Clinical Evaluation of Medical Device

13.1 INTRODUCTION

Clinical evaluation - This has a strong relationship with design validation. In fact, clinical evaluation might be used as a means of validating the device. The twist here is that clinical evaluation can have different meanings depending on who you ask. For example, under the same umbrella, you might find clinical investigation, testing or usage.

Clinical evaluation is applicable to your particular product. You may perform actual or simulated use testing. It is multi-layered - you need to understand the intent that the evaluation is addressing. Is it actual or simulated use of your device with test subjects, clinicians or end users?

13.2 Purpose

The clinical evaluation of medical devices is the assessment procedure conducted by registration applicants to validate whether the application requirements or intended use of the device(s) under application can be achieved based on clinical literatures, clinical experience data and information gathered from the clinical trial(s). A technical guidance is provide to registration applicants for conducting clinical evaluation and to food and drug administrative authorities for reviewing the clinical evaluation data.

13.3 Legal Basis

I. Regulation on the Supervision and Administration of Medical Devices (Decree of the State Council No. 650);

II. Measures for the Administration of Registration of Medical Devices (Decree No. 4 of China Food and Drug Administration); and

III. Related provisions on clinical trial quality control of medical device.

13.4 Scope of Application

The technical guidance on clinical evaluation of specific medical device product available, it should be followed for the clinical evaluation of the corresponding product. It is applicable to the clinical evaluation for registration application of Class II and Class III medical devices, and is applicable to the clinical evaluation of in-vitro diagnostics administrated as medical devices. In case there is technical guidance

13.5 Basic Principles

The clinical evaluation should be thorough and objective. Corresponding data should be collected by multiple means including clinical trial(s). Clinical performance and safety data collected during clinical evaluation (including both favorable and unfavorable data) should be included in the analysis. The depth and extent of clinical evaluation and non-clinical studies, and required data type and volume should be appropriate to the product design features, critical technologies, intended use, and risks of the device.

A clinical evaluation should verify the clinical claims made about the device, including the application of the device (e.g., target treatment group, the site of application to/in the body, method of contact with human body, indications, severity and state of the disease, application requirements and operation environment, etc.), method of application, contraindications, precautions, and warnings, etc.

The registration applicant should be able to reach the following conclusions through clinical evaluation: the product can achieve the expected performance in normal use conditions; the product risks are acceptably balanced with expected benefits; clinical performance and safety of the product are both supported by sufficient evidence.

13.6 Clinical Evaluation Technical File

If a company wanting to market your medical device in Europe, then they will be

required to write and maintain a Clinical Evaluation Report (CER). This is part of their technical file submission. The EU has very specific requirements for clinical evaluation documentation and reviews. An evaluation can include devices that have similar intended uses to your device and meet relevant essential requirements.

This is all part of being issued a European Conformity (CE) Marking Certificate for the EU, but you are still required to maintain that CER once you have the certificate.

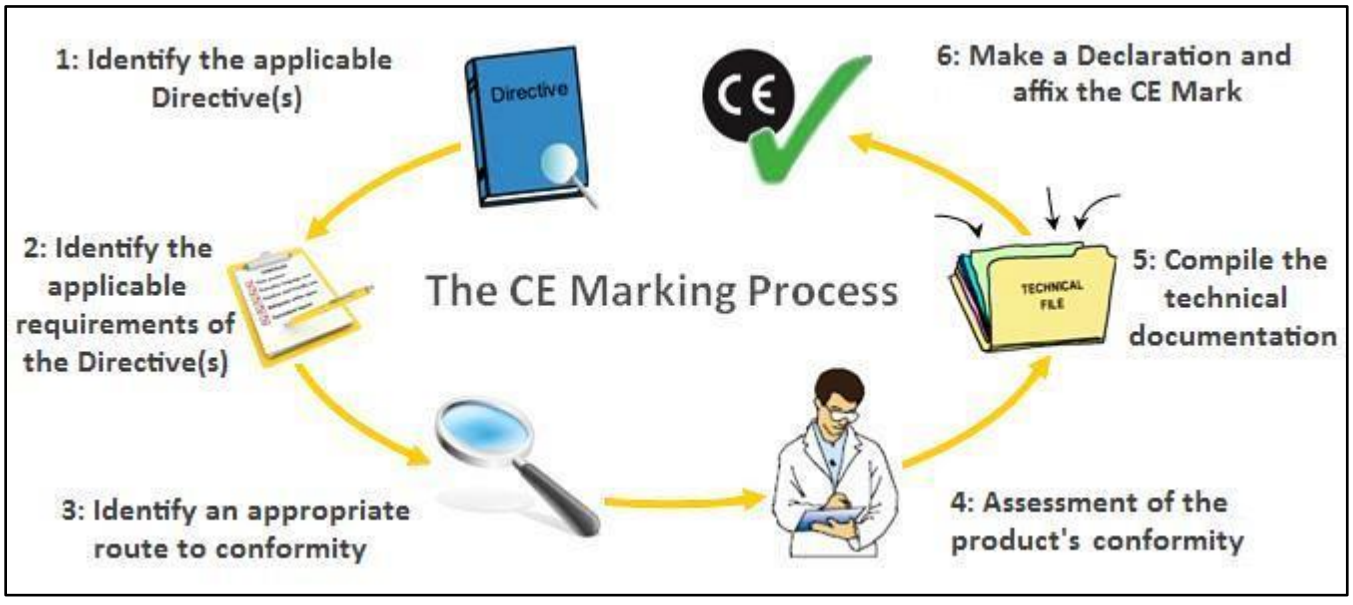
WHAT IS CE MARKING?

The CE Mark is a symbol stamped onto approved products and is an abbreviation of the French phrase "Conformité Européene", (European Conformity).

When a manufacturer stamps their product with this mark, they are declaring that the product is compliant with essential European regulations. The mark also:

- Indicates to government officials that the product may legally be placed on the market in their country
- Allows for the free movement of the product within the EU

The manufacturer's responsibility to affix a CE marking to their device, it is also their responsibility to ensure they are compliant with the regulations for keeping it.



The CE Marking Process, via CE Marking Association

13.6.1 THE TECHNICAL FILE

At step 5 in the above diagram, compiling the technical documentation (or technical file) is an essential part of the CE marking process. For medical devices, the technical file must consist of the following to satisfy the criteria of the Harmonized Standards:

- Product description and specifications
- Manufacturing information
- Risk management file
- Design verification and validation test reports
- Clinical evaluation
- Labeling

The clinical evaluation is just one part of the requirements for the technical file.

13.7 The Requirements of Clinical Evaluation

1) For the Products Listed in the Catalogue of Medical Devices Exempted from Clinical Trial

I. Comparison between the device under application and corresponding information in the Catalogue;

II. Comparison between the device under application and an equivalent medical device in the Catalogue that has obtained domestic registration approval. The comparison description should include *Comparison Table of the Device under Application and an Equivalent Medical Device Listed in the Catalogue that has Obtained Domestic Registration Approval (see Annex1)*and relevant supporting documents.

2) Requirements for Clinical Analysis and Evaluation Based on Data Obtained from Clinical Trial(s) or Clinical Application of the Equivalent

Medical Device

a) Equivalent Medical Device

The device under application can be considered as substantially equivalent with the equivalent medical device in the case that no adverse effects on the safety and effectiveness of the device are caused by the differences between the two devices.

b) Determination of Equivalent Medical Device

In order to prove the safety and effectiveness of the device under applicationutilizing the data from the clinical application experience or clinical trial(s) of the equivalent medical device, the applicant needs to compare the device under application with one or more equivalent medical device(s) and prove the substantial equivalence between the devices.

c) Evaluation Path

d) Collection of Data from Clinical Trial(s) or Clinical Application of Equivalent Medical Device

1. Collection of Clinical Literature Data
2. Collection **of Clinical Experience Data**

Collection of clinical experience data should include collection of data from completed clinical studies, adverse events, and corrective action related to clinical risks.

3) Collection of Data from Completed Clinical Studies

4) Collection of Adverse Events Data

The registration applicant should collect the corresponding adverse event data from the complaints and adverse events database established by himself, and the adverse events database issued by the regulatory authorities of all nations.

The registration applicant should provide the following information related to the equivalent medical device: number of complaints and adverse events, reasons classification of complaints and adverse events, number of complaints and adverse

events classified by different reasons, and the relationship of the adverse events with the product. For serious adverse events, the specific information such as event description, cause analysis, and corrective solutions should be summarized in the form of atable.

For the device under application, specific information such as the time on market in different countries, accumulated sales and outcome of serious adverse events should also be provided.

5) Data Collection of Corrective Measures Related to Clinical Risks

The applicant should collect and provide specific information on corrective measures associated with clinical risks of the equivalent medical device (e.g. recall, announcements, warnings, etc.), and the risk control measures that have been taken.

13.8 Analysis and Evaluation of Clinical Data from Equivalent Medical Device

13.8.1 Quality Evaluation of Data

The registration applicant should classify the data involved in the analysis in accordance with generally accepted evaluation criteria of clinical evidence level (e.g. the Evaluation Criteria of Clinical Evidence level established by Oxford Center for Evidence-based Medicine). The clinical data found to be unsuitable for validity evaluation can be applied to the safety evaluation of the device if applicable.

13.8.2 Establishment of Data Sets

The collected clinical data can be grouped into several data sets based on their different data type and data quality. The registration applicant may also create data sets according to different evaluation purposes. For example, if ethnic differences exist within the clinical performance and/or safety of certain products, the Chinese subgroup data sets can be established for evaluating the safety and /or efficacy of theproduct in Chinese population.

13.8.3 Statistical Analysis of Data

The appropriate data analysis methods should be adopted to conduct statistical analysis in different data sets. For the data sets with multiple study results, the analysis method should include the qualitative analysis and quantitative analysis.

13.8.4. Data Evaluation

Based on the analysis results of different data sets, the applicant should evaluate whether the device under application could reach the expected performance in normal conditions of use, and whether the risks are acceptable compared to the intended benefits.

13.9 Clinical Evaluation Report

A clinical evaluation report should be prepared after completionof the clinical evaluation(see Annex 8for the format), and should be submitted as a part of the clinical evaluation materials during registration application.

13.9.1 Requirements for Clinical Trials

For medical devices with clinical trials conducted in China, these trials should be conducted by a qualified clinical trial institution in accordance withQuality Management Regulations for Clinical Trial(s) of Medical Devices. When applying for registration, the registration applicant should submit clinical trial protocol and report.

For imported medical devices with clinical trials conducted overseas, the registration applicant can submit the clinical trial data provided to foreign authorities on medical devices during its marketing approval, as long as such trials comply with relevant Chinese regulations and requirements defined in technical guidance for registration, e.g. sample size, control group selection, evaluation indexes and principles, and efficacy evaluation indexes. Such data should at least contain opinions of the ethics committee, clinical trial protocol, and the clinical trial report. The applicant also needs to provide

supporting documents that demonstrate any ethnic difference of the product concerning clinical performance and/or safety.

WHAT DOES THE CER INVOLVE?

The clinical evaluation report documents the entire process of your clinical evaluation. This evaluation involves the assessment and analysis of clinical data for your device to verify its safety and performance. The data used may be both pre and post-market that is relevant to verify intended use. This includes data specific to the device as well as any data relating to devices claimed as equivalent by the manufacturer. Cromsource provides a table below which outlines the clinical data sources for a clinical evaluation:

Clinical Data Source	Manufacturer's Device	Equivalent Devices*
Published Data	X	X
Clinical Investigation	X	
Post-Market Surveillance Data	X	
Public Adverse Effect Databases e.g. FDA MAUDE	X	X
Compassionate Use Data	X	
Internal Corrective and Preventive Actions (CAPAs)	X	

** Devices that are demonstrated by the manufacturer to be equivalent in some or all aspects to the manufacturer's own device*

Here is how the evaluation works, as taken from Cromsource:

"The clinical evaluation needs to cover: any design features that pose special performance or safety concerns; the intended purpose and application of the device; and the specific claims made about the clinical performance and safety of the device. It is important to describe the merit and limitations of any data cited or included in the evaluation.

The manufacturer's risk assessment documentation is included in the review process to ensure that all risks identified are discussed and addressed/mitigated in it. The instructions for use (IFU) for the device are reviewed during the process to ensure that data is gathered from the same population using the device in the same way for the same indications, as described in the IFU. Finally, conclusions are drawn about whether the Essential Requirements relevant to clinical safety and performance are met."

13.9.2 Recent EU changes

It may have heard other manufacturers commenting that the EU CE Mark process is simpler and more predictable than the FDA; as Thomas Jull discusses, the tune is set to change with some recent updates made to EU regulations.There's a shift more toward the FDA way of doing things and those changes will affect new devices and those that already bear the CE Mark. There are new rules on classification and heavier post-market surveillance requirements, among others, meaning more emphasis on post-market clinical evaluation.

"Post-Market Clinical Follow-Up (PMCF) must be planned in, as the information gathered will be used to analyze the safety and performance of the device.

This, for most device classes, will now be reported annually to the authorities, of the MDR for what needs to be included in the plan.) Along with the aims of this system to reduce risks, unannounced audits are expected to become more common and frequent."

Browse through Jull's article for Medical Design Technology Magazine for more information on the changes.

13.9.3 An ongoing process

Getting back to design validation and the inter-relationships with clinical evaluation, as we determined earlier, you might use clinical evaluation as part of your design validation, which is an activity that happens pre-market.

However, overall, clinical evaluation is something that is an ongoing process throughout the life cycle of a medical device. Once you've completed the initial evaluations that help get your CE Mark or help you to meet the requirements of other regulatory authorities, there will be occasions to reevaluate the clinical evaluation as new clinical information becomes available (such as from studies or use) or as any changes are made to the device.

As we've seen with the updating of regulations, there is an expectation that you will continue to gather clinical data and use it to prove the safety and effectiveness of your product.

13.9.4 THE BOTTOM LINE: SAFETY AND EFFECTIVENESS

The differences between design validation and clinical evaluation lie in the context under which the evaluation is conducted. While design validation is a pre-market requirement to demonstrate that you've developed the correct product for users, clinical evaluation might be part of that demonstration.

Clinical evaluation is taken further as it is used under several other circumstances, including for your technical file if you're seeking a European CE Mark. Unlike design validation, clinical evaluation is a lifecycle activity which continues well into post-market. The overall aim is, as always, to prove that you have a safe and effective device.