EU MDR Rule 21
Substance Based Devices

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By Royal Charter

Poll Question

What do you think about the introduction of Rule 21 in the MDR ?

a. **Good and needed to have a level approach for all**
b. **Bad for innovation**
c. **No strong feeling**
d. **Difficult to interpret when it applies**

Agenda

- Background and History under MDD
- Key Definitions and Guidance
- Conformity Assessment process
- Common Issues
- Team-NB Work Group Activities

Rule 21: Background & History

MDR Rule 21, Annex VIII

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 are classified as:

— class III if they, or their products of metabolism, are systemically absorbed by the human body in order to achieve the intended purpose;

— class III if they achieve their intended purpose in the stomach or lower gastrointestinal tract and they, or their products of metabolism, are systemically absorbed by the human body;

— class IIa if they are applied to the skin or if they are applied in the nasal or oral cavity as far as the pharynx, and achieve their intended purpose on those cavities; and

— class IIb in all other cases.

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Medicinal Products

Medical Devices

Definition of medicinal product Vs medical device

Medicinal product

Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by **exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis**

Medicinal Products Directive (MPD) 2001/83/EEC

Medical device

Any instrument, apparatus, appliance, software, implant, reagent material or other article, intended to be used alone or in combination for human beings for the following specific medical purposes…,

and **which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means** but which may be assisted in its function by such means

Medical Devices Regulation (MDR)

EU 2017/745

Medicinal Products

Medical Devices

Rule 21 Devices

- Must have a medical purpose and meet the definition as a medical device
- Similar in formulation and include components that are traditionally used in areas such as food, cosmetics or medicinal products
- Similar in presentation to medicinal products, tablets, creams, capsules etc.
- Achieve their intended purpose by a physical / simple chemical means
- Generally, for Customer Self-Care Products
- Can be available as “over the counter” or via “Websites”
- Must not achieve its principal intended action by pharmacological, metabolic or immunological means, but can be assisted by such means

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Assessment under MDD ?

- Many products exist that function by physical means
  - MDD legislation didn’t foresee the development of such products
  - Historically regulated as medicinal products

- No specific Rule existed under MDD
  - Rule 5, Annex IX often used but never intended to cover such products
  - Invasive devices wrt body orifices, used in the oral cavity as far as the pharynx
  - Risk Classification Class I – IIb

- Divergence in the EU
  - Simethicone preparations for oral administration

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Why the Change ?

MDR *Whereas (59)*

"Rules under the old regime applied to invasive devices do not sufficiently take account of the level of invasiveness and potential toxicity of certain devices which are introduced into the human body. In order to obtain a suitable risk-based classification of devices that are composed of substances or of combinations of substances that are absorbed by or locally dispersed in the human body, it is necessary to introduce specific classification rules for such devices.

The classification rules should take into account the place where the device performs its action in or on the human body, where it is introduced or applied, and whether a systemic absorption of the substances of which the device is composed, or of the products of metabolism in the human body of those substances occurs. "

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Why Change ?

- The Cranberry Decision May 2017
  - ANSM wanted to revoke a Class IIb medical device status of cranberry products patented by a French Company
  - Useful in reducing urinary tract infections
  - Contain proanthocyanidins (PACs), stable phenolic compounds with anti-adhesion activity against E. Coli
- Ensure the legislation is future proof
- Implement appropriate risk classification and scrutiny of such devices proportionate to the nature of the risk presented by the device
- Ensure the safety of the *"constituent(s) responsible for achieving the principal intended action"* by analogy to Medicinal Products Directive 2001/83/EEC

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Public Perception and Potential Interactions

Public Perception and Product Safety

The implant files
Healthcare industry

This article is more than **4 years old**

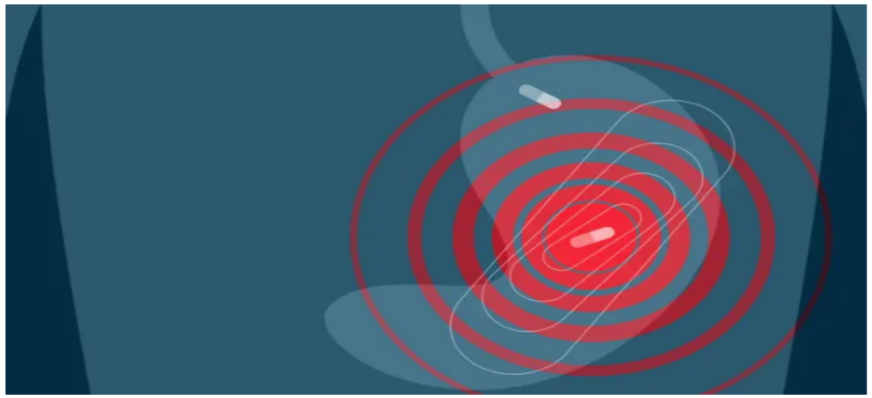
Not a drug: why EU rules on diet pills mean fewer safety checks

Critics say classification as medical devices allows firms to avoid more rigorous testing

- **Revealed: how faulty implants harm patients worldwide**
- **Why we're examining the implants industry**

Hilary Osborne

Sun 25 Nov 2018 17.00 GMT



Some of the pills rapidly expand in the stomach to up to 200 times their initial size. Illustration: Guardian Design/Christophe Gowans

The investigation into medical devices has uncovered all kinds of anomalies - and one of the more startling involves diet pills.

To the millions of people who buy them to lose weight, the pills are exactly that - capsules to swallow.

But EU regulators have taken a different view. To them, the pills are not drugs that need to be tested in the usual manner, they are classified as "medical devices" - and as such, they can get to customers more easily.

This has led some experts to warn that the pills - some of which rapidly expand in the stomach "like a balloon" to up to 200 times their initial size - are getting safety approval through the backdoor.

Among the diet aids that are marketed with a CE (Conformité Européenne) mark, which indicates they meet EU safety standards, are pills containing dietary fibre that promise to swell up in the stomach. These can be found on the shelves of high-street chemists and supermarkets.

Critics of the system say manufacturers are able to obtain safety certificates without the kind of testing that would be required if the products were classed as drugs, and are allowed to make claims they would not be able to make if the products were classed as food supplements.

Dr Matt Capehorn, the clinical manager at the Rotherham Institute for Obesity, said manufacturers were using the rules to get safety approval through the back door. He said that while product approval through the pharmaceutical route involved testing on "hundreds if not thousands of people, it can be just 10 for a medical device".

The Guardian

Types of Devices

- Orally ingested products – Capsules, Tablet, Suspension dosage forms for the treatment of obesity, constipation, diarrhoea
- Devices applied to the skin, creams & ointments for hydration
- Solutions for nasal application, throat sprays
- Gels for vaginal moisturizing / lubricants
- Ear Drops to soften wax
- Eye drops for hydration

Risk Classification

Class	Rule 21	Examples
III	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 are classified as: — class III if they, or their products of metabolism, are systemically absorbed by the human body in order to achieve the intended purpose;	
III	— class III if they achieve their intended purpose in the stomach or lower gastrointestinal tract and they, or their products of metabolism, are systemically absorbed by the human body;	• Na/Mg alginate, xyloglucan • Fat absorbers that are systemically absorbed, themselves or their metabolites
IIa	— class IIa if they are applied to the skin or if they are applied in the nasal or oral cavity as far as the pharynx[1], and achieve their intended purpose on those cavities; and	• Substance-based formulations for skin treatment • Salt water used e.g. as nose or throat sprays • Oral cough treatments achieving their intended purpose in the oral cavity as far as the pharynx
IIb	— class IIb in all other cases.	• Simethicone preparations for oral administration • Active coal for oral administration • Gel for vaginal moisturizing / vaginal lubricants • Eye drops for hydration • Ear drops[1, 2] • Medical devices, for oral administration, for the treatment of diarrhoea, e.g. kaolin, diosmectite • Medical devices, for oral administration, for the treatment of obesity, e.g. fructooligosaccharides, glucomannan

When is Rule 21 not applicable

- Non-invasive conductive gels such as ultrasound gels
- Medical devices used *in vitro*
  - Rule 3 devices for extracorporeal treatment of body fluids / tissues / embryos for reintroduction into the body
    - Solution of organ preservation and transportation
    - IVF Media
- Surgically Invasive devices
  - Drug Eluting Stents
  - Bone Cements

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Key Definitions & Guidance

What is a Substance ?

- Defined in 2001/83/EEC but this definition includes substances not permitted in medical devices such as
  - Viable biological materials or organisms
  - Viable animal tissues / cells / derivatives
  - Viable human cells/ tissues / derivatives
- Meeting the definition of “substance does not mean that the product may not be qualified as a medical device

3. *Substance:*

Any matter irrespective of origin which may be:

— human, e.g.

human blood and human blood products;

— animal, e.g.

micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products;

— vegetable, e.g.

micro-organisms, plants, parts of plants, vegetable secretions, extracts;

— chemical, e.g.

elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis.

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Key Definitions

Systemic absorption

The process by which substances or their metabolites enter the body and are distributed into the body via the blood and / or lymphatic system

Local dispersion

The condition by which substances remain in a specific site without being distributed into the body via the blood and/or lymphatic system

Reference: MDCG 2021-24

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Useful Guidance

MDCG 2022 – 5

Guidance on borderline between medical devices and medicinal products under Regulation (EU) 2017/745 on medical devices

April 2022

AESGP

Association of the European Self-Care Industry

AESGP Position Paper on Classification Rule 21

MDCG 2021-24

Guidance on classification of medical devices

October 2021

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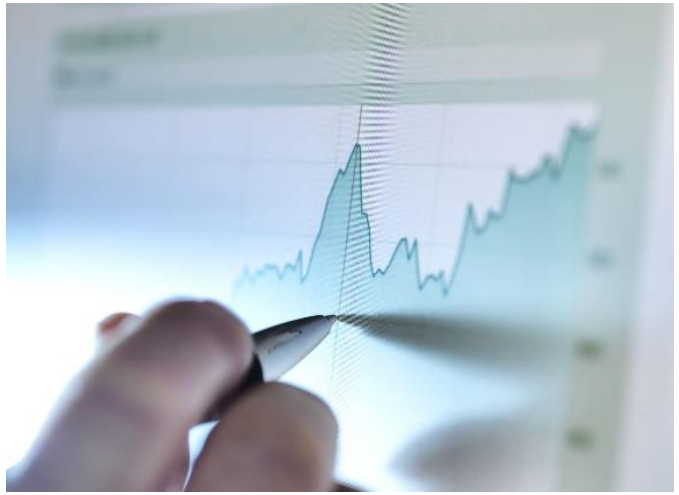
Poll Question

What are your main concerns when thinking about requirements for Rule 21 Devices ?

a. **The NB won’t agree that my product is a medical device**
b. **Conformity Assessment process requires a consultation**
c. **Unknown data requirements to meet GSPR 12.2**
d. **Additional labelling requirements**
e. **Other**



Conformity Assessment

GSPRs specific to Rule 21 Devices

- GSPR 12.2
- GSPR 23.2 (r) – Information on the label
- GSPR 23.4 (t) – Information in the ifu

Rule 21 Devices – GSPR 12.2

12.2. Devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body, and that are absorbed by or locally dispersed in the human body shall comply, where applicable and in a manner limited to the aspects not covered by this Regulation, with the relevant requirements laid down in Annex I to Directive 2001/83/EC for the evaluation of absorption, distribution, metabolism, excretion, local tolerance, toxicity, interaction with other devices, medicinal products or other substances and potential for adverse reactions, as required by the applicable conformity assessment procedure under this Regulation.

- Where applicable & limited to the aspects not covered by MDR
- Evaluation by analogy to Medicinal product directive for evaluation of adsorption, distribution, metabolism, excretion
- Consideration of local tolerance & toxicity
- Interactions with other devices, medicinal products or other substances
- Potential for adverse reactions

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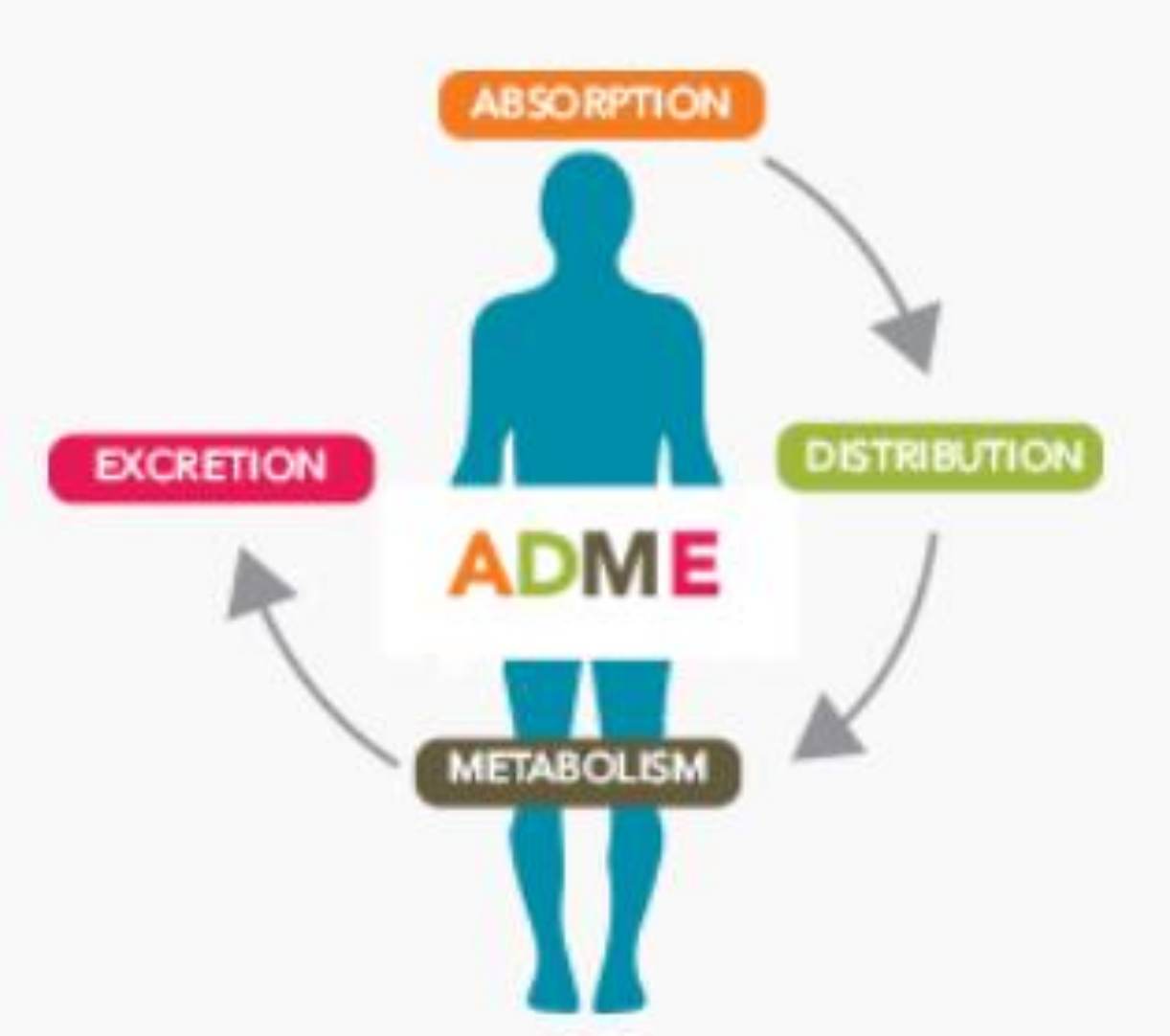
ADME of Substances

- Absorption
  - Active, passive..
- Distribution
  - Blood stream, lymph, cell to cell
- Metabolism
  - Liver, kidneys
- Excretion
  - Faeces or urine or accumulation



Rule 21 – Labelling & IFU

Label

- Qualitative composition of the device
- Quantitative information on the main *"constituent responsible for principal intended action"*

(r) in the case of 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, the overall qualitative composition of the device and quantitative information on the main constituent or constituents responsible for achieving the principal intended action;

IFU

- Warning & precautions re potential interactions
- Contraindications, undesirable side effects and risks of overdose

(t) in the case of devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body and that are absorbed by or locally dispersed in the human body, warnings and precautions, where appropriate, related to the general profile of interaction of the device and its products of metabolism with other devices, medicinal products and other substances as well as contra-indications, undesirable side-effects and risks relating to overdose;

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Conformity Assessment

- MDR Annex IX, 5.4 details requirements
- Quality & safety verified where applicable for the evaluation of ADME, local tolerance, toxicity, interactions and potential for adverse reactions
- Introduces the requirement for the NB to seek a scientific opinion from a medicines CA / EMA
  - A 150 day procedure
  - Documentation requirements for the consultation not prescribed

Medicines Agency Consultation

(b) In addition, for devices, or their products of metabolism, that are systemically absorbed by the human body in order to achieve their intended purpose, the notified body shall seek a scientific opinion from one of the competent authorities designated by the Member States in accordance with Directive 2001/83/EC or from the EMA, either of which to be referred to in this Section as 'the medicinal products authority consulted' depending on which has been consulted under this point, on the compliance of the device with the relevant requirements laid down in Annex I to Directive 2001/83/EC.

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NB Expectations for Rule 21 Devices

- The Manufacturer has considered and identified the "*constituent(s) within the device responsible for achieving the intended purpose*"
- The Manufacturer's technical documentation and data available to demonstrate
  - The ADME of the main constituent(s)
  - Data on the local tolerance & toxicity of the substance(s)
  - Consideration of potential interactions
    - other devices, medicinal products or other substances
  - Potential for adverse reactions
- Labelling & IFU requirements met and appropriate for lay person use

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Common Issues

Common Issues

- Misinterpretation of the Rule 21 Devices that require a Medicines CA Consultation
- GSPR 12.2 and its applicability to other devices
- Interpretation of what is meant by locally dispersed
- Data requirement expectations and need to conduct extensive ADME Studies
- For topically applied products an unwillingness to accept that such products may be absorbed or locally dispersed

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Team NB Rule 21 Working Group

Rule 21 Working Group Aims

To share experience and examples of Rule 21 Devices

To agree interpretation of requirements

To ensure a level playing field for manufacturers across NBs and develop a consistent approach between NBs

Guidance in Draft

Aim to publish Q4 2023

To ensure the Commission are made aware of implementation challenges and difficult cases in a timely manner

To publish additional guidance on documentation requirements for such devices

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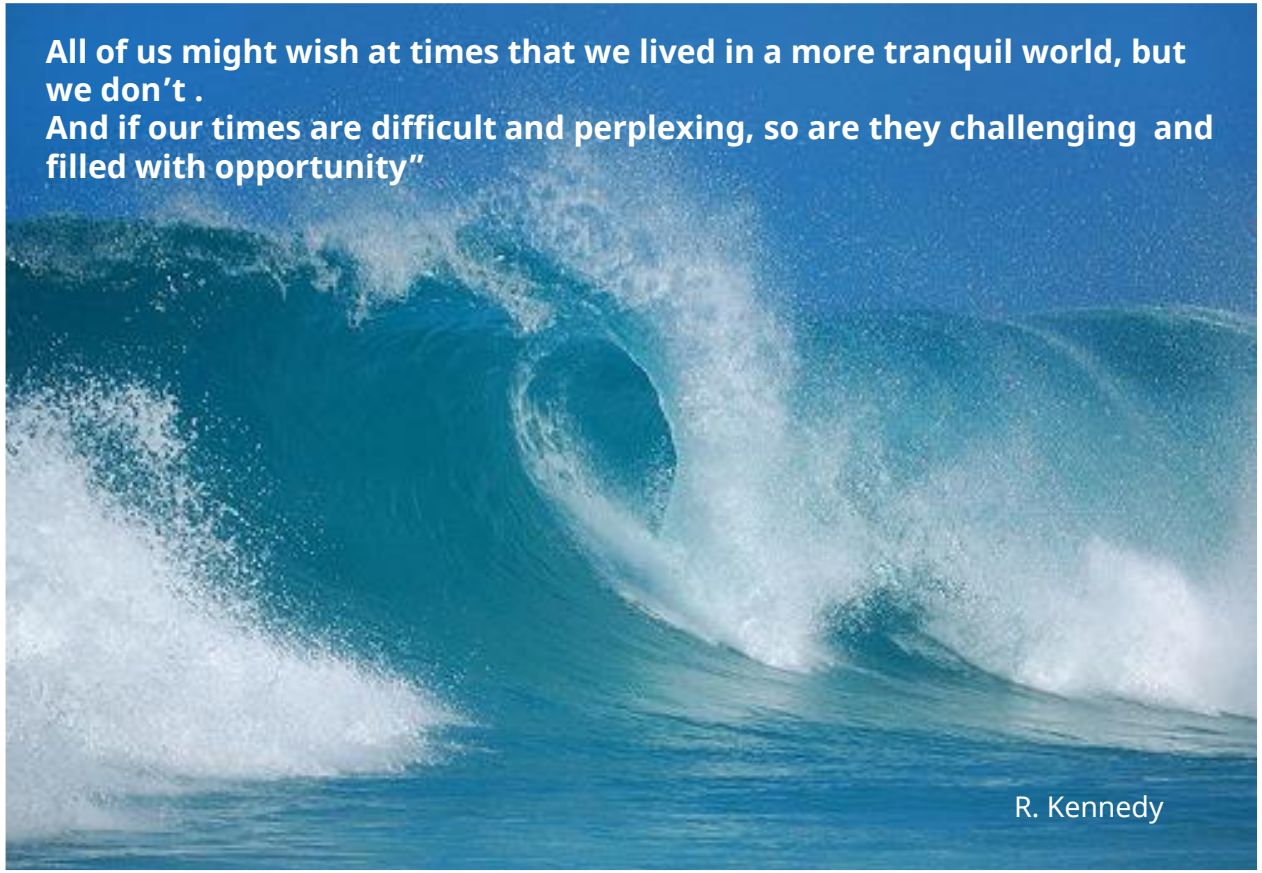
Key Takeaways on Rule 21

- Understanding the history and intent of this Rule is a good starting point
- This is a new rule for all and it shall evolve
- Team-NB guidance is coming



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BSI Medical Devices – Use Our Resources

Brochures, Guides and Documents

MDR guidance

MDD Best Practice Guidelines >
MDR Best Practice Guidelines >
MDR Mapping Guide >
MedDev 2.7.1 Rev 4 changes >
MDR Conformity Routes >
MDR Readiness Review >

Webinars

MDR Conformity Assessment Routes webinar

MDR - What we know

Download the presentation >

White Papers and Articles

Person responsible for regulatory compliance (PRRC) - MDR/IVDR Article 15

With the MDR and IVDR, European regulators aim to ensure companies have a regulatory expert – a Person Responsible for Regulatory Compliance (PRRC) – at their disposal, to ensure that the company is meeting certain specific EU requirements.

Software as a medical device - A comparison of the EU's approach with the US's approach

The International Medical Device Regulators Forum (IMDRF) aims to accelerate international medical device regulatory convergence. Through the IMDRF, regulators reached consensus on what software is considered a medical device. Regulators call it 'software as a medical device' (SaMD). This paper provides a comparison of how SaMD is regulated in the US and in the EU.

Machine learning AI in medical devices

How is AI different from traditional medical devices and medical software and what are the implications of those differences? What controls are necessary to ensure AI in healthcare is safe and effective?

Medical device clinical investigations – What's new under the MDR?

The conduct of a clinical investigation is one of the most time consuming and resource intensive activities that a medical device manufacturer can face. This paper discusses important new requirements for pre-market and post-market clinical investigations under the European MDR.

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Thank you for joining today

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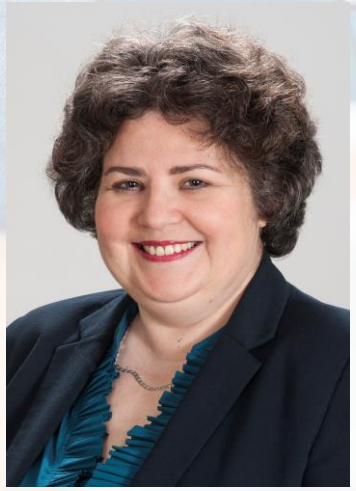

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