Developing a Companion Diagnostics in parallel to a medicinal product – Legal and Regulatory requirements in Europe and in the US

"Companion Diagnostics" are in vitro diagnostic medical devices device specifically intended for the selection of patients to be treated with a specific medicinal product. In order to develop medicines fitting specific patients' needs without putting patients to unnecessary risk, medicinal products are often developed in parallel to the respective companion diagnostic in vitro diagnostic device. It is important to understand the legal and regulatory requirements for the development of companion diagnostics in order to ensure that this combined development is performed according to the existing rules. The requirements for the development of companion diagnostics differ depending on the stage of development. The specific requirements in Europe and in the US for the different stages of development of companion diagnostics are outlined in the following:

Current status EU (reflecting Directive 98/79/EC)

Although the phrase "Companion Diagnostics" is established in Europe the term as such is currently not defined in Europe. "Companion Diagnostics" fall under the legal definition of "in-vitro diagnostic medical devices" in Europe and are regulated in Directive 98/79/EC. Relevant definitions defining the different stages of development of companion diagnostics according to the current European legislation are the following:

'In vitro diagnostic medical device' - Article 1(2)(b) of Directive 98/79/EC:

'In vitro diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:

— concerning a physiological or pathological state, or

— concerning a congenital abnormality, or

— to determine the safety and compatibility with potential recipients, or

— to monitor therapeutic measures.

Specimen receptacles are considered to be in vitro diagnostic medical devices. 'Specimen receptacles' are those devices, whether vacuum-type or not, specifically intended by their manufacturers for the primary containment and preservation of specimens derived from the human body for the purpose of in vitro diagnostic examination.

Products for general laboratory use are not in vitro diagnostic medical devices unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for in vitro diagnostic examination.

'device for performance evaluation' - Article 1(2)(e) of Directive 98/79/EC:

'device for performance evaluation' means any device intended by the manufacturer to be subject to one or more performance evaluation studies in laboratories for medical analyses or in other appropriate environments outside his own premises;

'research use only products' - Recital 8 of Directive 98/79/EC:

Whereas instruments, apparatus, appliances, materials or other articles, including software, which are intended to be used for research purposes, without any medical objective, are not regarded as devices for performance evaluation

The differentiation between 'device for performance evaluation' and 'research use only products' might not be completely clear from the respective legal definitions. Clarification is provided in the MEDDEV Guideline 2.14/2 rev 1 from February 2004, where it is clearly stated that the intended use of the in-vitro diagnostic in a specific evaluation as defined by the manufacturer implies whether the IVD is a research only product or a device for performance evaluation:

Therefore once a medical device is intended by the manufacturer to be used for medical purposes it must either fall under the category of a product undergoing performance evaluation for the purpose of CE marking or be a product which is CE marked. 'For research use only' products do not have an intended medical purpose. When a medical purpose has been established based on sufficient and broadly agreed upon scientific, diagnostic and clinical evidence, then the product must comply with the requirements of the Directive before the manufacturer can place it on the market with an intended IVD use.

Furthermore, the MEDDEV Guideline lists specific examples of possible situations where RUO products could be used and which therefore fall outside the scope of the IVD Directive. The first two examples are:

(a) *RUO products used for Basic Research*: These are products used for research conducted to study all aspects of human life in an attempt to better understand all underlying mechanisms. In such studies / experiments animal and / or human models are used. No medical purpose is defined, as the specimens taken are not being used for the purpose identified in the definition of an IVD device in the IVD Directive, article 1 2(b). In such practice there is no potential to misuse RUO products.

(b) *RUO products used in Pharmaceutical Research*: This is research conducted to find new drug compounds. The RUO products are used to verify the reactions to compounds in animal and / or human models. In such practice there is no potential to misuse RUO products.

Furthermore, the term "performance evaluation" is not defined in the IVDD; however, it is defined in the European harmonised standard, EN 13612:2002, Performance evaluation of in vitro diagnostic medical devices. The standard states that "performance evaluation" means "investigation of the performance of an in vitro diagnostic medical device based upon data already available, scientific literature and/or performance evaluation studies." The standard defines "performance evaluation studies" as "investigation of an in vitro diagnostic medical device intended to validate the performance claims under the anticipated conditions of use."

The term "Laboratory developed test" as used in the US is neither defined nor established in Europe. Despite that Directive 98/79/EC clarifies that laboratory tests comparable to LDTs in the US do not fall under the scope of the Directive:

This Directive shall not apply to devices manufactured and used only within the same health institution and on the premises of their manufacture or used on premises in the immediate vicinity without having been transferred to another legal entity. This does not affect the right of Member State to subject such activities to appropriate protection requirements.

Requirements for Research Use Only products

In Europe there are no specific requirements defined for Research Use Only products. Accordingly, there are no defined requirements regarding documentation or quality systems.

Requirements for Devices for Performance Evaluation

Specific legal requirements for Devices for Performance Evaluation are defined in Annex VIII of Directive 98/79/EC. For devices for performance evaluation the manufacturer or his authorized representative shall draw up a statement describing specific details of the planned evaluation and ensure that the relevant provisions of this Directive are met. Furthermore, a statement is required, that the device in question conforms to the requirements of the Directive, apart from the aspects covered by the evaluation and apart from those specifically itemised in the statement, and that every precaution has been taken to protect the health and safety of the patient, user and other persons. Documentation allowing an understanding of the design, manufacture and performances of the product, including the expected performances, so as to allow assessment of conformity with the requirements of this Directive has to be kept available for the competent authorities. This

documentation must be kept for a period ending at least five years after the end of the performance evaluation. Manufacturers of devices for performance testing have to comply to the notification requirements as described in Article 10(1), (3) and (5) of Directive 98/79/EC.

Further national requirements for performance evaluation studies

It needs to be checked on a national level, whether it is necessary to notify the competent authority of a performance evaluation or whether authorization of a performance evaluation study is required.

As an example the national requirements in Germany are outlined:

§24 Medizinproduktegesetz

Performance evaluations with IVDs need to be authorized by the competent authority in the following cases:

1. Specimen are taken in an invasive way only or mainly in order to conduct the performance evaluation study

2. Other invasive or burdensome evaluations are conducted as part of the performance evaluation

3. The results of the performance evaluation will be used for diagnostic purposes without being confirmed by established methods.

In situations as described under 1) and 2) above waiving of the authorization of a performance evaluation study is possible upon request. The respective requirements are defined in the respective communication on the submission of a request for waiving the authorisation of a clinical trial or a performance evaluation to the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) in accordance with Section 20 sub-section 1 sentence 2 of the German Act on Medical Devices.

Commercial In-vitro diagnostic – Article 9 Directive 98/79/EC

In order to be able to commercialise an in-vitro diagnostic an EC declaration of conformity procedure according to Annex IV, V or Annex VII (for IVD as defined in Annex II) or according to Annex III (all other products) need to be followed in order to be allowed to affix the CE marking.

Conclusion on requirements for IVDs in different stages of development of a companion diagnostic:

In order to clearly define the existing legal requirements for in-vitro diagnostic medical devices during development, the differentiation between 'devices for performance evaluation' and 'research use only products' is essential.

EN 13612 defines that performance evaluation studies are intended to validate the performance claims under the anticipated conditions of use.

Furthermore, MEDDEV Guidance 2.14/2 includes the specific example that Research Use Only products are used to verify the reactions to compounds in animal and / or human models in pharmaceutical research. Only in case a medical device is intended by the manufacturer to be used for medical purposes it must either fall under the category of a product undergoing performance evaluation for the purpose of CE marking or be a product which is CE marked.

Accordingly, any in-vitro-diagnostic used in animal models (pre-clinical studies) is a Research Use Only product as it is not intended for medical purposes and is not falling into the scope of Directive 98/79/EC.

Whether an in-vitro diagnostic used in clinical studies is considered to be a Research Use Only product or a Device for Performance Evaluation depends on the objective of the clinical study conducted as well as on the intended medical purpose of using the device.

It might be understood that as long as clinical studies are performed to evaluate pharmacodynamic reactions to a pharmaceutical compound and in-vitro diagnostics are used to verify the reactions to the

compounds, the IVD in this study is still considered to be a Research Use Only product and is not falling into the scope of Directive 98/79/EC. Depending on the objective of the respective study, this might be the situation in a Phase I and Phase II studies evaluating pharmacodynamic effects of an investigational medicinal product, where the specimen are shipped to the manufacturer of the IVD for analysis.

As soon as an IVD is used with a medical purpose – i.e. to provide information concerning a physiological or pathological state, or concerning a congenital abnormality, or to determine the safety and compatibility with potential recipients, or to monitor therapeutic measures - the IVD would be considered a Device for performance evaluation and falls into the scope of Directive 98/79/EC. Performance evaluation studies are intended to validate the performance claims of the device under anticipated conditions of use, that is, how actual users are expected to use the device. Performance evaluation studies are a type of design validation conducted outside a manufacturer's facility and under anticipated conditions of use.

Irrespective of the classification of the IVD as Research Use Only product or Device for Performance Evaluation Article 1(5) of Directive 98/79/EC clearly defines that this Directive shall not apply to devices manufactured and used only within the same health institution and on the premises of their manufacture or used on premises in the immediate vicinity without having been transferred to another legal entity ("Laboratory developed tests").

In case the use of the IVD in a planned evaluation is classified as Research Use Only product there are no specific requirements regarding documentation or quality systems. Despite that it should be taken into consideration that the data generated with an IVD as Research Use Only product might be used later in development to support the use of the IVD as Device for Performance Evaluation or for the EC declaration of conformity. Accordingly, the generation of data with a Research Use Only product might follow a sufficient level of diligence.

If the respective evaluation is a performance evaluation study and the IVD is classified as Device for Performance evaluation, then the requirements defined in Directive 98/79/EC apart from the aspects covered by the evaluation and apart from those specifically itemised in the statement according to Annex VIII of Directive 98/79/EC need to be fulfilled. Accordingly all legal requirements defined in Directive 98/79/EC regarding documentation and quality systems need to be fulfilled for a Device for Performance Evaluation except those aspects evaluated with the specific performance evaluation. The respective documentation must be kept for a period of at least five years after the end of the performance evaluation and needs to be kept available for the competent national authority to allow assessment of conformity with the requirements of Directive 98/79/EC.

The manufacturer cannot choose whether a device is considered to be a Research Use Only product or a Device for Performance Evaluation in a specific stage of development, but the respective classification will be driven by the intended use of the IVD in the respective evaluation.

Changing legal environment in Europe (Regulation 2012/0267)

Regulation 2012/0267 is currently in the ordinary legislative procedure. The European Parliament adopted as its position at first reading on 02 April 2014 the text adopted on 22. October 2013. The Regulation is currently awaiting first reading in the European Council.

The following outline of the most important changes impacting the development of companion diagnostics reflects the text as adopted by the Parliament in April 2014. As the legislative procedure is still ongoing, this is just an interim assessment.

An official legal definition of a companion diagnostic is planned to be included in the Regulation. The current version of the definition is "'companion diagnostic' means a device specifically intended for and essential to the selection of patients with a previously diagnosed condition or predisposition as suitable or unsuitable for a specific therapy with a medicinal product or a range of medicinal products". Companion diagnostics are at least classified as class C products. They might fall under class D in case they fulfill other classification criteria for these products.

Specific legal requirements are defined on clinical evidence and clinical performance studies. A "clinical Trial Application" will be required for interventional clinical performance studies.

"Laboratory developed tests" will not be generally exempted from the new regulation, but will fall within the scope of the legislative text. Only tests manufactured and used in a single health institution are exempted under in case specific conditions are fulfilled. Tests manufactured and used in commercial laboratories will not be exempted.

USA

The following definitions might be of relevance when developing a companion diagnostic in the US:

In vitro diagnostic products - 21 CFR 809.3:

(a)In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the act), and may also be biological products subject to section 351 of the Public Health Service Act.

Laboratory Developed Test (LDT):

There is no legal definition of Laboratory Developed test. A regulatory definition is provided in the Clinical Laboratory Improvement Amendments (CLIA) document "LDT and CLIA FAQs":

The FDA defines a Laboratory Developed Test (LDT) as an in vitro diagnostic test that is manufactured by and used within a single laboratory (i.e. a laboratory with a single CLIA certificate). LDTs are also referred to as in-house developed tests or "home brew" tests.

"Research Use Only" in vitro diagnostic products:

No concrete legal/regulatory definition is provided for IVDs labeled for Research Use Only. An indirect definition is provided in 21 CFR 809.10 (c)(2)(i):

For a product in the laboratory research phase of development, and not represented as an effective in vitro diagnostic product, all labeling bears the statement, prominently placed: "For Research Use Only. Not for use in diagnostic procedures.

Further clarification on the definition of Research Use Only In Vitro Diagnostics is provided in the Guidance for Industry and Food and Drug Administration Staff on the distribution of in vitro diagnostic products labeled for Research Use Only or Investigational Use Only issued on 25 November 2013 in section III A.:

An RUO product is an IVD product that is in the laboratory research phase of development and is being shipped or delivered for an investigation that is not subject to part 812. During the research phase of development, the focus of manufacturer-initiated studies is typically to evaluate design, limited-scale performance, and issues such as usability of the test. Some examples of products FDA would consider to be in this research phase include:

• Tests that are in development to identify test kit methodology, necessary components, and analytes to be measured.

• Instrumentation, software, or other electrical/mechanical components under development to determine correct settings, subcomponents, subassemblies, basic operational characteristics, and possible use methods.

• Reagents under development to determine production methods, purification levels, packaging needs, shelf life, storage conditions, etc.

FDA also recognizes that there are certain products, such as instruments, systems, and reagents that are labeled for research use only and intended for use in the conduct of non-clinical laboratory research with goals other than the development of a commercial IVD product, i.e., these products are used to carry out research and are not themselves the object of the research. These include products intended for use in discovering and developing medical knowledge related to human disease and conditions. For example, instruments and reagents intended for use in research attempting to isolate a

gene linked with a particular disease may be labeled for research use only when such instruments and reagents are not intended to produce results for clinical use.

“Investigational Use Only” in vitro diagnostic products:

No concrete legal/regulatory definition is provided for IVDs labeled for Research Use Only. An indirect definition is provided in 21 CFR 809.10 (c)(2)(ii):

For a product being shipped or delivered for product testing prior to full commercial marketing (for example, for use on specimens derived from humans to compare the usefulness of the product with other products or procedures which are in current use or recognized as useful), all labeling bears the statement, prominently placed: "For Investigational Use Only. The performance characteristics of this product have not been established."

Further clarification on the definition of Investigational Use Only In Vitro Diagnostics is also provided in the Guidance for Industry from 25 November 2013 in section III B.:

An IUO product is an IVD product that is being shipped or delivered for product testing that is not subject to 21 CFR part 812 (with the exception of §812.119, Disqualification of clinical investigator) prior to full commercial marketing (for example, for testing of specimens derived from humans to compare the usefulness of the product with other products or procedures which are in current use or recognized as useful). Examples of IVD products under investigation that FDA considers to fall in this category include those that are being evaluated in comparison studies that use archived or fresh specimens to determine performance characteristics.

As defined in 21CFR809.10(c)(2) labelling of an IVD as “Investigational Use Only” product is foreseen only in case of shipment or delivery for an investigation that is not subject to part 812, so in case the planned investigation does not fall under an IDE. Guidance on whether an investigation of an IVD falls under the IDE requirements can be found in 21CFR812.2(c)(3):

(c) *Exempted investigations*. This part, with the exception of 812.119, does not apply to investigations of the following categories of devices:

(3) A diagnostic device, if the sponsor complies with applicable requirements in 809.10(c) and if the testing:

(i) Is noninvasive,

(ii) Does not require an invasive sampling procedure that presents significant risk,

(iii) Does not by design or intention introduce energy into a subject, and

(iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

For an investigation to be exempt from most of the requirements of the IDE regulation, it must meet all of the conditions listed above. If the investigation does not fit into one of the three categories listed above the sponsor must have an approved IDE (21 CFR 812.2) before beginning the investigation, including any shipment of the investigational IVD. If there is no medically established diagnostic product or procedure and clinical investigators use the results from the investigational study to decide on treatment, FDA would not consider the study exempt from IDE requirements under 21 CFR 812.2. Labelling the product as “Investigational Use Only” would be misleading in this case.

Investigational device - 21 CFR 812.3(g):

Investigational device means a device, including a transitional device, that is the object of an investigation.

IVD products intended for investigational use in a manner that is not consistent with an exempted investigation must comply with the Investigational Device Exemption (IDE) requirements in 21 CFR part 812 in order to be exempt from many requirements otherwise applicable to medical devices. According to 21CFR812.5(a) they must be with the following statement: "CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use."

IVD Companion Diagnostic device:

There is no legal definition of an IVD Companion Diagnostic Device. A regulatory definition is provided in the Draft Guidance for Industry and Food and Drug Administration Staff – In Vitro Companion Diagnostic Devices issued 14 July 2011:

An *IVD companion diagnostic device* is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents of the therapeutic product.

An IVD companion diagnostic device could be essential for the safe and effective use of a corresponding therapeutic product to:

· Identify patients who are most likely to benefit from a particular therapeutic product6

· Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product

· Monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness

Specific Requirements for Laboratory Developed tests

Similar to other in vitro diagnostic tests, LDTs are considered "devices," as defined by the Federal Food, Drug, and Cosmetic Act (FD&C Act, FFDCA), and are therefore subject to regulatory oversight by FDA. Although the FFDCA requires manufacturers of all in vitro diagnostic devices (IVDs), including LDTs, to comply with the regulatory requirements governing device safety and effectiveness (such as quality controls for device design and other aspects of device manufacturing, premarket clearance/approval, etc.), the FDA has generally exercised enforcement discretion so that the agency has generally not enforced these requirements for LDTs. LDTs, therefore, generally have not undergone FDA premarket review, which assures both the analytical validity (e.g. analytical specificity and sensitivity, accuracy and precision) and clinical validity of IVDs.

Under the CLIA regulations, when a laboratory uses a test system that has not received FDA clearance or approval, such as a LDT, the laboratory may not release any test results prior to establishing certain performance characteristics relating to analytical validity for the use of that test system in the laboratory's own environment, see 42 CFR 493.1253(b)(2) (establishment of performance specifications). CLIA and its implementing regulations do not affect FDA's authority under the FDCA to regulate LDTs or other devices used by laboratories.

Further, CMS' CLIA program does not address the clinical validity of any test – that is, the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient. On the other hand, FDA evaluates the clinical validity of a test under its premarket clearance and approval processes and as a result, has expertise in this area. In other words, the FDCA encompasses clinical validity whereas CLIA does not.

Specific Quality System requirements for IVDs/Companion diagnostics during development

According to 21CFR812.1(a) an Investigational Device falling under the IDE requirements are exempted from the GMP requirements except the requirements for Design Controls as defined in 21CFR820.30.

Furthermore, it is defined in 21CFR812.20(b)(3) that the description of used methods, facilities and controls submitted with the IDE to the FDA for approval need to provide a sufficient level of detail to assess the quality control applied.

In addition, 21CFR812.140(b)(4)(v) requires that the sponsor of an IDE investigation of a device other than a significant risk device shall keep a statement on the GMP status in his records available for FDA inspection and copying.

Investigational devices exempted from the IDE requirements according to 21CFR812.2(c) (Research Use Only products and Investigational Use Only products) are not exempted from the QSR requirements. Despite that FDA clarified in their Guidance for Industry and FDA Staff - In Vitro Diagnostic (IVD) device Studies – Frequently Asked Questions issued on 25 June 2010 that they generally do not intend to enforce such requirements for investigational IVDs that are exempt from most 21 CFR Part 812 requirements; except for design controls.

Application requirements for IVDs/Companion diagnostics during development

In-vitro diagnostic devices in investigational use can be exempted from the IDE requirements in case they fulfill all requirements listed in 21CFR812.2(c)(3). In case one the requirements listed there is not fulfilled, than the investigation falls under the IDE requirements.

Depending on the classification as a significant risk device the IDE requirements might either require submission and approval of the IDE by the FDA according to 21CFR812.20 or the investigations are considered to have approved applications for IDEs in case the abbreviated requirements as defined in 21CFR812.2(b) are fulfilled.

By definition Research Use Only IVD products and Investigational Use Only IVD products are exempted from the IDE requirements, so there is no requirement for an application.

In order to decide whether a planned investigation with a companion diagnostic is exempted from the IDE requirements, the question whether the IVD "is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure" might be of high relevance. In case no diagnosis is made with the device or in case the diagnosis is confirmed by another, medically established diagnostic product or procedure an exemption from the IDE requirements might be possible. In case no confirmation of the diagnosis is foreseen or if there is no medically established diagnostic product or procedure and clinical investigators use the results from the investigational study to decide on treatment, then the investigation falls under the IDE requirements.

As stated in the Draft Guidance for Industry and Food and Drug Administration Staff – In Vitro Companion Diagnostic Devices issued 14 July 2011, companion diagnostics are by definition used to make critical treatment decisions, such as patient selection, treatment assignment, or treatment arm. Therefore, a diagnostic device generally will be considered a significant risk device under 21 CFR 812.3(m)(3) because it presents a potential for serious risk to the health, safety, or welfare of the subject. In case the investigation is not exempted from the IDE requirements the sponsor of the diagnostic device will be required to comply with the investigational device exemption (IDE) regulations that address significant risk devices. In such cases, FDA will expect the sponsor to conduct the trial under full IDE regulations.

Registration and listing requirements for IVDs/Companion diagnostics during development

As defined in 21 CFR812.1 an IDE approved under 812.30 or considered approved under 812.2(b) exempts a device from the requirements of registration, listing , and premarket notification under section 510 of the Act.

According to 21CFR807.20(a) an owner or operator of an establishment who is engaged in the manufacture, preparation, propagation, compounding, assembly, or processing of a device intended for human use shall register and submit listing information for those devices in commercial distribution. As neither Research Use Only IVD products nor Investigational Use Only IVD products are in commercial distribution, no registration or listing requirements occur for these products. The same is confirmed in 21 CFR807.65(f), where it is stated that "Persons who manufacture, prepare, propagate, compound, or process devices solely for use in research, teaching, or analysis and do not introduce such devices into commercial distribution.".

Accordingly, no registration or listing is necessary for IVDs/Companion diagnostics during development.

Commercial Companion In-vitro diagnostic products

As stated in the Draft Guidance for Industry and Food and Drug Administration Staff – In Vitro Companion Diagnostic Devices issued 14 July 2011 the level of risk together with available controls to mitigate risk will establish whether an IVD companion diagnostic device requires a premarket application (PMA) or, a 510(k) as regulatory pathway.

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Autor:

Kirsten Vonde
Senior Consultant
Granzer Regulatory Consulting & Services
Zielstattstr. 44
D-81379 München
Germany

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EN 13612/2002

Gesetz über Medizinprodukte (Medizinproduktegesetz – MPG)

http://www.gesetze-im-internet.de/bundesrecht/mpg/gesamt.pdf

Information on submission of a request for waiving the authorisation of a clinical trial or a performance evaluation to the Federal Institute for Drugs and Medical Devices (Bundestinstitut für Arzneimittel und Medizinprodukte, BfArM) in accordance with Section 20 sub-section 1 sentence 2 of the German Act on Medical Devices

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Clinical Laboratory Improvement Amendments (CLIA) – LDT and CLIA FAQs

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