



**IRISH MEDICINES  
BOARD**

## **GUIDANCE NOTE 5**

**Guidance Notes for Manufacturers on Clinical Investigations  
carried out in Ireland**

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## 1. INTRODUCTION

The purpose of this Guidance Note is to outline the requirements in relation to clinical investigations and to provide guidance on how to fill in the application form for clinical investigations to the IMB.

This Guidance Note does not purport to be the definite interpretation of the law and/or regulations and is for guidance purposes only. Manufacturers are advised to consult the relevant legislation relating to medical devices.

Information and assistance can be obtained from the IMB and the telephone number and address are included in this document.

## 2. BACKGROUND

A series of four Directives regulate the safety and marketing of medical devices throughout the European Community. They are as follows:

**Directive 90/385/EEC concerning Active Implantable Medical Devices (AIMDD) and S.I. No. 253 of 1994 European Communities (Active Implantable Medical Devices) Regulations 1994 which became mandatory on 1<sup>st</sup> January, 1995.**

This Directive covers all powered medical devices implanted and left in the human body, such as, pacemakers, implantable defibrillators, implantable infusion pumps, cochlear implants and implantable neuromuscular stimulators. This directive also includes implanted passive parts of active devices like pacemaker leads and adaptors, and external parts that are an essential part of the system.

**Directive 93/42/EEC concerning General Medical Devices (MDD) and S.I. No. 252 of 1994 European communities (Medical Devices) Regulations which became mandatory on 14<sup>th</sup> June 1998.**

This Directive covers most other medical devices over a wide range including simple bandages, orthopaedic implants and high technology radiology equipment.

**Directive 98/79/EC concerning *In-vitro* Diagnostic Medical Devices (IVD's) and S.I. No. 304 of 2001 European Communities (*in-vitro* diagnostic Medical Devices) Regulations**

This Directive covers any medical device, reagent, reagent product, kit instrument, apparatus or system which is intended to be used for the *in-vitro* examination of substances derived from the human body, such as blood grouping reagents, pregnancy testing kits and hepatitis kits.

***There is no clinical investigation system for in-vitro diagnostic medical devices. However performance evaluation may be carried out.***

**Directive 2000/70/EC amending council Directive 93/42/EEC as regards medical devices incorporating stable derivatives of human**

### **3. CLINICAL INVESTIGATION OR EVALUATION REQUIREMENTS**

#### **blood or human plasma.**

This Directive covers amending council Directive 93/42/EEC to include in its scope devices incorporating, as an integral part substances derived from the human blood or plasma. However, medical devices incorporating other substances derived from the human tissue remain excluded from the scope of this Directive.

The Directives quoted above list the essential requirements that must be met before any device can be placed on the market or put into service.

They also specify the requirements for clinical investigations. The Directives are intended to ensure the safety and performance of medical devices and to prohibit the marketing of devices that may compromise the health and safety of patients, users.

The principles of clinical investigation of medical devices are set out in the European standard EN540 “ Clinical investigation of Medical Devices for Human Subjects” This is a harmonised standard providing presumption of conformity with Annex VII of the Active Implantable Medical Devices Directive and Annex X of the Medical Devices Directive.

In order to obtain a CE mark for a device a manufacturer must demonstrate that the device complies with the essential requirements of the Directive. Clinical data is required to demonstrate compliance. This can be in one of two forms

- A compilation of relevant published scientific literature and in some cases a critical evaluation of the literature – Clinical Evaluation
- The results and conclusions of a specifically designed Clinical Investigation.

Clinical Investigation or evaluation may be needed for devices that already carry the CE mark when the device is to be used outside the terms of the CE mark.

A clinical investigation of a medical device will probably be required in the following circumstances:

- New Device: Where a new device is to be introduced into clinical practice where components, features and or methods of action, are previously unknown
- Modification of existing device: Where an existing device is modified and the modification might significantly affect the clinical performance and or safety of the device.
- Device containing previously untested materials: If a device contains materials previously untested in humans coming into contact with the human body
- Existing materials in a new location: Where existing materials are applied to a new location in the human body compatibility and

biological safety will need to be considered

- Existing materials for longer duration of use: Where a device incorporates existing materials but the device will be used for a significantly longer period of time
- Where a device is proposed for a new purpose or function.

**References:**

1. Co-ordination of Notified Bodies Medical Devices (NB-MED on Council Directives 90/385/EEC Recommendation NB-MED/2.7/Rec1 Guidance on Clinicals)
2. Co-ordination of Notified Bodies Medical Devices (NB-MED on Council Directives 90/385/EEC and 93/42/EEC Recommendation NB-MED/2.7/Rec3 Evaluation of Clinical data)

Where a clinical investigation is required, the investigation must:

- Be performed on the basis of an appropriate plan with well defined aims and objectives
- Be performed in circumstances similar to that of intended use.
- Make use of procedures appropriate to the device under examination.
- Include sufficient devices and human subjects to reflect the aims of the investigation taking into account the potential risk of the device
- Examine appropriate features involving safety and performance and their effects on patients so that the risk/benefit balance can be satisfactorily addressed.
- Fully record all adverse device events and all serious adverse events and report same to the IMB
- Be performed under the responsibility of one or more medical practitioners
- Include a final report signed by the investigators responsible which must contain a critical evaluation of all the data collected during the investigation with appropriate conclusions

The legal requirements and the ethical considerations relating to clinical investigations are set out in schedule 6 of S.I. No. 253 of 1994 European Communities Active Implantable Medical Devices Regulations 1994 and in schedule 10 of the S.I. No. 252 of 1994 European Communities (Medical Devices) Regulations. Reference should also be made to the European standard EN540 Clinical investigation of Medical Devices for human subjects.

For all clinical investigations falling within the scope of the Medical Devices Directive a relevant Local Ethics Committee opinion is required. In the case of multi-centre clinical investigations such opinions must be obtained from each participating centre. Only those centres that have provided the Local Ethics Committee opinion may commence clinical investigation when no objection has been raised by the IMB.

The number of devices to be used in a clinical investigation must be sufficient to demonstrate performance satisfactorily and to reveal significant risks to patients' health and safety. At the same time the

number should not be so great as to place at risk more patients than are necessary at a time when the third party assessment of device related risks have not been carried out by the Notified Body. The number therefore should reflect the aims of the investigation, taking into account the perceived risk of the device.

#### **4. CLINICAL STUDIES**

In certain cases, a clinical study may be initiated which does not require notification to the IMB. The following are exempt from clinical evaluation or investigation and are considered as studies.

- If a healthcare professional carries out clinical research within the professional and ethical use it does not need to be reported provided it is not for commercial use and serves for research purposes only.
- If a device is manufactured in-house by a clinician for hospital use with no intention to commercialise it then it is classified as a study.
- If additional studies are carried out on a CE marked product for marketing or regulatory reasons (i.e. Regulatory Bodies outside EU) they are classified as studies. For example if an Irish centre is used in support of an FDA application and device remains within the terms of the CE marking then a letter purely for information purposes will suffice.

#### **5. MAKING AN APPLICATION**

Before a device intended for clinical investigation is made available for use the manufacturer of the device must give 60 days notice to the IMB of the intention to make available for clinical investigation the device in question. If within that 60-day period the IMB does not give written refusal to proceed with the clinical investigation the manufacturer may proceed.

An application for assessment of a proposed clinical investigation must be made on form DSF-3-02-01/1 Clinical investigation Application Form.

The relevant fee should be included. All applications (including the supporting data) must be in English and four copies must be provided. All applications must contain a statement of compliance to the Essential Requirements with regard to the aspects of the device that are to be investigated.

#### **6. INSTRUCTIONS ON HOW TO FILL IN THE APPLICATION FORM**

The application form is divided into four sections as follows

- Administration details
- Device information
- Documentation to be attached
- Signed statement

**A. Administrative details**

1. Date of submission  
This is the date the application was made to the IMB
2. First or resubmission  
Fill in the word “first” or the word “resubmission”
3. If resubmission the previous submission date should be stated and the reference number allocated to the application at that time.
4. Is this part of a multi-centre clinical investigation? If so, enter the details of other centres.  
If it is a multi-centre investigation the name and address of the other centres should be filled in this section.
- 5/6. The manufacturers name, address telephone, fax number and email, site where manufacture of the device takes place.
- 7/8. If the manufacturer is not based in Europe the name, address telephone fax and e-mail address of the authorized representative.
9. Enter details of notified body approval of quality system or process at the site referred to in 5 above. Notified Body details including their unique identification number should be filled in here.
10. Fee payable to the IMB  
This can be found in the IMB guide to fees for medical devices.
11. Number of copies of supporting documentation.  
A minimum of four copies of the application should be supplied

**B. Device information**

12. Name of the device  
This is the trade name used for the device
13. Nomenclature or generic name of the device

The Global Medical Device Nomenclature System (GMDNS) is an international standardised, controlled nomenclature for medical devices and materials, clinical laboratory equipment and *in-vitro* diagnostics, disposables and supplies, selected hospital furniture, casework, and systems and instruments used to test clinical equipment. The Global Medical Device Nomenclature System has been adopted for use by the European Union as standard vocabulary for medical devices in support of the Medical Devices Directive. It is an internationally accepted nomenclature developed by members of Global Harmonisation Task Force, Study Group 1 in conjunction with standards bodies.

14. The device class  
This is the known or proposed classification for the device for clinical investigation.
15. The start and completion date of the clinical investigation
16. The contact name and address of the person responsible for the application.
17. The principle clinical investigator
18.  
(i),(ii) Other clinical investigators involved in the conduct of the study

**C. Documentation to be attached**

The supporting data must be paginated for ease of review at the IMB. The page reference must be clearly indicated in the boxes provided.

19. A copy of the opinion of the local ethics committee  
See section 3 “requirements” for further detail.
20. Copy of the informed consent
21. Data allowing identification of the device in question which included the generic name, model name and model number of the device
22. A general description of the product
23. The investigation plan in particular the purpose, scientific technical or medical grounds scope and number of devices concerned
24. Criteria for patient selection
25. Number of patients in clinical investigation

**Please note that for points 26 – 29, the details should be kept available for the IMB on request**

26. Design drawings, methods of manufacture envisaged, in particular as regards sterilization and diagrams of components subassemblies circuits etc.
27. The descriptions and explanations necessary to understand the above mentioned drawings and the operation of the product.
28. The results of risk analysis
29. The results of the design calculations and the of the inspections

and technical tests carried out

30. Summary of any experience with any similar device manufactured including length of time on the market and a review of performance related complaints
31. Details of new or previously untested feature of the device including where applicable, functions and principles of operation.
32. Photograph of the device.

#### **D. Signed statement**

All applications must contain a statement, firstly that the device in question conforms to the Essential Requirements with regard to those aspects of the device that are to be investigated.

In addition the applicant must undertake to keep available all documentation listed under Annex 6 of the S.I. No. 253 of 1994 European Communities (Active Implantable Medical Devices) Regulations, 1994 and Annex 10 of S.I. No. 252 of 1994 European Communities (Medical Devices) Regulations, 1994 for review by the Competent Authority for a five-year period.

## **7. PROCESS FOR REVIEW AT THE IMB**

On receipt of the clinical investigation application the IMB will validate the application and if acceptable the manufacturer is notified. At that time a reference number is assigned to the application that should be quoted on all future correspondence with the IMB. The commencement of the 60-day period in which the Competent Authority may refuse permission to start the clinical investigation commences at the date stated on this letter.

The clinical investigation then undergoes a preliminary review to determine if external experts are required to assist with the review. If external experts are used they will have signed a confidentiality agreement with the IMB that incorporates a declaration of conflict of interest. All external experts will be required to confirm destruction or return all submitted documentation issued to the IMB post review. A detailed review of the application is completed by day 30 and if further information is required by the IMB the manufacturer is contacted to provide this data. A response should be submitted by the manufacturer to the IMB by day 44. This additional data is then reviewed by the IMB expert team by day 49 and a final report is prepared. An internal meeting is convened by day 55 with all relevant experts involved in the assessment of the application. If after consideration of all the data provided by the manufacturer the IMB considers that there are no grounds relating to health and safety whereby the clinical investigation should not proceed, the IMB will notify the applicant of the decision by day 60.

## **8. GROUNDS FOR OBJECTION**

If the IMB in discharging its function is of the opinion that the device in question should not be made available for the purposes of clinical investigation until such time as queries raised are satisfactorily replied to, the IMB may suspend the 60 day clock on the basis of a concern for the health and safety of patients, users or others of the device. When a response has been received from the manufacturer or the authorised representative the clock will restart and continue.

It must be pointed out that if a response is not provided to the issues raised by the IMB within the timeframe it may result in rejection of the application due to incomplete data being available to support the application.

The Manufacturer or the Authorised Representative must prepare a written report on completion of the clinical investigation. This report must be kept at the disposal of the IMB. The IMB, may request a copy of the final written report of a clinical investigation. It is likely that a copy would be requested under certain circumstances e.g. where a serious adverse incident has occurred with a CE marked device which has undergone clinical investigation authorised by the IMB.

If after consideration of all the evidence provided by a manufacturer that there are grounds relating to health and safety whereby the clinical investigation should not proceed, the IMB will notify the applicant of the decision. Reasons for the objection will be clearly stated in the letter of objection.

Unjustifiable risks to public health or safety may exist:

- Where there are reasonable grounds to suspect that a device does not satisfy relevant Essential Requirements; or
- Where there are reasonable grounds to suspect that the clinical investigation is not subject to controls equivalent to the requirements of the relevant European Standard (EN540);or
- Where there exists professional opinion on the proposed clinical investigation that the risk benefit analysis given by or on behalf of the manufacturer is inaccurate and that, were the investigation to take place, there would be a significant probability of serious illness, injury or death to the patient or user; or
- Where insufficient information has been submitted to enable a proper assessment of the safety aspects of the proposed clinical investigation to be made; or
- Where the manufacturer has delivered any documentation necessary for the assessment so late that insufficient time remains within the sixty-day notification period for the IMB to complete the assessment.

The applicant may re submit with revised documentation providing the reason for refusal of the original application is addressed with the accompanying appropriate fee.

**9. CHANGES OR MODIFICATIONS IN PROTOCOL**

All changes in protocol whether relating to the device, aspects of the clinical investigation plan, investigator's of investigation institutions must be notified to the Competent Authority and not implemented until a letter of agreement has been obtained from the Competent Authority.

The Competent Authority retains the right to request a new clinical investigation notification if the modification to the protocol is thought to increase the risk to either the patient or the user, or if the Competent Authority consider that the changes proposed constitute a new investigation.

**10. ADVERSE INCIDENTS**

Any serious incident involving a device under clinical investigation within the scope of the Medical Devices Directive should be reported to the IMB as required by the Medical Devices Regulations 1994 S.I. No. 252 of 1994.

Such notifications should include incidents directly attributable to the device or the use of the device in addition to those that may be indirectly related to the device. In particular, adverse incidents should be notified if they have led to prolonged hospitalisation, additional surgery or medical intervention or death. While the reporting of adverse incidents for active implantable medical devices is not required by the Active Implantable Medical Devices Regulations 1994, S.I. No. 253 of 1994 the IMB strongly advise that any serious incidents involving the device under clinical investigation should be reported to the IMB in the same way as those for general medical devices are reported.

**11. LABELLING OF DEVICES FOR CLINICAL INVESTIGATION**

All devices intended for clinical investigation must bear the wording "exclusively for clinical investigation". It is recommended that manufacturers draw this requirement to the attention of all clinical investigators, requesting that such investigators ensure that the meaning of this wording is clearly understood by all staff using or coming into contact with the device being investigated and that the device under investigation is segregated, where possible, from any similar devices in use.

Medical devices intended for clinical investigation must not bear the CE mark, unless they have already been placed on the market for an intended purpose other than that under investigation.

**12. GLOSSARY OF TERMS**

This Guidance Note should be used in conjunction with Guidance Note 6: Glossary of Terms. Guidance Note 6 gives a comprehensive definition of terms referred to in the Medical Devices Directives.

**13. WHO TO  
CONTACT AT  
THE IMB?**

Clinical Investigation or Evaluation applications or queries should be directed to:

Medical Assessor for Medical Devices  
Medical Devices Department  
Irish Medicines Board  
Earlsfort Centre  
Earlsfort Terrace  
Dublin 2

Telephone: +353 (01) 6764971-5  
Fax: +353 (01) 6767836  
Email: [medicaldevices@imb.ie](mailto:medicaldevices@imb.ie)  
Website: [www.imb.ie](http://www.imb.ie)

Communication can be made by telephone, fax, email or by post to the above address.