Clinical evaluation according to MDR Annex IV
and its relationship to surgical instruments

Background to clinical evaluation

The new EU directive for medical products (Medical Device Regulation – MDR 2017/745) has been in force since 25 May 2021. New products must be approved according to this directive and can no longer be marketed according to the 'old' guideline, 93/42/EEC. It is not just since the new EU-MDR was introduced that clinical evaluation has been a standard component of technical documentation, and therefore mandatory for every medical products manufacturer. Clinical evaluation was already mentioned in the 93/42/EEC guideline (the MDD) and explained there. However, a search for the keyword 'clinical evaluation' in both documents, the MDR and MDD, clearly shows the major extent to which this has concept has been foregrounded in the new regulation: in the MDD it turns up 9 times, in the MDR there are as many as 59 matches.
Article 2, para. 44 of the MDR reads as follows:" Clinical evaluation" means a systematic and planned process to continuously generate, collect, analyses and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer.'

A clinical evaluation is therefore a systematic search and analysis of the available specialist literature and other data in order to demonstrate that the product meets the requirements of safety and performance. Its aim it's to indicate the clinical benefits and, by so doing, already demonstrate that the product does not entail any increased risk. In this context, 'increased risk' means that the risk-benefit ratio turns out to be positive, in other words, that the benefits exceed the risks. And here we already come up against the first challenge presented by the evaluation: how can I verify the safety and performance requirements for my product, or its clinical benefits, by reference to the literature if I am launching an original, and perhaps even highly innovative product on the market? There will be little or no data in the literature about an original product, above all at the time of its first approval. It is here that the concept of 'equivalent device' comes into play. An 'equivalent device' is a product that possesses a

high level of similarity to your own product. In this context, the MDR refers to ‘equivalence’. Annex XIV, section 3 specifies the three categories comprising this equivalence, i.e. technical, biological and clinical characteristics. According to this, an equivalent product can only be classified as such if no differences are found, or only clinically insignificant ones. The MDCG Guideline 2020–5 may also be consulted for more details on this. This guideline itemizes the requirements, investigates specific points within the categories and, at the same time, contrasts the requirements of the MDR with those of MEDDEV 2.7/1 rev. 4, the guideline for clinical evaluations under the MDD. Criteria for equivalence:

- **Technical equivalence:** Technical equivalence means that the product has the same or a similar design, is used under similar conditions, and that the physical and chemical properties correspond. In its use of the term ‘similar’, therefore, the MDR provides a certain scope for freedom. Here it refers to comparable principles which, in the final analysis, add up to the same result. Here too, the rule is that the ‘equivalence’ should not influence the clinical intention. The MDR also goes one step further here by mentioning software algorithms. These too should have a similar way of functioning and method of development.

- **Biological equivalence:** Here the MDR requires the manufacturer to check their medical device and potentially equivalent products to see whether the same substances come in contact with the same tissues, and whether these possess similar qualities with regards to degradation products and leachable. This must occur for a comparable, i.e. similar, time period. The difference between ‘similar’ and ‘same’ is also to be understood in exactly the same way in the directive. It is therefore important that two equivalent products are actually made of the same materials or use the same substances to achieve their clinical effect. As for as the exposition goes, here again the MDR allows a certain free scope. It goes without saying that one should not stretch the term too far.

- **Clinical equivalence:** This section is certainly the least ambiguous, since it refers directly to the indicated clinical condition and the purpose of the medical product. Obviously, in the case of an equivalent device, these must also be the same. Here the MDR is also quite strict, and gives no scope for discretion where the clinical condition is concerned. Here, only severity and the stage of disease come under the term ‘similar’, and should be assessed accordingly.

In addition to searches for equivalent products in the literature with their associated data, results from post-market surveillance are also incorporated into clinical evaluation. Observing the market after the product has been launched is one of the manufacturer's responsibilities, and it generates valuable data for clinical evaluation. It includes looking at signals from the market and complaint management, but also reports in relevant databases such as that of the German Federal Institute for Drugs and Medical Devices (BfArM).

The challenge for surgical instruments

The MDR specifies requirements pertaining to the development, production, use and monitoring of medical devices that pose significantly greater hurdles when compared with the previous legal position. Manufacturers are facing a variety of challenges as a result of these changes, particularly those concerning the content of technical documentation, clinical evaluations and post-market surveillance. The scope of the new requirements will lead in many instances to a longer, stricter conformity assessment procedure for medical devices. In addition to this, there is the small number of notified authorities and the outbreak of the coronavirus pandemic – an obstacle for many companies.

The MDR makes no distinction between whether the product is intended for a very large market or for rare diseases. Exceptions for niche applications, e.g. in the case of small patient groups, are expected to be few and far between. Any firm that wishes to bring medical devices to market must in future meet the requirements under the new MDR regulatory framework, and thus be able to create and present a clinical evaluation (see MDR, Annexes II and III).

This equally applies to the field of surgery and naturally concerns all medical technology companies in and around Tuttlingen, The MDR is also specifying changes affecting reusable surgical instruments – for example, risk class I is being expanded to include a new sub-category (class Ir) for reusable surgical instruments.

MDR Annex VIII, item 2.3:

"'Reusable surgical instrument" means an instrument intended for surgical use in cutting, drilling, sawing, scratching, scraping, clamping, retracting, clipping or similar procedures, without a connection to an active device and which is intended by the manufacturer to be

reused after appropriate procedures such as cleaning, disinfection and sterilization have been carried out.'

Manufacturers of relevant devices will be expected to have these recertified. The manufacturer must go through a procedure in accordance with either MDR Annex IX Chapter I (quality management system) or MDR Annex XI Part A (production quality assurance) with a notified body. For these devices, the notified body's participation in these procedures is, however, limited 'to the aspects relating to the reuse of the device, in particular cleaning, disinfection, sterilization, maintenance and functional testing and the related instructions for use'.

Requirements of the literature search

After you have become clear about equivalent devices and the data situation, the biggest task is the literature search itself. Over the years, and with the introduction of the MDR and various guidelines, the requirements in this area have increased and, in particular, become more clearly defined. Whereas earlier a clinical evaluation was prepared 'to the best of one's knowledge and belief', nowadays there are precise specifications for the forms that the literature search, literature assessment and final evaluation must take. Here, guideline N56 of the International Medical Device Regulators Forum (IMDRF) is a useful source of good recommendations for action.

First of all, it is important that the search process is transparent and traceable, and relies on established scientific practice. The person (or group of persons) who has carried out the search should be made known, and recorded in the later report. The date or timespan of the search should also be clearly defined, as should the period of time it covers. When a clinical evaluation is first drawn up, it is certainly advisable to incorporate as long a period of time as possible, even if it does not include all literature up to the time of creation. In the case of medical products that rely on older, already well-known procedures, it is of course necessary to consider carefully whether/which specialist literature can be considered, and which contains outdated results. The aim of this is to ensure transparency regarding the literature that has been selected, and to show that the search has been limited and has taken account of the current state of knowledge.

Then, when the time comes to update the clinical evaluation in the course of its life cycle – a procedure that is also required by law – the search records will show that the search was

conducted without any omissions. Obviously, during the update it is then possible to consider the period that has elapsed between the last evaluation at the current date. As part of this, of course, attention must be given as to whether new findings change anything about the evaluation of the medical product. For example, if it has become known over the course of time that substances or materials used pose a (potential) danger for users or patients, then this must be considered and mentioned. Of course, such dramatic discoveries should be identified even before the update and addressed with appropriate action, but this explains the thought process. It is also important to think about criteria for inclusion in and exclusion from the literature before the literature search. The aspects according to which the literature is to be evaluated, and the reasons for excluding certain sources, must be clear before starting. Here too, the decision must be based on scientifically recognized criteria and cannot be arbitrary. A suitable approach is therefore to limit the search to established platforms (e.g. PubMed etc.) or to exclude specialist articles written in languages that those conducting the search do not understand. It is also possible to make exclusions if a search term yields too many matches, e.g. because it is phrased too generally.

This also leads us to the next important point: the selection of search terms. Here it is important to make an appropriate selection that delivers sound, trusted results about your product (or equivalent products), but which is not so general that the volume of data is no longer manageable. A search term that is too specific can mean that two few results are found, or that conclusions cannot be further substantiated. Choosing the right degree here is therefore a matter of intuitive feeling, sound scientific work and, finally, experience. If there are too few results, the search may need to be extended; on the other hand, if there are too many, other criteria for selection and limitation must be chosen.

Figure 1 shows the search procedure suggested by the IMDRF. Here too, guidelines N56 and MEDDEV 2.7/1 rev. 4 provide recommendations for action that are designed to help track down a publication in terms of its content.

Researching the literature is therefore a complex procedure that calls for scientific procedure, and completing it successfully requires personal expertise regarding such a working method and, of course, regarding the product itself.

Summary

A clinical evaluation exhibits a systematic, scientific approach that should enable you to evaluate whether your medical product entails any known risks, whether it conforms to the

current state of the technology and whether it performs its clinical purpose. These data are collected from the literature and evaluated in the clinical evaluation report. Here it is possible, and sometimes also necessary, to rely on other products, as long as these can be classed as similar or equivalent. Applicable guidelines provide good recommendations for action so that the literature search and evaluation can be carried out systematically and effectively, and the equivalence of products assessed. A clinical evaluation is required by the MDR as part of the conformity assessment process, and must be maintained and updated throughout its entire life cycle.

In this way it is possible to guarantee that all necessary information from the current state of technology and science is considered, and that the medical product is safe for patients, users and third parties according to the present state of knowledge.

- Figure 1: Search algorithm according to IMDRF (source: IMDRF MDCE WG N56)
- Surgical instruments in use