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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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 applications for drug-device combination products. 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 (January 2010) but may be further updated in light of amendments to the EC Medical Devices Directive and European guidelines relating to Medicines. Please refer to the current version of Guidance Note 31 available on the MHRA 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

These products are 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.

*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’ is used in this document to represent such a competent body within the meaning of Directive 2001/83/EC, 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.
By means of the consultation process the Competent Authority may make available relevant information concerning risks related to the use of the substance (e.g. resulting from pharmacovigilance). The Competent Authority will inform the Notified Body of its opinion, taking into account the manufacturing process and the data related to usefulness of incorporation of the ancillary medicinal substance.

The Notified Body should take into account the opinion of the Competent Authority 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 according to the format set out in Section 2.4 of this Guidance note will facilitate the 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 Agency for the Evaluation of Medicinal Products (EMEA) may be consulted, where the substance involved has been included in a medicinal product which has been authorised through the Centralised Procedure. The EMEA 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

In order 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.

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
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 and available on the MHRA website (see section on application forms).

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 Submissions Centre: Submissions.Centre@mhra.gsi.gov.uk (State in the subject line ‘NB Consultation number allocation’). Insert this reference number on the consultation form and include it 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 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.)

Please note that an invoice will be generated when the consultation Case Folder is set up on the MHRA Information Management System (Sentinel). The Notified Body should arrange for payment to be made to MHRA. The invoice may be paid directly by the device manufacturer providing that 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. The fees should preferably be paid by automated transfer and should be paid within 30 days of receipt of the invoice.

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

The consultation form and all accompanying information should be in English and should be submitted electronically on Compact Disk to:

Information Processing Unit
Area 5
Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road
Vicotria
London
SW1W 9SZ

All disks should be clearly identified with the name of the Notified Body and the reference number.

The disk should include the following:

- 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

Please see Annex B for detailed submission instructions. This guidance has been adapted from medicinal product Marketing Authorisations applications as published in Special MAIL 5 and supplements. If you have any specific queries on submission formatting, please contact the Submissions Centre for advice. Submissions.Centre@mhra.gsi.gov.uk

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 the MHRA via the Regulatory Information Service (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 information management system - Sentinel.

The data will then be accessed by a Pharmaceutical Assessor to review the Quality aspects (data on active substance alone and section 2b); a Pre-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 risk / benefit ratio 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 medicinal substance from a known source the report will normally be available within 90 days of receipt. For other cases the target time for assessment is 120 days from receipt. In all cases, the overall assessment time should not exceed the 210 day limit 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 are able to verify the quality, safety and usefulness 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 with a preliminary report on one or more parts of the consultation. If however, the additional information required is deemed to necessitate major further work, the consultation will receive a negative opinion and recommendations will be given to explain the additional work that would be needed to gain approval. In this case, a supplementary consultation should 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 90 or 120 day net review time (i.e. whilst all data requested is with MHRA). In order 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 on CD to the Submissions Centre as detailed above, with the NB reference number stated on the CD as well as covering letter, with clear reference to the fact that the disk contains responses.

3.4 Informing the MHRA of the decision of the Notified Body

The Notified Body is required to give due consideration to the MHRA’s report when making its decision, and then to communicate its decision to the MHRA using Form NB 202 (see attached). 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 have an effect on 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 in order to facilitate linking of Case Folders within the MHRA. The target time for assessment of these applications is 60 days from receipt, but will vary depending on the complexity of the consultation.
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;
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.

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 (EMEA) website are included below, which may change in future. Please consult the EMEA 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
  o ancillary medicinal substance itself
  o 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.

2) Quality Documentation

a) For the ancillary medicinal substance raw material:

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: EDOM website) Note: Review of the application will be greatly facilitated in the case of medicinal substances supplied with a PhEur 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: 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 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.

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. 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 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.

Guidelines: [Process Validation CPMP/QWP/848/96; Annex II: Process Validation - Non-Standard Processes CPMP/QWP/2054/03; Manufacture of the Finished Dosage Form CPMP/QWP/486/95](#)

- **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 PhEur specification, but compliance with the PhEur 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](#)’ 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;
  - 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 (hyperlink/reference). 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.

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.


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 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.
Annex B

DETAILED SUBMISSION INFORMATION WITH FREQUENTLY ASKED QUESTIONS

This detailed guidance is adapted from MHRA Special MAIL 5 and Special MAIL 5 Frequently Asked Questions and is designed to supplement information included in MHRA Guidance note 31.

MHRA no longer accepts paper documentation for applications or consultations. Instead, an electronic information management system 'Sentinel' is used which has been designed to support new market authorisation (MA) applications and variations according to the eCTD (electronic Common Technical Document) format.

It is acknowledged that the data requirements for Notified Body Consultations with MHRA on ancillary medicinal substances used in devices are generally not as comprehensive and some of the advice published in Special MAIL 5 is not relevant. Therefore, the information below is intended to aid preparation of suitable documentation that will be compatible with the MHRA Sentinel system and improve efficiency of the Consultation procedure.

Sending submissions to MHRA

The following disk formats are acceptable:
• CD-ROM
• CD-R
• CD-RW
• DVD-R
• DVD-RW
The following formats are not acceptable:
• DVD-ROM
• DVD-RAM

All files submitted on disk must be in PDF (e.g. Adobe Acrobat) format

Guidance on preparing PDF documents

As far as possible all data should originate from electronic files rather than from scanned data.

In order to process PDF documents efficiently MHRA assessors need to be able to easily navigate and manipulate the document (e.g. copy and pasting sections of the document or splitting a large document into multiple smaller documents). To facilitate this process the following points should be noted when creating PDF documents:

• All PDF documents should be created directly from e.g. Word or undergo optical character recognition (OCR – e.g. using “paper Capture” in Adobe Acrobat) at the time of creation. PDF document scanned images should not be provided as it is not possible to cut-and-paste data in this format.
• PDF documents should not be file protected as this prevents the printing and manipulation of the document.
• Fonts that are not supported by Microsoft Word should not be used on PDF documents.
• All PDF documents should be 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.

Notified Body Consultation submission format

All documents should be submitted in PDF format with one PDF file for each document (preferably < 25MB each).

• 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.

* If supplying section 2a) as an Active Substance Master File, this may be submitted on a separate disk provided directly by the Active Substance Manufacturer (see below for submission information for ASMFs) – please make this clear in the cover letter and ensure that the NB Consultation reference number is clearly stated on documentation provided by the third party.

Summary reports on validation studies are acceptable – full reports including raw data are not necessary unless specifically requested.

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’.

The disk itself should be submitted as a flat file with no directory structure. It is essential that the individual document filenames comply with the convention outlined above.
Clear labelling of documents in this way will greatly improve the efficiency of the review process. 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.

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.

**Responses to requests for information (RFIs) sent by the MHRA**

Responses, and any supporting documentation, should be submitted in PDF format.

The NB Consultation number and indication that it is a response disk should be clearly stated on the CD and covering letter. Separate files for Quality, Non-clinical and Clinical responses would be helpful.

**Posting disks**

The address to be used for sending disks to the MHRA will depend on the type of submission. All disks for NB Consultations should be sent to the address below ensuring the area number is quoted, and not to individual assessors.

Information Processing Unit  
Area 5  
Medicines & Healthcare products Regulatory Agency  
151 Buckingham Palace Road  
Victoria  
LONDON  
SW1W 9SZ

**Labelling disks**

Each disk should be labelled in the following manner:
• NB Consultation number.
• Description of contents (e.g. Initial Consultation, Response to RFI)
• Company name.
• Date sent.

Example label:
NB 99000/1234
Supplementary Consultation
(Previous Consultation no. NB99000/1233)
AnyCompany plc
11 July 2009

The disk may be printed or labelled with an adhesive paper label or a permanent marker pen. Please ensure the disk itself is labelled as the disk and case may become separated.

For any queries regarding submission procedures and formatting, please contact the Submissions team Submissions_Centre@mhra.gsi.gov.uk for advice stating in the subject line: 'REQ: NB Consultation submission advice'
FREQUENTLY ASKED QUESTIONS RELEVANT TO NB CONSULTATIONS.
ADAPTED FROM MHRA SPECIAL MAIL 5 SUPPLEMENT:

Document names and file structures:

Q1. Why do you require the CTD section number to be prefixed to the relevant document name?

A1. All documents are indexed against the CTD structure on Sentinel. Including the CTD section code in the document name allows our staff to quickly identify where the document should be indexed on our system. There is now a facility for Marketing Authorisation Applicants to submit applications in eCTD folder format, but since NB Consultations do not require full CTD submission, this option is not yet available.

Q2. The disk is formatted using a folder structure, do the individual files still have to have the section prefix?

A2. Prior to indexing the submission documents on Sentinel, the folder structure on the disk is collapsed to a flat folder structure. All information on the individual files that can be derived from the folder structure is, therefore, lost. This makes it essential that the CTD section number is prefixed to the individual file names.

Q3. Special MAIL 5 states that "failure to label the files correctly may lead to the submission being rejected". Is there any contact with the validation team and possibility to re-submit prior to rejection?

A3. If a submission is rejected we will make it clear by e-mail the reason for the rejection and ask that you resend the entire submission correctly formatted. Submissions are rejected at an initial screening step where all submissions are checked. No details on the submission will be entered on the Sentinel system and no fee levied. If you feel that the submission has been wrongly rejected, please contact the Submissions Centre to discuss.

It is our intention to enforce the guidance in a reasonable and pragmatic manner. Submissions that do not comply with the guidance in a minor way will not be pedantically rejected if the non-compliance does not significantly affect our ability to efficiently process the data.

However, poor quality submissions lead to significant and unpredictable delays for everyone and will be returned to the applicant. If in doubt, please contact us before sending the submission.

Q4. With regard to appendices of study reports, do we need to create one PDF file that contains all appendixes of the study reports? Can we create this PDF file for each study separately?

A4. We are happy to receive multiple PDF for the appendices. The important requirement in this area is that the individual appendices names are descriptive and, hence, support an assessor in rapidly locating the relevant data. E.g. 'm-2-clinical-Clinical Report xyz Vol.1' or 'm-2-clinical-Clinical Report xyz Appendix1'.

If the section document can be submitted as a single merged PDF of reasonable size (less than 50 pages) we would prefer to receive the data in this format. It is essential that each PDF file is bookmarked to allow easy navigation between sections in the document (see section on bookmarking below).
Bookmarking:

Q1. Are you able to provide us with any guidance on the use of bookmarks in our PDF files?

A1. All documents larger than 50 pages should be bookmarked to section headings (will happen automatically if headed documents are converted from MS Word). Bookmarking to primary headings is sufficient. Short documents should be considered for bookmarking if they are particularly complex and/or require frequent cross referencing within the document. In making this judgement please consider whether bookmarking would help an assessor to work more efficiently.

Q2. How should I submit literature references?

A2. Literature references can be submitted in one of two ways, either “volumised”, for example:
   m1-bibliography-ref-a-m.pdf
   m1-bibliography-ref-n-z.pdf
   With the PDF bookmarked to individual references. Or by individual author, for example:
   m1-bibliography-arthur-2001.pdf
   m1- bibliography-2005.pdf
   Either way should allow an assessor to efficiently locate a study.

References should be provided in either the Vancouver or ChemAbs naming conventions

Q3. Concerning bookmarks and hyperlinks, my understanding is that, due to the MHRA uploading process, all external bookmark and hyperlinks are broken, and are therefore not required or used. Please can you confirm this, as there is additional hyperlinking that could be provided to aid reviewer navigation of our submissions. Currently we provide no hyperlinking in MHRA submissions unless it is required elsewhere. We would consider a degree of hyperlinking to support review if it were utilised.

A3. Bookmarking within a document is preserved when we load documents onto the Sentinel system and we require that documents are bookmarked (see Q1, this section). Due to a technical issue with third party software, hyperlinks are not currently supported within the Sentinel system. However, this issue is still outstanding, but we do still strongly encourage the use of hyperlinking within the submission.

Q4. In converting a submission to the MHRA’s file naming requirements we are aware that the existing hyperlinks in the document will no longer function. Will the submission be accepted?

A4. Yes, we will accept files under these circumstances.

NBA 201 form and Annexes:

Q1. The NBA 201 application form has 6 annexes. How should the files for these be labelled?
A1. They may be merged with the form, or submitted as a separate “m1-annexes.pdf” document. We will also accept individual annex pdfs.

Labelling of submissions, sending in submissions:

Q1. How exactly should we label our CDs? To avoid including a paper covering letter with a CD, what could we include on the label?

A1. Remember to always label the actual disk not the case – the two can become separated.

Please label the disk as indicated in the section ‘Labelling disks’ above. In addition, including a contact e-mail address on the label will help us to quickly contact you if the disk is unreadable.

OCR requirements:

Q1. Why do the MHRA require that all scanned PDF CTD and CTA documents undergo Optical Character Recognition (OCR)?

A1. The MHRA’s Sentinel system provides a fully searchable electronic document store of all MHRA documents and supports fully electronic assessment of submissions. Text-searchable PDFs allow assessors to cut and paste and otherwise manipulate the documents in support of their assessment which speeds up the assessment process.

Crucially the OCR layer added to scanned PDFs also supports text searching within the document and across the entire MHRA document store. This ability to locate any documents on our system allows us to respond efficiently to any public health issues that may arise. As a measure of how important we consider this requirement, over 14 million pages of historical paper data was scanned and loaded onto the Sentinel system prior to “go live” and we ensured that every page underwent OCR.

However, it should be noted that Special MAIL 5 was ambiguous in this regard. It is certainly not a requirement that all of the documents are printed and OCR’d. In fact, wherever possible, we would prefer that the PDF files are created from original electronic source text, by converting the electronic text into a PDF which is searchable and can be manipulated.

Q2. Can I use the OCR system in my scanner? How do I OCR an image using Abode Acrobat?

A2. You should preferably use the OCR facility in Adobe Acrobat (or another suitable piece of software) to OCR files, not any OCR functionality built into your scanning system.

To create a searchable PDF document (in Adobe Acrobat 6.0 Professional)
1. Open up the pdf document produced from scanning a printed document
2. Go to the toolbar and click on ‘Document’
3. Click on ‘Paper Capture’ and a side drop folder will appear
4. Click on ‘Start Capture’
5. A grey screen will appear
6. Click in the circle next to ‘All Pages’
7. Click on ‘Edit’
8. Another screen will appear. Click into the field next to the title ‘PDF Output Style’ and choose ‘Searchable Image (Exact)’ * click ‘OK’
9. Click into the field next to the title ‘Primary OCR Language’ and choose English (UK) click ‘OK’
10. Click on ‘Primary OCR English (UK)’
11. Click on ‘OK’
   *MHRA recommended setting
The process will begin to configure each page.

This can be used on any scanned image PDF produced by you or sent to you - it can be done retrospectively.
A 100% quality check on the resulting OCR by the applicant is not required.

**Q3. There are also certain documents that are provided to us by a third party that arrive in PDF format. It is not known if these documents have been scanned or converted from electronic files.**

A3. If there is any doubt as to whether the PDF has undergone OCR, then the procedure in Q2 (this section, using Adobe Acrobat as an example) should be followed. Third party documents provided in paper format must be scanned into PDF format and undergo OCR.

Please note that you should carry out the OCR prior to merging any documents, as otherwise OCR may not perform correctly. For example in Adobe Acrobat an error concerning “renderable text” occurs if part of the document is already fully electronic text.

We would advise that third parties providing documents that are to be part of a submission are made aware of the requirements of Special MAIL 5. The minimum resolution requirement in Adobe Acrobat to perform OCR is 200dpi.

We would recommend applicants work to a minimum of 300dpi. Higher resolution will produce consequently larger files.

**Q4. Special MAIL 5 stated PDF documents should originate from electronic files rather than scanned documents. I normally submit everything on a CD and would normally submit a scanned signed covering letter and also scanned signature pages of the Application Form. Should I continue? Does the covering letter really need a signature or is this not really necessary?**

A4. The signature page of the application form may be signed for inclusion on the disk, although the MHRA does not require this. Please print, sign, scan and then merge the signature page with the relevant PDF. A separate signature page can be included if merging presents difficulties for applicants.

Signatures are not required in the case of cover letters.
Please note that The MHRA do not currently accept digital signatures.
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:
“Summary of requirements for active substances in part II of the dossier”, including the Certification of Suitability of monographs of the European Pharmacopoeia and Active Substance Master File procedure.
“Chemistry of the New Active Substance” and “Chemistry of Active Substance”
“Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances”

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 Nonproprietary 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.
<table>
<thead>
<tr>
<th><strong>1. Name of product</strong></th>
<th><strong>2. Consultation reference number</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NB / (Insert number allocated by MHRA – see section 2.4 of Guidance for Notified Bodies)</td>
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</table>

<table>
<thead>
<tr>
<th><strong>3. Name of the ancillary medicinal substance</strong> (one name, preferably rINN or PhEur name)</th>
<th><strong>4. Previous consultation reference number(s)</strong> (Insert MHRA reference numbers of any previous consultations in respect of this device with ancillary medicinal substance)</th>
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<thead>
<tr>
<th><strong>5. Fee category for this product</strong> (Tick as appropriate)</th>
<th><strong>6. This consultation is the</strong></th>
<th><strong>7. Fee payable to MHRA</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>No fee (current PL held) [ ]</td>
<td>first [ ]</td>
<td>£ (Insert appropriate fee - MHRA fees)</td>
</tr>
<tr>
<td>Known substance/ known source [ ]</td>
<td>second [ ]</td>
<td></td>
</tr>
<tr>
<td>Known substance/ new* source [ ]</td>
<td>subsequent [ ]</td>
<td></td>
</tr>
<tr>
<td>New active substance [ ]</td>
<td>for this product [ ]</td>
<td></td>
</tr>
<tr>
<td>* Not previously reviewed by MHRA</td>
<td>(Tick as appropriate)</td>
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</tr>
</tbody>
</table>

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<tr>
<th><strong>8. Notified Body</strong> (Insert name, address, e-mail, telephone, fax and name of contact person)</th>
<th><strong>9. Device manufacturer seeking device approval</strong> (Insert name and address and contact details for person authorised for communication throughout the consultation)</th>
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<tr>
<th><strong>10. Manufacturer of device (if different from section 9)</strong> (Insert name and address)</th>
<th><strong>11. Manufacturer(s) of intermediate products</strong> (Insert name, address, telephone and fax numbers of each supplier) attach flow chart.</th>
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</table>

<table>
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<tr>
<th><strong>12. Manufacturer(s) of the active substance</strong> (Insert name, address, telephone and fax numbers of each supplier)</th>
<th><strong>13. Pharmacotherapeutic classification</strong> (Use ATC classification system, [WHO ATC weblink])</th>
</tr>
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<tbody>
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</table>
14. Active Substance Master File  
(Insert reference if applicable)  

15. Ph Eur Certificate of Suitability  
(Insert reference number if applicable)  

16. Description of device with ancillary medicinal substance  
(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.)

**Description of device and intended purpose**

<table>
<thead>
<tr>
<th>Ancillary medicinal substance(s)</th>
<th>Quantity</th>
<th>Unit</th>
<th>Reference / Monograph standards e.g. PhEur</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
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<tr>
<td>2.</td>
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<td></td>
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<tr>
<td>3.</td>
<td></td>
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</tbody>
</table>

**Packaging components and pack size**

<table>
<thead>
<tr>
<th>Proposed Shelf-life (unopened)</th>
<th>Proposed Shelf-life (in use)</th>
<th></th>
</tr>
</thead>
</table>

**Recommended storage conditions**

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

<table>
<thead>
<tr>
<th>NBA 201 application form</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Body of data according to MEDDEV 1) – 5), formatted in accordance with Annex B instructions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attachments (see below for applicable documents)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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
- 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 9001 certificate for manufacturing sites
- 1.5 Letter(s) of access to Active Substance Master Files or copy of Ph. Eur. Certificate of Suitability
1.6 Copy of written confirmation from the manufacturer of the ancillary medicinal substance to inform the applicant in case of modification of the manufacturing process or specifications according to Annex 1 of Directive 2001/83/EC as amended.

1.7 Declaration of compliance with principles of GMP for active substances ref Article 47 of Directive 2001/83/EC as amended

1.8 TSE Statement and supporting documentation where the ancillary medicinal substance is manufactured using materials of animal origin
<table>
<thead>
<tr>
<th>1. Name of product</th>
<th>2. Consultation reference number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NB / (Insert number allocated by MHRA)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Notified Body</th>
<th>4. Applicant seeking device approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Insert name, address, telephone, fax and e-mail address of contact person)</td>
<td>(Insert name and address)</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>5. Decision of Notified Body</th>
<th></th>
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<tbody>
<tr>
<td>(Please comment as appropriate)</td>
<td></td>
</tr>
</tbody>
</table>

Signature ___________________________ Date ___________________________
Capacity in which signed ___________________________

Please complete all boxes and return form via e-mail to:
Elizabeth Baker
Group Manager
Licensing Group 1 and Drug-Device Enquiries
MHRA
Elizabeth.baker@mhra.gsi.gov.uk