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Abstract	The new EU Regulation (EU) 2017/745 on medical devices, which took effect on May 26, 2017, is crucially important for medical device manufacturers and CE certification, as well as the recertification of their products. On clinical evaluation, the present contribution discusses the main differences between EU Directive 93/42/EEC and EU Regulation 2017/745 in the following six areas: (i) Stronger requirements for clinical safety and evidence of clinical efficacy, (ii) Classification, (iii) Clinical evaluation, possibly including clinical trials, (iv) Post-market clinical surveillance, (v) Clinical documentation and reporting, and (vi) Introduction of the European Commission's scrutiny procedure.	

Clinical Evaluation of Medical Devices in Europe

Hans P. Zenner and Mijo Božić

Abstract The new EU Regulation (EU) 2017/745 on medical devices, which took effect on May 26, 2017, is crucially important for medical device manufacturers and CE certification, as well as the recertification of their products. On clinical evaluation, the present contribution discusses the main differences between EU Directive 93/42/EEC and EU Regulation 2017/745 in the following six areas: (i) Stronger requirements for clinical safety and evidence of clinical efficacy, (ii) Classification, (iii) Clinical evaluation, possibly including clinical trials, (iv) Post-market clinical surveillance, (v) Clinical documentation and reporting, and (vi) Introduction of the European Commission's scrutiny procedure.

1 Introduction

The new EU Medical Device Regulation (MDR)[1] is of crucial importance for manufacturers of medical devices when it comes to certification and recertification of their products, with the exception of in vitro diagnostic medical devices. In addition to comprehensive extensions, the MDR combines provisions of the Directive 93/42/EEC concerning medical devices (MDD) and Active Implantable Medical Devices Directive 90/385/EEC (AIMDD), which it supplemented. The older MDD and AIMDD remaining in force until 2020 contain provisions for putting a medical device into service based on clinical evaluation.

[1]For the main reasons behind the adoption of the new Regulation on medical devices see for example Gemke (2017) p. 15 or Handorn (2018) p. 95.

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Unlike the directives, the new EU regulation is directly applicable in all EU states. An additional adaptation of national laws on medical devices like the Medizinprodukte gesetz (MPG) in Germany remains possible.

A separate EU regulation applies to in vitro diagnostics—the Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR) from April 5, 2017, replacing the hitherto valid Directive 98/79/EC on in vitro diagnostic medical devices.

The new MDR and certification procedure resulting from this are much more complex than the procedures previously applied under MDD/AIMDD/MPG. Compared to the MDD, the MDR contains a hundred additional provisions. The number of annexes has increased, and there is a series of further legal documents, the preparation of which is still ongoing.

However, there are no significant differences in many areas. Despite more detailed wording, no entirely new requirements are foreseen.

2 Results and Discussion

2.1 Regulatory Sphere

The MDR will apply from May 26, 2020. The manufacturers will have to follow the MDR when placing medical devices on the market for the first time. Products already approved on the market must be adapted to MDR no later than 5 years after the date of application of MDR. For products approved under MDD/AIMDD/MPG from the second quarter of 2020, this period will be shortened to 4 years. If there is no new EU declaration of conformity because, for example, the clinical evaluation in the technical documentation is incomplete, the EU certificate may be refused.

Each medical device is assigned to a particular class. This classification system is based on the potential hazard, type of application, and approval requirements. Classification was previously performed under rules set out in MDD/AIMDD.

In the case of a first-time CE certification under the MDR, the medical device (if applicable, also some products intended for non-medical use) is assigned to a class according to 22 classification criteria set out in Annex VIII "Classification rules". Annex VIII to EU MDR also provides for a different classification. In the course of MDR, the previous assignment of some medical devices to a particular class will be changed compared to the procedure applied under MDD/AIMDD, which is expiring in 2020.

Two new MDR classification rules for active medical devices are particularly notable. Under Rule 11, stand-alone software is hardly assigned to class I any longer, as most software falls at least in class IIa or higher, especially if the software can cause death or persistent adverse health effects. From class IIa on a notified body involvement is required. Under Rule 22, a number of systems (e.g., closed-loop feed-back systems: invasive control systems, such as active therapeutic devices with

integrated or embedded diagnostic function) and implants (e.g., orthopedic joint and spinal implants) previously assigned to class IIb are now supposed to meet the more stringent requirements of class III. All products that contain or consist of non-material are also affected (Rule 19). The same holds for invasive devices with respect to body orifices, which are intended to administer medicinal products by inhalation (except surgically invasive devices; Rule 20), as well as devices composed of substances or combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by or locally dispersed in the human body (Rule 21). Devices manufactured utilizing animal or human tissue or drugs (e.g., insulin) are subject to more stringent requirements.

Under the MDR, manufacturers of products that have been put into service under MDD/AIMDD must timely review the new classification rules and update their technical documentation, including clinical evaluation and possibly including a clinical trial. Class IIa, IIb, and III medical devices may require a systematic clinical reassessment. In doing so, they must consider the new provision on the equivalence of the products, as well as the options under which a clinical trial can legitimately be dispensed. If such a review is omitted, the CE certificate may be invalid.

Under the new EU MDR, this evidence of the clinical efficacy of a medical device and patient safety is generally provided by a clinical evaluator who is a specialist in the relevant medical specialty possessing personal clinical experiences in the application of the specific or similar medical devices and/or in the diagnosis and management of the conditions intended to be diagnosed or managed by the device.[2]

More often than before, a clinical trial will be required. The MDR sets out in detail how clinical evaluations and clinical trials should be performed. Clinical evaluation of medical devices is part of the technical documentation relating to a medical device. At the same time, the manufacturer must submit a clinical development plan, including a plan for post-market clinical follow-up.

An explicit rule relating to non-critical products, which would allow a waiver of clinical evaluation, does not exist. A waiver of clinical data for a clinical evaluation, however, is basically permitted for absolutely non-critical products, such as screws, wedges, plates, and instruments.

In addition to the EU MDR, there are other regulations and standards that require a clinical evaluation of medical devices. These include the established MEDDEV guidelines[3] to ensure compliance with the old guidelines.

[2]MEDDEV 2.7/1 rev 4, p. 15: "With respect to the particular device under evaluation, the evaluator should in addition have knowledge of: - the device technology and its application; - diagnosis and management of the conditions intended to be diagnosed or managed by the device, knowledge of medical alternatives, treatment standards and technology (e.g. specialist clinical expertise in the relevant medical specialty)".

[3]European Commission's guidance documents to assist stakeholders in implementing directives related to medical devices. List of Guidance MEDDEVs available on: https://ec.europa.eu/growth/sectors/medical-devices/guidance_en, accessed on July 28th 2018.

Furthermore, not only the manufacturers, but also the suppliers, importers, distributors, and sales organizations (economic operators) can be affected. Exceptions in this regard are economic operators of component parts, such as screws, wedges, plates, and instruments.

If comparable devices are used for clinical evaluation, then these reference products must be technically, biologically, and clinically equivalent to investigated products being subject to evaluation. As with the MEDDEV 2.7/1 rev 4 there should be no clinically relevant differences. Manufacturers must demonstrate an equivalence by providing the data for the reference product. Class III and implantable devices can only refer to data of comparable validity if the manufacturer has the reference devices in its possession and able to generate the necessary data. As a rule, they (manufacturers) need contractually regulated access to all data and test results relating to the reference product.

In addition to the new MDR clinical trials of medical products must be planned and performed under EN ISO 14155[4] "Clinical investigations of medical devices for human subjects - Good clinical practice" and other relevant regulations.[5]

The reporting system includes the results of the clinical evaluation, possibly including (if applicable) the clinical trial protocol documents, investigator's brochure, patient information, and informed consent, as well as additional reports and plans, such as the Clinical Development Plan and the Summary of Safety and Clinical Performance. The MEDDEV 2.7/1 rev. 4 also sets out requirements to be met. The clinical evaluation combined with risk management can be tested as well.[6] Furthermore, documents on clinical post-market surveillance are required.

Post-market Surveillance is a continuous process that updates the clinical evaluation (Annex XIV Part B). This applies in particular to class III medical products and implantable devices that are subject to more stringent clinical requirements as set out in EU MDR. Clinical post-market surveillance includes:

- Post-market Clinical Follow-up (PMCF)
- Other studies
- Vigilance system/reporting of incidents to responsible national authorities—in Germany, the Federal institute for Drugs and Medical Devices
- Customer contacts
- Screening of scientific literature and other sources of clinical data
- Identifying possible systematic misuse or off-label use of the device
- Continuous review and update of clinical evaluation.

[4]ISO 14155 is now a single standard that consolidates the previous 14155-1 and ISO 14155-2. ISO 14155 does not apply to in vitro diagnostic medical devices.

[5]These include national regulations, such as the German Regulation on Clinical Trials with Medical Devices and the German Medical Devices Safety Plan Regulation. On the other hand, the following provisions will no longer apply: Medical Devices Act sec. 20 ff., and the Ordinance on Clinical Trials with Medical Devices.

[6]Such a test is meant to show if the results of clinical evaluation are consistent with the statements in the risk management file.

Additional reports and plans under the MDR include the Post-market Surveillance Report, Periodic Safety Update Report (PSUR), and Summary of Safety and Clinical Performance. As part of the PMCF for class III and implantable devices, the safety/clinical evaluation/performance summary reports must be updated at least once annually.

An important issue in this context is the reporting of serious incidents.[7] They should be reported without delay within the framework of the vigilance procedure. 'Incident' means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error because of ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side effect (MDR Art. 2 no. 64).

'Serious incident' within the meaning of MDR Art. 2 no. 65 means any incident that directly or indirectly led, might have led, or might lead to any of the following:

(a) The death of a patient, user, or other person
(b) The temporary or permanent serious deterioration of a patient's, user's, or other person's state of health
(c) A serious public health threat.

Responsible national authorities (in Germany, the Federal institute for Drugs and Medical Devices, BfArM) evaluate the risk resulting from the incident. At the same time, the manufacturer undertakes corrective measures in cooperation with the national authorities to eliminate existing risk.

Manufacturers are also required to report any significant increase in the frequency or severity of incidents that are not serious or are expected to have undesirable side effects that could have a significant impact on the benefit-risk analysis (Art. 88 (1) MDR). Furthermore, serious adverse events (SAEs) must be reported in the course of a clinical trial or performance evaluation (Medical Devices Safety Plan Ordinance, sec. 3 (5)).

2.2 Classification of a Medical Device

Classification has a significant impact on the necessity and extent of a potentially required clinical evaluation, including clinical trials and clinical post-market surveillance.

The MDD contains 18 rules, which are divided into rules relating to non-invasive, invasive, and active products, as well as special rules. Each MDD/AIMDD medical device is assigned to one of four classes based on the hazard potential, type of application, and licensing requirements.

In the case of a first time CE certification and recertification according to MDR the classification of a medical device—and some products not intended for medical

[7] See more on these issues in Lippert (2018), pp. 299–303.

use[8]—will be conducted according to 22 classification criteria set out in Annex VIII "Classification criteria".

In the case of CE certification (2020 at the latest) or recertification according to MDR (no later than 2024), the assignment of some medical devices to a particular class will change compared to the currently applicable MDD/AIMDD expiring in 2020. Two new classification rules relating to active medical devices should be mentioned.

Software intended to provide information that is used to make diagnostic or therapeutic decisions—especially if such decisions have an effect that may cause death or an irreversible deterioration of a person's state of health—is classified as class IIa and higher.

A number of systems (e.g., closed-loop feedback systems: invasive control systems, such as active therapeutic devices with integrated or embedded diagnostic function) and implants (e.g., orthopedic joint and spinal implants[9]) previously assigned to class IIb, are now expected to meet the more stringent requirements of class III. Active therapeutic devices with an integrated or incorporated diagnostic function, which significantly determines patient management by the device, such as closed loop systems or automated external defibrillators, are classified as class III.

All devices incorporating or consisting of nanomaterial (Rule 19); all invasive devices with respect to body orifices, with the exception for invasive devices, which are intended to administer medicinal products by inhalation (Rule 20); and devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by or locally dispersed in the human body (Rule 21), are affected as well.

All devices manufactured utilizing tissues or cells of human or animal origin, or their derivatives (e.g., insulin) will have to meet more stringent requirements.

Not only the manufacturers, but also suppliers, importers, distributors, and sales organizations (economic operators) included in a supply chain, can be affected.

[8]Under the MDR, a total of six product groups can be optionally marked with "CE". They are listed in Annex XVI "Products without an intended medical purpose". A prerequisite is that they meet requirements relating to medical devices provided for in the EU MDR.

[9]Prostheses for all joints and many, if not all, joint prostheses in the body are currently assumed to fall in future into the class III. It is not clear if this (rebuttable) presumption applies to all joints equally. The MDR significantly expands the range of joint implants that were already classified higher by Directive 2005/50/EC. Under Rule 8, partial joint replacements and other joint implants also fall into class III. For manufacturers, it may be helpful to think in advance of whether their products affect joints as defined by the MDR, e.g., the hand or tarsal bones or temporomandibular/jaw joint. Spinal disc replacement implants and implantable devices that come into contact with the spinal column are assigned to class III. However, the phrase "implantable devices that come into contact with the spinal column" raises questions. Strictly speaking, it could also include bone cements for vertebral body erection. An exception applies to (ancillary) components, such as screws, wedges, plates, and instruments. It is not yet clear how a rod or screw system should be classified and what is meant by a wedge in spinal column surgery. Therefore, further publications are needed to make the content, meaning, and scope of this rule more precise.

Their activities can be subjected to auditing by notified bodies and, thus, be part of a clinical evaluation. The exception in this regard applies to manufacturers' economic operators dealing with minor components, such as screws, wedges, plates, and instruments.

The MDR is a novelty, as it provides for manufacturers to submit a clinical development plan, including a plan for clinical follow-up. Consequently, in addition to the normative and technical requirements relating to a new product, the specification will have to include evidence of clinical safety, minimal possible stress, and effective benefits.

The planning and execution of an essential part of preclinical tests relating to a new medical device will of course be influenced by the subsequent clinical use of the product in question. Therefore, in the course of examining the technical documentation, the notified body will also consider the clinical interpretation of the preclinical tests relating to medical devices.

2.3 Clinical Evaluation of the Medical Device

The new EU regulation significantly increases the requirements regarding the burden of proof for safety and efficacy by means of a clinical evaluation and, if applicable, the manufacturer's own clinical examination. Under the MDR, this proof of the clinical efficacy of a medical device and patient safety is generally performed by a clinical evaluator by means of a specialist clinical evaluation of medical devices. The clinical evaluation of medical devices is a substantial part of the technical documentation for each medical device. For some medical devices, clinical evaluation will also require a complex clinical trial. Clinical trials will tend to be the exception rather than the rule. In a large number of cases in the future, clinical evaluation will also be performed without clinical trials.

The evaluation includes evidence of the clinical function being claimed, including the effect size and related efficacy in patients. Notified bodies may also consider further claims of the manufacturer in their examination, which may then also be clinically proven. Further, risk-benefit analysis will be required.

Further clinical aspects may include, for example hygiene requirements up to the sterilizability, biocompatibility, impermeability, stability, or measuring the accuracy of a product. Issues such as compatibility with other products, including third-party products, safety, and operating instructions, and training programs for healthcare professionals may be tested as well.

The evaluation is completed by assessment of the acceptability of the benefit/risk ratio. In this final consideration of risk, burden, and benefit, the benefits must clearly outweigh the risks.

Procedure Without Clinical Trial A benefit-risk analysis and the related assessment are based on the collection and review of the data and literature. The clinical

evaluation is based mostly on clinical data,[10] which must already exist. Necessary data and literature selection are determined by whether the medical device is novel or comparable to an already existing technology. For existing data, clinical evaluation will be based primarily on data from literature databases recognized by the US Federal Drugs Agency (FDA) and/or BfArM notifications, or data from competing companies.

As required by MEDDEV 2.7/1 rev. 4, the reference product must be technically, biologically, and clinically equivalent to a product in question to such an extent that there are no clinically relevant differences. Moreover, the manufacturers must demonstrate an equivalence by providing the data for the reference product. In the case of class III and implantable devices, the manufacturer can only refer to data of comparable validity if it has the reference devices in its possession and is able to generate the necessary data. As a rule, they need contractually regulated access to all data and test results relating to the reference product. Otherwise, the company will have to submit its own clinical results.

In contrast to the integrated software of a medical device, which is clinically evaluated together with the medical device, stand-alone software[11] is characterized by having only two essential interfaces:

1. Graphical user-product interface (GUI)
2. Product (data) interface.[12]

Unlike pharmaceutical law, medical device law protects not only the patient, but also users and third parties. The scope of protection is broader, which usually requires more effort related to the clinical risk assessment of medical devices.

The results of the clinical evaluation significantly influence risk management. Only the clinical evaluation can support the assumptions of benefit and, thus, the acceptance of the benefit-risk ratio as presented in the risk management file. The clinical evaluation must also support the assumptions in the risk management file related to risk. The results of the post-market clinical follow-up should also be considered in clinical evaluation and risk management.

A clinical evaluation without clinical data may apply to some non-critical products only. The exception shall be justified by a clinical evaluation demonstrating compliance with the essential requirements by means of a technical performance assessment, product testing, and preclinical assessment, considering the features of the body-product interaction, the intended clinical performance, and the manufacturer's information.

[10]Regarding the clinical evaluation requirements for medical devices, the MDR is a novelty as it provides that manufacturers must produce a clinical development plan, including a post-market clinical follow-up plan.

[11]See more on medical device software in Lücker (2018), p. 282 ff.

[12]See more on clinical evaluation of stand-alone software in Terhechte (2018), p. 324 ff.

Clinical Trials of Medical Products If sufficient clinical evidence is not available to demonstrate the required clinical safety and performance of a product, clinical trials must be performed. Novel products, implantable medical devices, and class III devices must always undergo a clinical trial. In particular cases, this can be waived if existing clinical data are sufficient. A clinical trial is to be performed without exception on:

- New indication
- New anatomical region of the human body
- Modifications to a product being placed on the market/put into service when these might have a significant effect on safety or efficacy
- Significant extension of application time
- Insufficient literature on effectiveness/efficacy and risks.

Clinical trials on medical products must be planned and performed under EN ISO 14155 "Clinical investigations of medical devices for human subjects - Good clinical practice" and other relevant regulations.[13]

The requirements of EN ISO 14155 are comparable to those of the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use—Guideline for Good Clinical Practice (ICH-GCP) for clinical trials with medicinal products. Further provisions to be followed can be found in the German Regulation on Clinical Trials with Medical Devices ("Verordnung über klinische Prüfung von Medizinprodukten", MPKPV) and in the German Medical Devices Safety Plan Regulation ("Medizinproduktesicherheitsplanverordnung", MPSV).

The conduct of clinical trials with medical products and IVD requires approval by the responsible national authorities. Thus, In Germany this requires under MPG sec. 20 (1), approval by the responsible higher federal authorities, such as the Federal Institute for Drugs and Medical Devices (BfArM), or the Federal Institute for Vaccines and Biomedicines (PEI, Paul Ehrlich Institute), and a favorable opinion by a legally approved ethics committee, such as of a public law Chamber of Medicine (Landesärztekammer) or of a university hospital (Universitätsklinikum). Applications must be submitted via the German Institute of Medical Documentation and Information (DIMDI).

2.4 Documentation and Scrutiny Procedures

In addition to the medical or clinical quality of the clinical evaluation, documentation and traceability form part of the complex and demanding reports and plans.

The reporting system includes the results of the clinical evaluation, including any applicable clinical trial protocol documents, investigator's brochure, patient

[13] See footnote number 6.

information, and informed consent, as well as additional reports and plans, such as the Clinical Development Plan and the Summary of Safety and Clinical Performance. The MEDDEV 2.7/1 rev. 4 also sets out requirements to be met. By the notified body accordance of the risk management with the clinical evaluation may be checked as well.[14] Furthermore, documents on clinical post-market surveillance are required.

As far as notified bodies are concerned, the supervision of their activities by the competent authorities will be intensified, which may result in increased documentation burden and the growing pressure of self-justification on their side.

This includes the new scrutiny procedure, which focuses on reviewing the submitted clinical evaluation. To meet this task, the notified body will create a CEAR for implantable class III products and active class IIb products intended to administer drugs/medicinal products in the human body based on the clinical evaluation, with exceptions for cases in which recertification or mere modification is being carried out. The CEAR will be submitted to the Medical Device Coordination Group (MDCG), an expert committee of the European Commission, which must decide within 21 days whether it will present a scientific opinion on the CEAR.

If applicable, the panel must provide the scientific opinion on the CEAR within 60 days. The notified body must consider the scientific opinion by making its decision and, if necessary, grant the certificate with restrictions or conditions. If the opinion is not completed by the deadline, the notified body may proceed with the certification with no amendment.

2.5 Post-Market Clinical Follow-Up (PMCF)

Following the placement of a medical device on the market, the EU MDR requires a manufacturer to carry out PMCF continuously to assess the benefits and risks related to the device. The main purpose of PMCF is to identify potential long-term risks that could not be detected within the pre-market clinical evaluation. The results of the follow-up should be considered within the continuous update of the clinical evaluation and risk management. Clinical evaluation is therefore an ongoing process that must be repeatedly documented through regularly reviewed plans and reports by the notified body.

To assess potential safety risks, manufacturers need to gather clinical data continuously. The manufacturer is supposed to create a structured system of long-term follow-up including clinical trial results, registers, controls, or spot checks.

The documentation should comprise essential updates, including but not restricted to additional reports and plans such as a post-market surveillance report, PMCF report, Periodic Safety Update Report (PSUR), and Summary of Safety and Clinical Performance. For specific product groups, manufacturers must submit

[14] See footnote number 7.

safety/clinical evaluation/performance summary reports relating to the safety and performance of their products on an annual basis. This applies in particular to class III medical devices and implantable products, which are subject to more stringent clinical requirements for PMCF.

Certain incidents during post-market surveillance and during clinical trials are to be reported to the National Authorities i.e. in Germany the Federal Institute for Drugs and Medical Devices (BfArM) or the Paul Ehrlich Institute (PEI) via the electronic system for vigilance and post-market surveillance (currently DIMDI). 'Incident' means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error because of ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side effect (MDR Art. 2 no. 64).

The EU MDR extends the notified body's powers regarding post-market clinical surveillance. Unannounced audits, spot checks, and product tests strengthen the role of the EU in implementing procedures and help reduce risks resulting from unsafe medical devices.

2.6 Recertification

After first-time certification, the notified body carries out annual reaudits. Moreover, medical devices must be recertified by notified bodies no later than 5 years after the CE mark is awarded. Upon successful completion of the (re)audit, a product is awarded with a renewed Certificate of Conformity. Exceptions are currently being negotiated.

Under the still applicable MDD/AIMDD rules, recertifications by the notified bodies are only possible until the end of the transitional period ending on May 26, 2020. From that date forward, manufacturers must be able to produce an EC certificate under the new MDR for the recertification of medical devices. Thus, manufacturers have the option to apply for an extension of their existing certificates immediately prior to May 26, 2020. These would be valid then until the middle of 2024 at the latest.

Under the MDR, proof of the clinical effectiveness of a medical device and its safety in the course of recertification should be provided by means of a specialist clinical evaluation only in exceptional cases. A waiver of clinical data for clinical evaluation is basically permitted only for non-critical products, such as screws, wedges, plates, and instruments.

The evaluation is completed by assessing the reasonableness of the benefit/risk ratio. In this final balance of risk, burden, and benefit, the benefits must clearly outweigh.

The benefit-risk analysis and assessment is based on the collection and review of data and the literature. The clinical evaluation is based on clinical data from

recognized literature databases, FDA and BfArM notifications,[15] personal data from PMS, or data from competing companies.

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[15] BfArM notifications, FDA reports on problems (Manufacturer and User Facility Device Experience, MAUDE database), clinical trial results being published, e.g., in PubMed (only clinical data from "peer-reviewed" publications can be considered), feedback from the field.

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