**Guidance Notes for Medical Devices**

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## Appendix 1: Guidance notes on medical devices incorporating tissues of animal origin

The following additional information should be provided as part of the clinical investigation submission.

• A clear justified statement on the decision to use animal tissues or derivatives, the expected clinical benefit, the evaluation of similar materials of animal origin and other synthetic alternatives that achieve the desired product characteristics and intended purpose.

• An overview and assessment of the key elements adopted in the risk management to minimise the risk of infection including:

1. The availability of suitable alternatives
2. The selection procedures and systems for sourcing the tissue/

derivative

1. The details of the production processes and animals used
2. The source country including the assessment of geographical

risk

1. The nature of the starting materials
2. The systems for inactivation or removal of transmissible agents
3. The quantity of animal starting tissues or derivatives required to

produce one unit of medical device

1. The tissues or derivatives of animal origin coming into contact

with the patients and users, and the route of application

1. The practices of post market surveillance system including

gathering and assessment of new information of the potential

risks arising from the use of the end product.

## Appendix 2: Guidance Notes on Clinical Investigations of Active Devices

This guidance should be read in conjunction with Annexes 2, 3 and 5 of the Clinical investigations of medical devices – guidance for manufacturers and the MHRA’s guidance document [Biological safety assessment from](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/820465/biological_safety_assessment.pdf)

The following information must be provided as part of the clinical investigation submission to support claims of compliance with the essential requirements of Medical Devices legislation.

**2.1 General**

1. Essential Requirements Checklist detailing how these requirements have been addressed, including references to harmonised standards as appropriate.

NB: The application of harmonised standards is voluntary, and it is acceptable to choose alternative methods of demonstrating compliance with the Essential Requirements. For example, compliance with international, national or in-house standards. This should be supported by a risk benefit analysis.

1. Documentary evidence supporting compliance with any of the standards referenced. This may include certification by an independent body, or test house. Alternatively, self-certification is acceptable, providing this is supported with evidence of design input and subsequent in-house verification.
2. For those applicants choosing self-certification against EN 60601-1 (which includes protection against electric shock hazards, mechanical hazards, fault conditions, constructional requirements, etc) a checklist for that standard, or equivalent, should be provided. This should be completed and signed by a competent engineer. Where clauses are considered not applicable, a justification should be given. Where measurements of leakage currents are made, the values should be recorded.
3. When the medical device is to be used with other devices as part of a system, e.g. connection to laptop computers, etc an additional EN 60601-1-1 checklist or equivalent covering the whole system under investigation should also be provided.
4. **Specialist technologies including infra-red, laser, microwave, MRI, RF ultrasound, ultraviolet, X-ray etc -** Details of how this technology has been incorporated in the design and what steps have been taken to assure the safe application in the device. Information pertaining to output power, justification of safety limits used and reference to appropriate standards should be included, e.g. the relevant part 2 of the EN 60601 series.

**2.2 Active Implants**

1. A summary of the Failure Mode, Effects [and Criticality] Analysis (FMEA/FMECA).
2. The results of animal studies.
3. Performance statistics and adverse incident data of earlier model, when device is the next generation of an earlier design.

**2.3 Software and programmable devices**

For medical devices that include a software component (either stand-alone software or software incorporated into a medical device) the following should be addressed in the notification: The Clinical Investigation Application form on IRAS has been designed to assist manufacturers in setting out the information required by the MHRA as a basis of assessment of software. Please provide copies of all documents referenced in the answers given to the software questions in the Clinical Investigation Application form. Please provide documentation to demonstrate that the software has been developed in accordance with its safety classification. At a minimum the following is necessary: • Software Development Plan • Risk Management Plan and Report – specifically including the software hazard analysis. • Software Configuration Management Plan • Software System Requirements Specification • Software System Verification Plan and Report • Documented Software Problem Resolution Process. • Evidence of review of completeness for software release For stand-alone software, please ensure the whole system is considered and hazards caused by the platform/hardware the software is run on are addressed.

Guidance on Medical device and stand alone software can be found on this link on [Guidance on Medical device](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/717865/Software_flow_chart_Ed_1-05.pdf) website.

**Appendix 3 - Medical devices: conformity assessment and the CE mark**

A notified body is an organisation that has been designated by an EU member state (the designating authority) to assess whether manufacturers and their medical devices meet the requirements set out in legislation.

The Medicines and Healthcare products Regulatory Agency (MHRA) is the designating and competent authority in the UK.

Manufacturers can apply to any notified body in the EU and once they have the necessary certification their products can be sold anywhere in the EU. Following an appropriate assessment, the notified body will issue relevant certification allowing manufacturers to put CE-marks on their products and put them on the market in the EU.

Information on any medicine or human blood derivative incorporated into the device

Additional information required with regard to the medicinal substance and/or the human blood derivative: • Intended purpose of the inclusion of the medicinal substance in the context of the device and the risk analysis. • Source, marketing authorisation (where applicable) and the quantity/ dosage of the medicinal substance, incorporated into the device. • Method of manufacture (solvents/reagents used in processing, residuals). • Qualitative and quantitative tests carried out on the medicinal substance in the device. • Stability data in relation to the expected shelf-life/ lifetime of the device. Patient information regarding storage of the device should be included. • Clinical documentation (clinical data demonstrating the usefulness of the medicinal substance). Additional information required with regard to the medicinal substance only: • Control of the medicinal substance - medicinal substance specifications e.g. summary of the European Drug Master File, EDQM Certificate of Suitability, reference to European Pharmacopoeia or national monograph of a European Member State. - Manufacturers may wish to cross-reference a granted Clinical Trial Authorisation (CTA). - Please refer to ‘The rules governing Medical Products in the European Community’ volume III, Addendum II. • Toxicological profile (summary of results of toxicity testing / biological compatibility). - This should include the effect on reproductivity, embryo/fetal and perinatal toxicity and the mutagenic / carcinogenic potential of the medicinal substance. • Pharmacodynamics of the medicinal substance in relation to the device. • Pharmacokinetic characteristics (local/ systemic exposure patterns, duration and maximum exposure and the maximum plasma concentration peak taking into account individual variability). - active substances should address the release of the substance from the device, its subsequent distribution and elimination. MHRA Guidance on legislation Clinical investigations of medical devices 13/13 • Local tolerance (particularly where the route of exposure is different to the conventional application) e.g. the results of EN/ISO 10993 testing, or a review of scientific literature. Additional information required with regard to the human blood derivative only: • Control of the human blood derivative - control of plasma source e.g. summary of the European Plasma Master File, - production of the blood derivative - Manufacturers may wish to cross-reference a granted Clinical Trial Authorisation (CTA) or marketing authorisation for a medicinal product. • Pharmacodynamics of the human blood derivative in relation to the device.

## 3.1 Role of the notified body

## A notified body’s tasks will vary depending on the classification of the products concerned and the conformity assessment route a manufacturer has chosen. The conformity assessment procedures can be found in the annexes of each of the 3 pieces of legislation.

Typical activities that can be undertaken by a notified body include:

* full quality assurance: the notified body will carry out an assessment of the manufacturer’s quality system, including design; they will sample across the range of products and processes to ensure that the requirements are being met
* examination of the design: the notified body will assess the full design dossier relating to each type of product to ensure that they meet the requirements
* type examination: the notified body will assess the full technical information relating to each type of product and carry out appropriate testing of a representative sample of production to ensure that it meets the requirements
* verification: the notified body will either test every unit or every batch of product to ensure that they are meeting the requirements before the manufacturer can place them onto the market
* production and product quality assurance: the notified body will carry out an assessment of either the manufacturer’s quality system covering production and inspection (production QA) or final inspection (product QA); they will sample across the range of products to ensure that relevant technical files are available as well as ensuring that the relevant processes being undertaken meet the requirements
* conduct unannounced audits of manufacturers - it’s now mandatory for notified bodies to conduct unannounced audits of manufacturers according to [Annex III of the Commission Recommendation (2013/473/EU) of 24 September 2013](http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:253:0027:0035:EN:PDF)

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