates of Analysis to demonstrate consistent compliance with the specification (preferably three batches). 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. Description of analytical methods and supported by appropriate validation studies, as necessary, should be included.

- **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 testing of the ancillary medicinal substance on an intermediate, rather than finished medical device may be acceptable with appropriate justification and validation that downstream processes do not affect quality, safety or performance of the ancillary medicinal substance.

- **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 final 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 of finished product, 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.

- **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

### **3) Non-clinical documentation**

- **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;

- all substances will require information on the release from the medical device. If, and if relevant, and especially with new active substances with limited data available, 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 ICH guidelines. This should include information on toxicity and biocompatibility of the medical device, and any extractables and leachables, 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) and in a country that is a member of the OECD Mutual Acceptance of Data.

- **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.

#### **4) Clinical evaluation**

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.

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

## 5) Labelling

Details supplied by the manufacturers of the labelling 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 labelling should clearly indicate the presence of the ancillary medicinal substance and the Instructions for Use should contain sufficient information on the contra-indications, precautions for use and potential side-effects 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 based on *in vitro* data only, this should be stated.

Marketing and promotional material regarding the ancillary medicinal substance should be in line with the agreed indications, otherwise re-consideration of the consultation may be recommended, with possible re-classification as a medicinal product.

A copy of IFU (mock-up or text) as well as the labels (mock-up or text) should be submitted.

## Annex B DETAILED SUBMISSION INFORMATION

MHRA no longer accepts paper documentation or physical media (CD/DVDs) for applications or consultations. Submissions should be made via CESP ([Common European Submission Platform](#))

This system is available from the Heads of Medicines Agencies (HMA) and provides a simple and secure mechanism for exchange of information between applicants and regulatory agencies.

The system helps to:

- Provide a secure method of communicating with the Regulatory Agencies
- Reduce the burden for both Industry and Regulators of submitting/handling applications on CD-ROM and DVD

If you are a first time CESP user and wish to setup up an organisation to manage multiple users on the system, register with CESP [here](#).

Once registered you will receive credentials to access the portal to your registered email address.

General CESP training is available to all registered users via CESP's training menu once logged into the system. Training on demand videos are available and you can also sign up to free online weekly live demonstrations. CESP encourage all users to attend training before using the system. View FAQs [here](#).

For Notified Body consultations, please select the following (see also below):

<b>Area:</b>	Medical Devices
<b>Regulatory Activity:</b>	NB Consultations with Medicines CA

For queries or help regarding the CESP submission process, please visit the CESP FAQ page [here](#).

To request confirmation that the submission has been received by MHRA contact [Area4-RENEW-PSUR-PIQ-BROMI-submission-queries@mhra.gov.uk](mailto:Area4-RENEW-PSUR-PIQ-BROMI-submission-queries@mhra.gov.uk).

## New Delivery File

Step 1 Step 2

Company \*  
\_CESP TEST Company

Area \*  
Medical Devices

Regulatory Activity \*  
NB Consultations with Medicines CA

Sub Activity \*  
H001 Not Applicable

Zip File Type \*  
WinZip

Comment  
Test

Next >

### Notified Body Consultation submission format

**NBA 201 Application form and appendices [file name(s) 'm1-form'; 'm1-form appendix 1.1' etc]**

**Information on the drug substance as detailed in Annex A:**

- 1) General information [file name 'm2-2-introduction']
- 2a) Quality documentation relating to the ancillary medicinal substance itself\* [file name 'm2-3-s drug substance']
- 2b) Quality documentation relating to the ancillary medicinal substance as incorporated into the medical device [file name 'm2-3-p drug product']
- 3) Non-clinical documentation [file name 'm2-4 non-clinical overview']
- 4) Clinical evaluation [file name 'm2-5 clinical overview']
- 5) Labelling [file name 'm1-3-1-label-and-leaflet']

Files for sections 2a), 2b), 3) and 4) should be bookmarked appropriately.

**Appendices** relating to

- Quality [file name(s) 'm2-Quality Appendix 1']
- Non-clinical [file name(s) 'm2-Non clinical']
- Clinical [file name 'm2-clinical']
- Bibliography [file name 'm2-bibliography']
- Miscellaneous (incl. risk analysis if included separately) [file name 'm1-additional']

**Please name the files as indicated in italics**, to ensure correct indexing of the documents. This system is based on the Common Technical Document (CTD) format for Medicinal Product Marketing Authorisation applications.

Summary reports on validation studies are acceptable and preferred – **full reports including raw data are not necessary** unless specifically requested and can cause delays to processing/assessment.

If large attachments are considered necessary, they should preferably be divided into files of < 25 MB and named appropriately for ease of reference e.g. '*m-1-clinical-Clinical Report xyz Vol.1*'.

It is extremely helpful if the individual document filenames comply with the convention outlined above.

It is also helpful if all PDF documents are appropriately bookmarked to ensure that assessors can jump directly to the sections of interest. Only the simplest of PDF documents (e.g. a simple letter responding to an RFI) should be submitted without bookmarks.

Unfortunately, consultations that are not submitted according to these guidelines cannot be processed by the administration team and may be rejected, requiring compliant resubmission.

#### **Active substance (drug) master file (ASMFs)**

All documents should be submitted in PDF format with one PDF file for each document named as below.

For new applications the following documents should be included:

- Covering 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.

Note that the Applicants Part, Restricted Part and Quality Overall Summary should be submitted as a number of individual PDF documents as defined in the relevant sub-sections of the CTD.

NOTE: For ASMFs submitted in conjunction with a Notified Body consultation only (i.e. not already authorised for a medicinal product) the data will be reviewed in the context of the medical device only and will not be considered to be approved for use in medicinal products.

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.

**Withdrawn**

**Archive copy for information only**

## Annex C

### NOTICE TO APPLICANTS, MODULE 3 (REF. "[THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN UNION](#)", VOLUME 2B) APPLICABLE EXTRACTS

**Note 1:** For a device containing more than one ancillary medicinal substance, the information requested for part "S" should be provided in its entirety for each drug substance

**Note 2:** Less detail is required for existing, well-known substances than for New Chemical Entities (NCEs) as referred to below. Nevertheless, each heading should be addressed.

**Note 3:** Reference guidelines: See EMA [Guidelines](#) website.

#### 3.2 Body of Data

##### 3.2.S DRUG SUBSTANCE 1 (NAME, MANUFACTURER)

##### 3.2.S.1 General Information

###### 3.2.S.1.1 Nomenclature

Information on the nomenclature of the drug substance should be provided. For example:

- Recommended International Non-proprietary Name (INN);
- Compendial name (e.g. European Pharmacopoeia) if relevant;
- Chemical name(s);
- Company or laboratory code;
- Other non-proprietary name(s), e.g., national name, United States Adopted Name (USAN), Japanese Accepted Name (JAN); British Approved Name (BAN), and
- Chemical Abstracts Service (CAS) registry number.

###### 3.2.S.1.2 Structure

###### New Chemical Entity (NCE):

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

###### 3.2.S.1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the drug substance.

##### 3.2.S.2 Manufacture

###### 3.2.S.2.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

###### 3.2.S.2.2 Description of Manufacturing Process and Process Controls

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information

should be provided to adequately describe the manufacturing process and process controls. For example:

**NCE:**

A flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g., temperature, pressure, pH, time).

Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in 3.2.S.2.5.

### **3.2.S.2.3 Control of Materials**

Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterisation.

### **3.2.S.2.4 Controls of Critical Steps and Intermediates**

**Critical Steps:** Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

**Intermediates:** Information on the quality and control of intermediates isolated during the process should be provided.

### **3.2.S.2.5 Process Validation and/or Evaluation**

Process validation and/or evaluation studies for aseptic processing and sterilisation should be included.

### **3.2.S.2.6 Manufacturing Process Development**

**NCE:**

A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, clinical, scale-up, pilot, and, if available, production scale batches.

Reference should be made to the drug substance data provided in section 3.2.S.4.4.

## **3.2.S.3 Characterisation**

### **3.2.S.3.1 Elucidation of Structure and other Characteristics**

**NCE:**

Confirmation of structure based on e.g., synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should

also be included.

### **3.2.S.3.2 Impurities**

Information on impurities should be provided.

## **3.2.S.4 Control of Drug Substance**

### **3.2.S.4.1 Specification**

The specification for the drug substance should be provided.

### **3.2.S.4.2 Analytical Procedures**

The analytical procedures used for testing the drug substance should be provided.

### **3.2.S.4.3 Validation of Analytical Procedures**

Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided.

### **3.2.S.4.4 Batch Analyses**

Description of batches and results of batch analyses should be provided.

### **3.2.S.4.5 Justification of Specification**

Justification for the drug substance specification should be provided.

## **3.2.S.5 Reference Standards or Materials**

Information on the reference standards or reference materials used for testing of the drug substance should be provided.

## **3.2.S.6 Container Closure System**

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided. The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.

## **3.2.S.7 Stability**

### **3.2.S.7.1 Stability Summary and Conclusions**

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

### **3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment**

The post-approval stability protocol and stability commitment should be provided.



### **3.2.S.7.3 Stability Data**

Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative.

Information on the analytical procedures used to generate the data and validation of these procedures should be included.

**Withdrawn**

**Archive copy for information only**

**MEDICINES AND HEALTH PRODUCTS REGULATORY AGENCY**  
Drug-Device Consultation Form

<b>1. Name of product</b>	<b>2. Consultation reference number</b> NB            / <i>(Insert number allocated by MHRA – see section 2.4 of Guidance for Notified Bodies)</i>
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<b>3. Name of the ancillary medicinal substance</b> <i>(one name, preferably rINN or Ph.Eur. name)</i>	<b>4. Previous consultation reference number(s)</b> <i>(Insert MHRA reference numbers of any previous consultations in respect of this device with ancillary medicinal substance)</i>
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<b>5. Fee category for this product</b> <i>(Tick as appropriate)</i> No fee (current PL held)                    [    ] Known substance/ known source        [    ] Known substance/ new* source        [    ] New active substance                      [    ] * Not previously reviewed by MHRA	<b>6. This consultation is the</b> first    [    ] second    [    ] subsequent                                     [    ] <b>for this product</b> <i>(Tick as appropriate)</i>	<b>7. Fee payable to MHRA</b> £ <i>(Insert appropriate fee - <a href="#">MHRA fees</a>)</i>
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<b>8. Notified Body</b> <i>(Insert name, address, e-mail, telephone, fax and name of contact person)</i>	<b>9. Device manufacturer seeking device approval</b> <i>(Insert name and address and contact details for person authorised for communication throughout the consultation)</i>
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<b>10. Manufacturer of device (if different from section 9)</b> <i>(Insert name and address)</i>	<b>11. Manufacturer(s) of intermediate products</b> <i>(Insert name, address and telephone numbers) attach flow chart.</i>
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<b>12. Manufacturer(s) of the active substance</b> <i>(Insert name, address and telephone numbers of each supplier)</i>	<b>13. Pharmacotherapeutic classification</b> <i>(Use ATC classification system, : <a href="#">WHO ATC weblink</a>)</i>
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<b>14. Active Substance Master File</b> <i>(Insert reference if applicable)</i>	<b>15. Ph Eur Certificate of Suitability</b> <i>(Insert reference number if applicable)</i>
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<b>16. Description of device with ancillary medicinal substance</b> <i>(Enter amount of active substance in each device, also concentration per unit volume/area as appropriate, description of device, packaging components, shelf-life details and recommended storage conditions. A single form may be used for a group of products where the active substance is qualitatively and quantitatively identical.)</i>  <b>Description of device and intended purpose</b>  			
Ancillary medicinal substance(s)	Quantity	Unit	Reference / Monograph standards e.g. PhEur
1.			
2.			
3.			
<b>Packaging components and pack size</b>  			
<b>Proposed Shelf-life (unopened)</b>		<b>Proposed Shelf-life (in use)</b>	
<b>Recommended storage conditions</b>  			

In the case of new Consultations, please complete section 17. For Supplementary Consultations, please complete section 18.

**17. Intended purpose of the ancillary medicinal substance as incorporated into the device with scientific explanation that the action of the medicinal substance is only ancillary to that of the device in line with MEDDEV guidance**  
*(attach Notified Body report on the usefulness of the ancillary medicinal substance)*

**18. Supplementary Consultation:**  
 Brief description of the proposed change and data provided in support of the change

**19. Checklist of data submitted**

NBA 201 application form				
Body of data according to MEDDEV 1) – 5), formatted in accordance with Annex B instructions				
Attachments (see below for applicable documents)				

Signature \_\_\_\_\_ Date \_\_\_\_\_

Capacity in which signed \_\_\_\_\_

**20. Attachments (where appropriate)**

- 1.1 Notified Body report on usefulness of the ancillary medicinal substance
- 1.2 Letter of authorisation for communication on behalf of the notified body, i.e. where direct communication with manufacturer or consultant is authorised (in these cases, NBs will be copied in to email communication)
- 1.3 Flow chart indicating the different sites involved in the manufacturing process of the ancillary medicinal substance as incorporated into the device
- 1.4 Good Manufacturing Practice inspection certificate /ISO 13485/ ISO 9001 certificates for manufacturing sites

- 1.5 Letter(s) of access to Active Substance Master Files or copy of Ph. Eur. Certificate of Suitability duly completed with authorisation, with written confirmation from the manufacturer of the ancillary medicinal substance to inform the applicant in case of modification of the manufacturing process or specifications
- 1.6 Declaration of compliance with principles of GMP for active substances ref Article 47 of Directive 2001/83/EC as amended
- 1.7 TSE Statement and supporting documentation where the ancillary medicinal substance is manufactured using materials of animal origin

**NOTE: Please provide these with prefix 'm1-Attachment 1.2' etc. If an attachment is not provided, a suitable rationale will be expected.**

**Withdrawn**

**Archive copy for information only**

**MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY**

**Notified Body decision  
Report to MHRA**

<b>1. Name of product</b>  	<b>2. Consultation reference number</b> NB       /  <i>(Insert number allocated by MHRA)</i>
<b>3. Notified Body</b> <i>(Insert name, address, telephone, fax and e-mail address of contact person)</i>	<b>4. Applicant seeking device approval</b> <i>(Insert name and address)</i>
<b>5. Decision of Notified Body</b>       <i>(Please comment as appropriate)</i>	
<b>Signature</b> _____ <b>Date</b> _____ <b>Capacity in which signed</b> _____	

**Please complete all boxes and return form via e-mail to:**  
**Pratibha Madan**  
**Service Co-ordinator (NB consultation applications)**  
**MHRA**  
**151 Buckingham Palace road, London**

[pratibha.madan@mhra.gov.uk](mailto:pratibha.madan@mhra.gov.uk)