Changes in Regulatory Sciences

"How to move from a reactive to a multistakeholder proactive attitude"

25-27 October, 2018 Pavia (Italy)

The new Regulations on medical devices and on in vitro diagnostics: a real revolution?

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–ACCREDIA Medical Devices (MDR) and in vitro diagnostic (IVDR) Project Manager Lead Assessor
– EA Network 6 Convenor - Medical Devices accreditation standards
– EA European Commission - JRC Breast Cancer Services Project Manager

- Yes
- the new Regulations represent
- a real revolution but
- mainly
- a strong challenge

MD

IVD

Revolution?

Challenge?

- Yes
- the new Regulations represent
- a real revolution but
- mainly
- a strong challenge

- **QUANTITATIVE TRANSFORMATION**,
- BUT ABOVE ALL,
- **QUALITATIVE REVOLUTION**
- PRINCIPAL POSSIBLE MARKET EFFECTS

Many or certainly some NBs and OEs (Economic Operators = Manufacturers, Authorized Representatives, Importers, Distributors, Sponsors, etc.) will not be able to comply with the new requirements (personnel competences, increase of new critical process, increase of responsibilities towards the designation authorities

- For NBS: waiver of notification or reduction of DM's typologies
- For EO: renounces of certifiction of all DMs or of certain DM's typologires
- However there will be many, advantages for customers (sanitary operators) and final users (patients)
  Greater safety, quality and performance of DMs and IVDs

Let's analyze some data

Without data, you're just another person with an opinion."
William E. Deming

The medical devices industry is a major employer in Europe, employing 675,000 people in the EU
Total sales amount to €110 billion
The sector represents some 27,000 companies, of which 95% are Small and Medium-sized Enterprises (SMEs) 10 to 15 employees (insider and outsourcers)
It generates about 25% of EU GDP and 75% of trade in goods between EU Member States. The EU intervenes in about a sixth of world trade in goods. Trade in goods between EU Member States was assessed at EUR 3.063 billion in 2015.

There are 28 Member States of the European Union involved (including the United Kingdom), the European Economic Area (Iceland, Liechtenstein and Norway) and through bilateral treaties, Switzerland. It is made up of over 500 million consumers and is characterized by a significant elderly population which, statistically, appears to be the largest user of DM. The free movement of goods is one of the fundamental stones of the European single market. This implies that a product authorized to circulate on the market of one of the Member States is also allowed to circulate on the markets of other Member States. To realize this idea of free movement, the Commission has updated (version 2016) the "Blue Guide" on the implementation of EU products, which lists three conditions that must be met:

They must be defined:

1. The essential requirements for products affected by free movement,
2. Methods to describe how compliance with product safety requirements is addressed;
3. The mechanisms for the supervision and control of the activities of all economic operators and other subjects involved in the design, production and distribution of products.

According to official EU data, DMs and IVDs in the territory are over 550,000;

Distributed in about 25,000 companies (most micro-enterprises and SMEs); annual sales in the European market amount to almost 100 billion euros (of which about 6-8% of DM annual sales and 10% of IVD sales are reinvested in research).

The aim of the new regulations is to modernize the current legislation through a very complex challenge for:

a) to raise the level of security, in order to avoid dramatic events such as the scandal of PIP and other prostheses

The aim of the new regulations is to modernize the current legislation through a very complex challenge:

b) make sure that new innovative devices are promptly made available to patients, also taking into account that in 2060 the number of elderly people will be about twice as much as today.

The predecessors of the Medical Devices Regulation (MDR), currently still in force, are:

- the Medical Devices Directive (MDD) 93/42 / EEC - e
- Active Implantable Medical Devices - Device Directive (AIMDD) 90/385 / EEC

However, these directives due to the continuous and dynamic changes in technologies and some intrinsic weaknesses, often due to national tra nsposition laws

Why Regulations and not Directives?

EU Directive:

- Applicable to all Member States
- Sets certain aims, requirements and concrete results that must be achieved in every Member State
- Sets a process for it to be implemented by Member States
- National authorities must create or adapt their legislation to meet these aims by the date specified in each given Directive

EU Regulation:

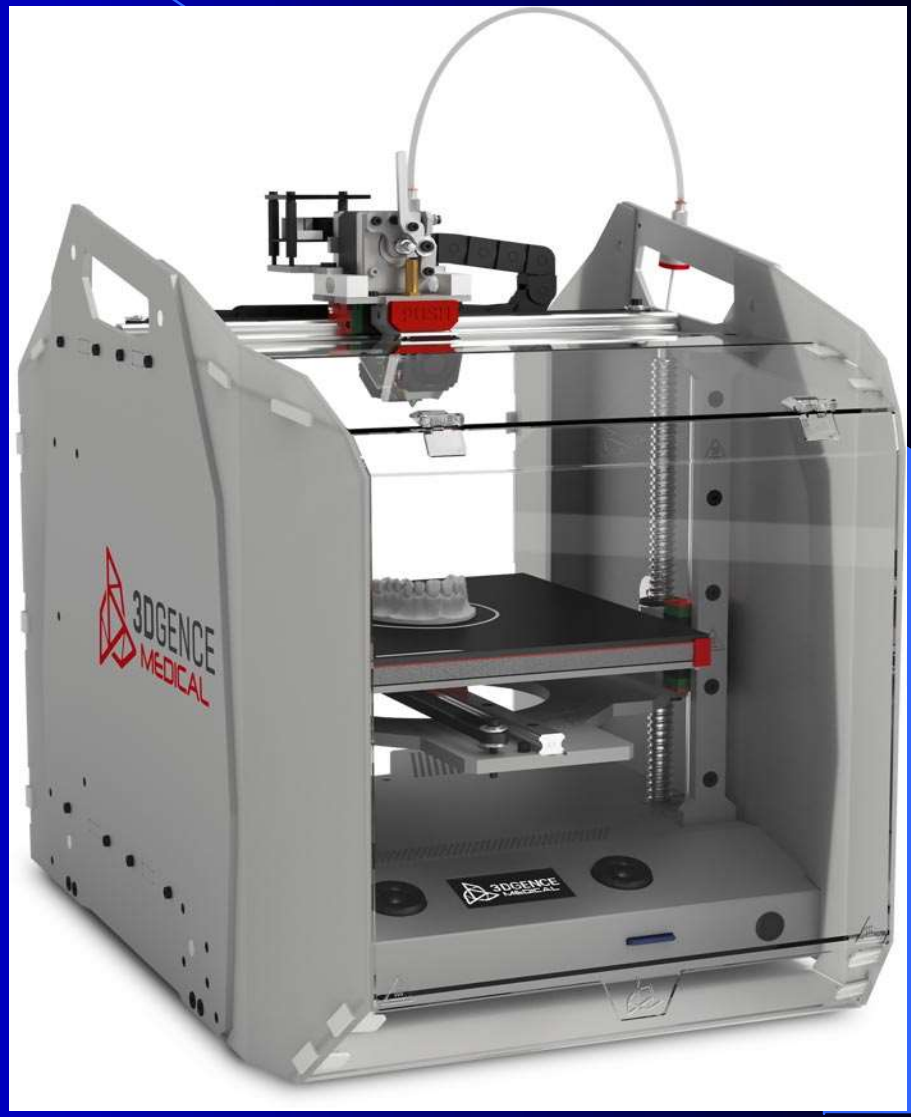
- Immediately applicable and enforceable by law in all Member States
- As good practice, Member States issue national legislation that defines the competent national authorities, inspection and sanctions on the subject matter.

For example, the use of three-dimensional printers in the field of dentistry and in the manufacture of cranial prostheses.
Sales of 3D printers increased by 75% in 2016 compared to the previous year.
Today, in fact, in dental offices it is possible to print in 3D a customized device without involving a laboratory or a dental technician.
For example: Does a dentist with a 3D printer face the same type of regulated procedure as an ODT laboratory to protect patients?

Are the design and development adapted to the complex product type (verification and validation of the SW)?

All 3D printersoffer the same level quality of a laboratory?

How it should be applied the Regulation on printer and on raw material?



In May 2016, the US FDA issued the document "Technical Considerations for Devices Manufactured with Additive Manufacturing Techniques" as a guide for this type of problem, also common in other sectors:

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm499809.pdf

In August 2016, the DM producers' association urged the FDA to add a note: a structure that installs and uses 3D printers to manufacture devices ... is subject to relevant FDA requirements

including the pre-market evaluation requirement, if possible, and post-market controls to establish and maintain quality systems and reporting adverse events. »

The issue of Directive 2007/47 / EC, which amended the MDD directives and the AIMDD, attempted to address these concerns, but the amendments did not meet all the expected objectives.

The issuance of the following Regulation Commission Implementing Regulation (EU) No 920/2013 of 24 September 2013 on the designation and the supervision of notified bodies under Council Directive 90/385 / EEC on active implantable medical devices and Council Directive 93/42 / EEC on medical devices has remedied other deficient points of the directives

Let's now look at the main market failures, in terms of adverse events caused to patients:
- The scandal that involved the defects of breast implants produced by the Poly Implant Prosthesis (PIP) in France (4 years in prison to the owner Jean-Claude Mas and 63 million euros to the ON and to the 3 importers), showed further weaknesses structural changes in the system..

TRANSVAGINAL MESHES (Urogynaecological meshes)
In this case, the principle of equivalence was applied, producing networks with 8 anchors - instead of 6 of the networks that had undergone clinical evaluation - with the awareness that those with 6 anchors,
they had created serious issues.
Transvaginal nets (J & J: Prolifix and Ultrapro - BARD: Avaulta and Marlex), for the containment of vaginal prolapse (one or more pelvic organs which tend to exit the vagina), which have shown serious drawbacks (erosion of the meshes, erosion of the walls vaginal, perforation of the organ, severe infections,

recurrent urinary problems, internal bleeding, severe discomfort during sexual intercourse, cracking and withdrawal of the vaginal walls). On FDA provision, there has been a "recall" of products that, however, is still the subject of numerous legal cases.

Ultimo, ma solo per la narrazione in questo contesto, lo scandalo delle protesi metalliche artificiali "HIP – metal o metal MOM" per rischio danni a ossa e muscoli (56.000 pazienti).
Il loro utilizzo ha manifestato problemi come la citotossicità locale e le reazioni di ipersensibilità che portano a danni tissutali morbidi e alla formazione di massa cistica (noti collettiva-mente come reazioni tissutali locali avverse).

- The Commission intervened, where it could. This is demonstrated by the suspensions and withdrawals of the notifications shown in the NANDO database
- In September 2012, the European Commission published the first proposals for the MDR-AIMD: Regulation (EU) 2017/745 and the In-Vitro Diagnostic Medical Devices: Regulation (EU) 2017/746 (IVDR).
- In April 2014, the European Parliament presented a total of **347** amendments for the MDR proposal and **254** amendments for the IVDR proposal.

The European Council replied in September 2015 to the proposals adapted by Parliament. The differences between these versions were so large that the European Commission decided to facilitate negotiations between the European Parliament and the European Council, through the so-called "Trilogues". Trilogues (EU procedure for co-decision and conciliation), which led to a compromise text in June 2016.

In autumn 2016, the texts translated into all European languages and errors / inconsistencies were corrected by the EU legal offices. The Regulation was formally published in the Official Journal of the European Union on 26 May 2017, announcing full implementation by 26 May 2020 during the official transition period.

Official Journal of the European Union

L 117

English edition

Legislation

Volume 60

5 May 2017

Contents

Question: All of this had to happen for
Issue of Regulations?
Answers:
No, if all the interested Parties they had respected the rules
Yes, to take account of New technologies and theevidence-based medicine, more than. on protocols / Guidelines
- yes, to treat the patient as well as the disease, taking into account his expectations (ie breast prosthesis - clinical, but also aesthetic aspects)

LET'S ANALYZE NOW THE TIME OF TRANSITION AND DEFINITIVE APPLICATION

REGULATION (EU) 2017/745 MDR			
▼	▼	▼	▼
26-05-2017	26-11-2017	26-05-2018	26-05-2010
ENTRY INTO FORCE	APPLICATION	APPLICATION	APPLICATION
	Article 123 Entry into force and date of application	Art. 102 Cooperation	Entire Regulation
	Notified bodies from Art. 35 to 50*		

* Only for NBs (CABs) that make the application for designation (Art. 38)

LET US SEE THE SINGLE DEADLINES NOW

- 26 May 2017: Official entry into force of MDR 2017/745 and IVDR 2017/746
- 26 November 2017: The OO.NN. can request the designation under MDR and IVDR
- March 26, 2020: Eudamed goes live
- May 26, 2020: date of application MDR and IVDR
- 26 May 2024: AIMD certificates (active implantable dir), MDD (medical devices) and IVDD (in vitro diagnostics devices) are unusable: no longer available on European devices market by virtue of these certificates
- 26 May 2025: after this date, it will not be possible to place in service devices in Europe using MDD, AIMD or IVDD certificates

We will examine, below, what are the main topics introduced in the MDR Regulation and the most significant changes, compared to the Directives which, it is worth remembering, are still in force for a long time, evaluated now, also in accordance with the Implementing Regulation (EU) N. 920/2013 of 24 September 2013 on the «Designation and monitoring of notified bodies under Council Directive 90/385 / EEC on active implantable medical devices and Council Directive 93/42 / EEC on medical devices» and of the «Commission Recommendation of 24 September 2013 No. 2013/473 / EU on the verifications and evaluations carried out by the notified bodies in the field of medical devices (product evaluation, quality system assessment, unannounced inspections).

The "quantitative" differences between the Directives

The Directives, still in force, are structured as follows:

Directive 93/42 / EEC: - general introduction 43 Pages - 23 Articles - 12 Annexes

Directive 90/385 / EEC: - general introduction 20 Pages - 17 Articles - 9 Attachments

The Regulation 2017/745is organized as follows:

175 Pages: Introduction 101 Points, 10 Chapters, 123 Articles, 14 Attachments

New acronyms and their definitions have been introduced:

- MDCG: Medical Devices Coordination Group
- **MDCF**: Medical Devices Clinical Follow up
- **MDPF**: Medical Devices Performance Follow up
- UDI-DI-PI: Unique Device Identification – Device Identifier – Production Identifier
- **PSUR**: Periodic Safety Update Report
- **SSPC**: Summary of Safety and Clinical Performance
- **CER**: Clinical Evaluation Report
- CFS: Certificate of Free Sales (CLV: Certificato di libera vendita)
- IFU: Instructions for use
- **PMS**: Post Market Surveillance
- **PMCF**: Post Market Surveillance Follow Up
- **SSCP**: Summary of Safety and Clinical Performance

- FSN: Field Safety Notice
- FSCA: Field Safety Corrective Actions
- FSPA: Field Safety Preventive Actions
- MDEG: Medical Device Experts Group
- GMDN: Global Medical Device Nomenclature
- **DoC**: Declaration of Conformity
- **EO**: Economical Operator
- GDPR: General Data Protection Regulation
- **GSPR**: General Safety and Performance Requirements
- **STED**: Summary Technical Documentation (GHTF – SG1)
- HIBCC: Health Industry Business Communications Council-SG1: Organismo di rilascio software per l'etichettatura (UDI)
- ICCBBA: Organismo di rilascio software per l'etichettatura (UDI)
- CoC: Code of Conduct

- The Regulations take into consideration the following figures:
Manufacturer - Manufacturer / Producer
Authorized Representative - Authorized Representative
Importer - Importer
Distributor - Distributor / Mandatory
Sponsor - Promoter
- The current MEDDEV document on ARs: MEDDEV 2.5 / 10 2012 "Guideline for authorized representatives"
it is substantially incorporated into the Regulations, which highlights the complementarity but the incompatibility of the role of the AR and the two other EOs (Distributor and Importer). There is also an article describing the process of replacing an AR. "Distance sales" are regulated in such a way that even devices sold to European citizens through the Internet must comply with the Regulations, although it is not clear how this type of control will be implemented.

- A consideration of particular interest is that which recognizes (5) the importance of the Global Harmonization Task Force (GHTF) Guides and the next organization that replaced it: the International Medical Device Regulators Forum (IMDRF) ["Harmonization" organizations]

  The IMDRF (International Medical Devices Regulatory Forum) is a voluntary group of medical device regulatory bodies from around the world who have joined together to build the strong fundamental work carried out by the Global Harmonization Task Force on medical devices

  (GHTF) and aims to accelerate the harmonization and international regulatory convergence of medical devices.

- The IMDRF was born in October 2011, when representatives of the regulatory authorities of medical devices in Australia, Brazil, Canada, China, the European Union, Japan and the United States, as well as the World Health Organization (WHO) met in Ottawa to take care of the establishment and operation of this new forum.

  The consideration (5) underlines the importance of "global convergence of standards" and of the unambiguous identification of the device (UDI) and of other areas that would benefit, increasing the level of global security protection (Harmonization of Regulations, documentation technique, classification rules, conformity assessment procedures ...)

- We come to the most significant changes
  ►1) EXPANSION OF THE PURPOSE - The definition of medical devices and active implantable medical devices covered under MDR is greatly expanded to include devices that are not intended for use in the medical field, such as colored contact lenses. Also included in the scope of the regulation are devices designed for a specific disease or health condition.
  ► 2) GREATER CLINICAL EVIDENCE - MDR requires manufacturers to conduct clinical studies on the performance of each specific device and to prove its safety and performance based on the risk associated with it. Device manufacturers are also required to collect and store post-sales clinical data as part of the ongoing assessment of potential security risks.

- ► 3) IDENTIFICATION OF THE "QUALIFIED PERSON" - DM producers are required to identify at least one person within their organization, responsible for all aspects of compliance with the MDR requirements. The organization must document its specific qualifications with respect to the required tasks.

  Note: for micro and small manufacturers and for agents, the person can be external (Recommendation 2003/361/ EC of the European Commission), but always permanently and continuously.

  ►4) UNIVOCAL IDENTIFICATION OF DEVICES (UDI - Unique Device Identification) - MDR imposes mechanisms for unique device identification (UDI). This requirement is expected to increase the manufacturer's ability to track devices in the supply chain, and to make it easier for manufacturers to recall devices that pose a safety risk quickly and efficiently. Furthermore, the European DM database (Eudamed) will be expanded to provide more information on "approved" devices.

► 5) RIGOROUS AFTER-SALES SUPERVISION - The MDR will guarantee the NBs a greater authority in the post-sales surveillance. Unannounced audits, tests and random checks will strengthen the enforcement regime and help reduce risks from unsafe devices. In many cases, producers will be asked to report on safety and performance annually.

► 6) TECHNICAL CHARACTERISTICS - The MDR requires the European Commission or "expert groups" to publish Common Specifications (Common Specifications), which must be taken into consideration by producers and NBs. The Common Specifications will exist in parallel with the harmonized standards and the State of the Art.

► 7) MORE REGULAR STANDARDS for the NBs, which is responsible for assessing the DM before they can be placed on the market (since the DM do not have prior authorization such as drugs)

► 8) INCLUSION OF MEDDEV GUIDE 2.7 / 1 * "Clinical evaluation: a guide to manufacturers and notified bodies under directives 93/42 / EEC and 90/385 / EEC" (clinical data evaluation). The most relevant, but also other elements of other MEDDEV Guides and parts of ISO 14155 (clinical investigations). Note: Chapter VI is entirely dedicated to clinical evaluation and clinical investigations

- MEDDEV 2.5 / 10 2012 "Guideline for authorized representatives"
- MEDDEV 2.12-1 Rev. 8 2013 "Guidelines on medical devices vigilance system

MEDDEV 2.12 / 2 Rev.2 2012 "Post Market Clinical Follow-up studies"

M A C' E' D E L L' A L T R O

The inclusion in the scope of products without medical purpose (Annex XVI).
Supply chain (of each entity) until the verification of the conformity of the previous supplier. See chapter II.
The introduction of a special procedure for certain high-risk devices. See Article 54.
The introduction of the specific responsibility of manufacturers for medical devices and in line with the liability provided for in Directive 85/374 / EEC.
Authorized representatives will be jointly and severally responsible for the devices they represent. See articles 10 (16) and 11 (5) respectively.
Substances which are carcinogenic or have other potential high risk effects on the human body may only be used in conjunction with a strictly defined justification (Annex I, section 10.4).

The introduction of strict rules for clinical investigations and

alignment with the regulation on clinical trials. See chapter VI, articles 62-82

The introduction of detailed rules for the execution and results of post-market surveillance Post-market clinical follow-up.

Reconditioning and further use of single-use devices is allowed only under specific conditions: the authorization from the member state is one of these. See Article 17.

The conditions to be met for devices produced in hospitals and to be used for their patients have been added in order not to meet the MDR requirements. See Article 5, paragraph 5.

The rules for the designation of the NBs have been strengthened. These are set out in Chapter IV, Annex VII and Annexes IX to XII. The procedures for the supervision and post-marketing surveillance are described in greater detail and the fact that they must be for the continuous assessment of compliance of the device are more detailed. See chapter VII.

ALSO FROM THE POINT OF PHARMACOLOGICAL VIEW, THERE ARE NEWS

Directive 93/42 / EEC: the effect of the substance on the human body is important
Regulation 2017/745: the presence of the substance is important (ancillary action to that of the DM)
The DM continues to be assessed for its quality, safety and usefulness of the substance, by analogy to the methods of Annex I of Directive 2001/83 / EC.

The ON assesses the usefulness of the substance and asks for a scientific opinion (on quality, safety and risks / benefits) to one of the competent authorities for medicinal products or to EMA (European Medicines Regulatory System): in the case of a DM containing as an integral part of a medicinal product, the ON does not issue the certificate in case of unfavorable scientific opinion

There is a lot to learn and above all to put into practice ....

Let's come now to the currentsituation in italy.

- THE STEPS that have to be done for 745/2017 designation

For the current one, it must be said that all the NBs have to face wiyh a new designation according to (EU) No 920/201 of 24 September 2013 REGULATION on the designation and the supervision of notified bodies under Council Directive 90/385/ EEC on active implantable medical devices and Council Directive 93/42 /EEC on medical devices and the COMMISSION RECOMMENDATION of dated 24 September 2013

on «the audits and assessments performed by the body in the field of medical devices»

ANNEX I: Product assessment

ANNEX II: Quality system assessment

General advice in case of outsourcing of the production via subcontractors or suppliers

Unannounced audits

The designation assessment is no longer conducted only by inspectors/experts of the Designating Authority of the member country where the ON is located (CAB), but by a Joint Assessment Team (JAT)

The European Commission appoints the JAT in conjunction with the Medical Device Coordination Group (MDCG). The JAT will include the European Commission experts, rxprts experts from two of European Countries and the assessment team of the desigmeting Authorities of the coutry where is locate the NB

COME ON…!!!!
WE ARE ALMOST AT THE END …….

- The purpose of the JAT is to assist in the assessment on the designation applications/assessment

and to provide an opinion to the EU Commission and the Regulatory Network on the proposed designation of a notified body (Assessment process according to document NBOG BPG 2017-1 rev. 1

- On «Designation and notification of conformity assessment bodies»

LA SITUAZIONE ATTUALE ITALIANA RISPETTO ALLE DIRETTIVE

Bodies

Found : 10

Search criteria :

Country : Italy

Legislation :

93/42/EEC Medical devices

Withdrawn/Expired/Suspended Notifications/NBs are not displayed in this list, you can find them in the Body module under the hyperlink "Withdrawn/Expired/Suspended Notifications/NBs"

Body type	Name ▲	Country ▲
NB 0051	IMQ ISTITUTO ITALIANO DEL MARCHIO DI QUALITÀ S.P.A.	Italy
NB 0068	MTIC InterCert S.r.l.	Italy
NB 0373	ISTITUTO SUPERIORE DI SANITA'	Italy
NB 0425	ICIM S.P.A.	Italy
NB 0426	ITALCERT SRL	Italy
NB 0476	KIWA CERMET ITALIA S.P.A.	Italy
NB 0546	CERTIQUALITY S.R.L. - ISTITUTO DI CERTIFICAZIONE DELLA QUALITA'	Italy
NB 1282	ENTE CERTIFICAZIONE MACCHINE SRL	Italy
NB 1370	BUREAU VERITAS ITALIA S.P.A.	Italy
NB 1936	TUV Rheinland Italia SRL	Italy

Bodies

Found : 1

Search criteria :

Country : Italy

Legislation :

98/79/EC In vitro diagnostic medical devices

Withdrawn/Expired/Suspended Notifications/NBs are not displayed in this list, you can find them in the Body module under the hyperlink "Withdrawn/Expired/Suspended Notifications/NBs"

Body type	Name	Country
NB 0373	ISTITUTO SUPERIORE DI SANITA'	Italy

Bodies

Found : 1

Search criteria :

Country : Italy

Legislation :

90/385/EEC Active implantable medical devices

Withdrawn/Expired/Suspended Notifications/NBs are not displayed in this list, you can find them in the Body module under the hyperlink "Withdrawn/Expired/Suspended Notifications/NBs"

Body type	Name	Country
NB 0051	IMQ ISTITUTO ITALIANO DEL MARCHIO DI QUALITÀ S.P.A.	Italy

- Regarding the compliance with REGULATION (EU) No 920/201 of 24 September 2013
  - some NBs have already been subject to theinitial designation assessments and some (4) have already had the first surveillance
  Regarding the compliance with the Regulation (EU) 2017/745
  - 1 NB has already passed the Preliminary assessment review (document NBOG F 2017-5 rev 1) and the JAT is scheduled for mid-November (7 Inspectors / experts + 4 translator, for 5 days)
  Applicable document: NBOG Design Authorities_Handbook

At the European level, on 9 October 2018 the Commission issued a document with the Action Rolling Plan. Among the various information on the Plan, I cite the most interesting for the designations. The most interesting information for the ON desigations according to Regulation (EU) 2017/745

ACTIONS/INITIATIVES (OTHER THAN IMPLEMENTING REGULATIONS/ACTS)

Designation of Notified Bodies under the MDR and IVDR. Designation of Notified Bodies under the Regulations is a pre-condition for carrying out of conformity assessments under the new Regulations

As many Notified Bodies as possible designated prior to May 2020

As of mid-September 2018, 33 applications received by the Commission services, 22 joint assessments scheduled. Full scope of MDR and IVDR covered in the applications

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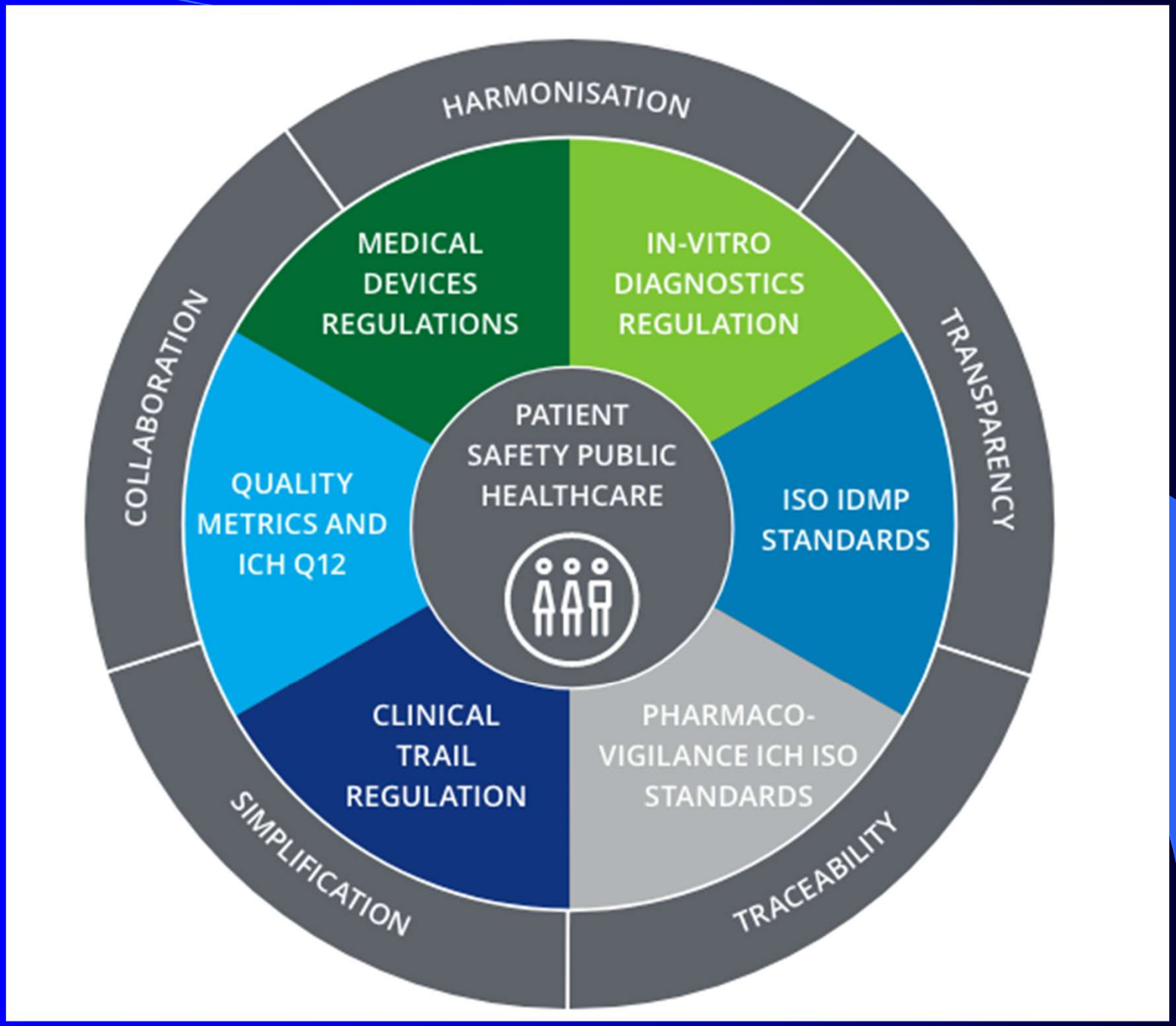
Non c'è il tempo di vedere alcuni grafici che aiutano a comprendere gli aspetti letterari esposti nella presentazione

Vengono inseriti per comodità, per chi vorrà utilizzare l'intera presentazione

Grafici esposti per gentile concessione di Deloitte


HARMONISATION
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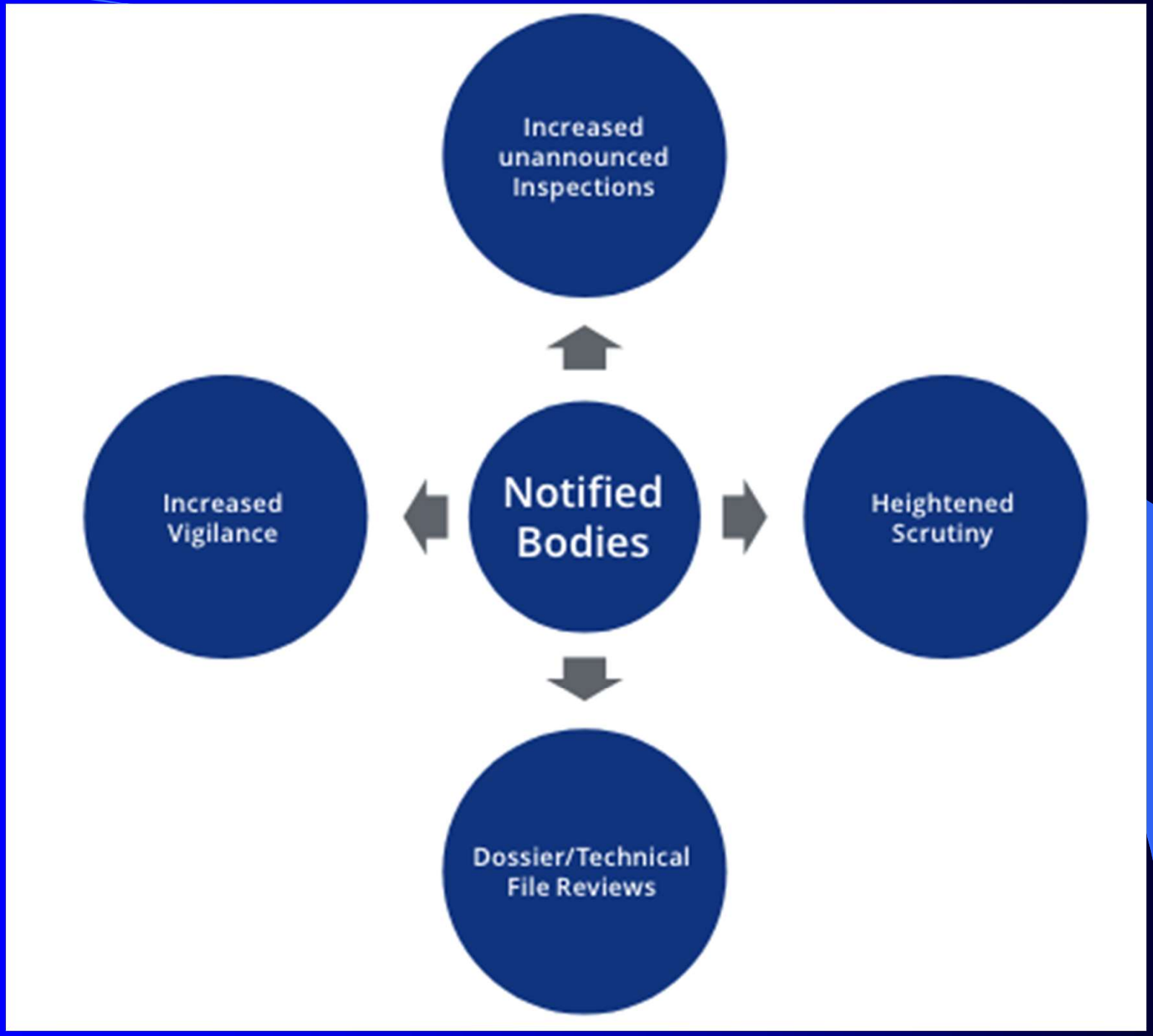
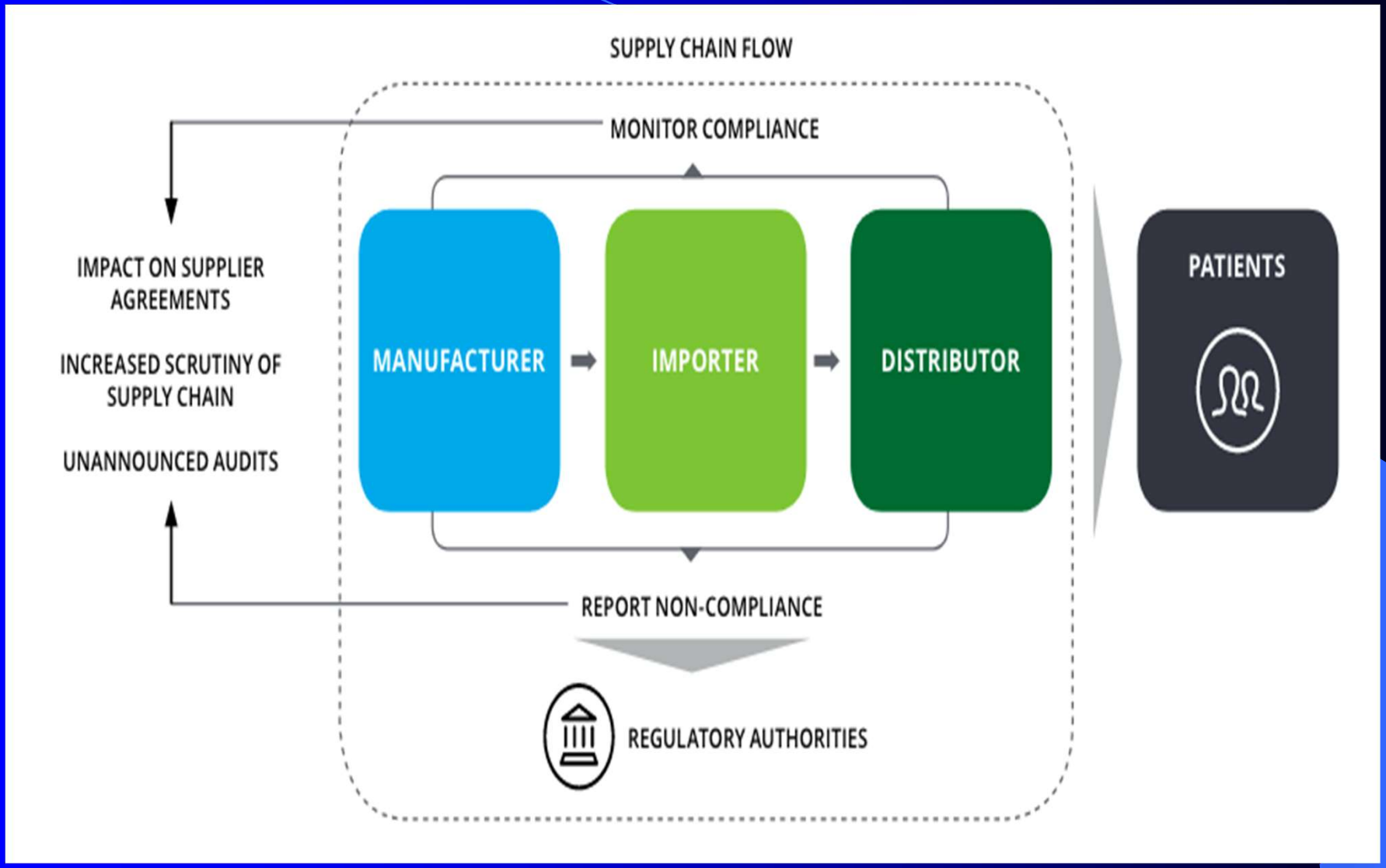
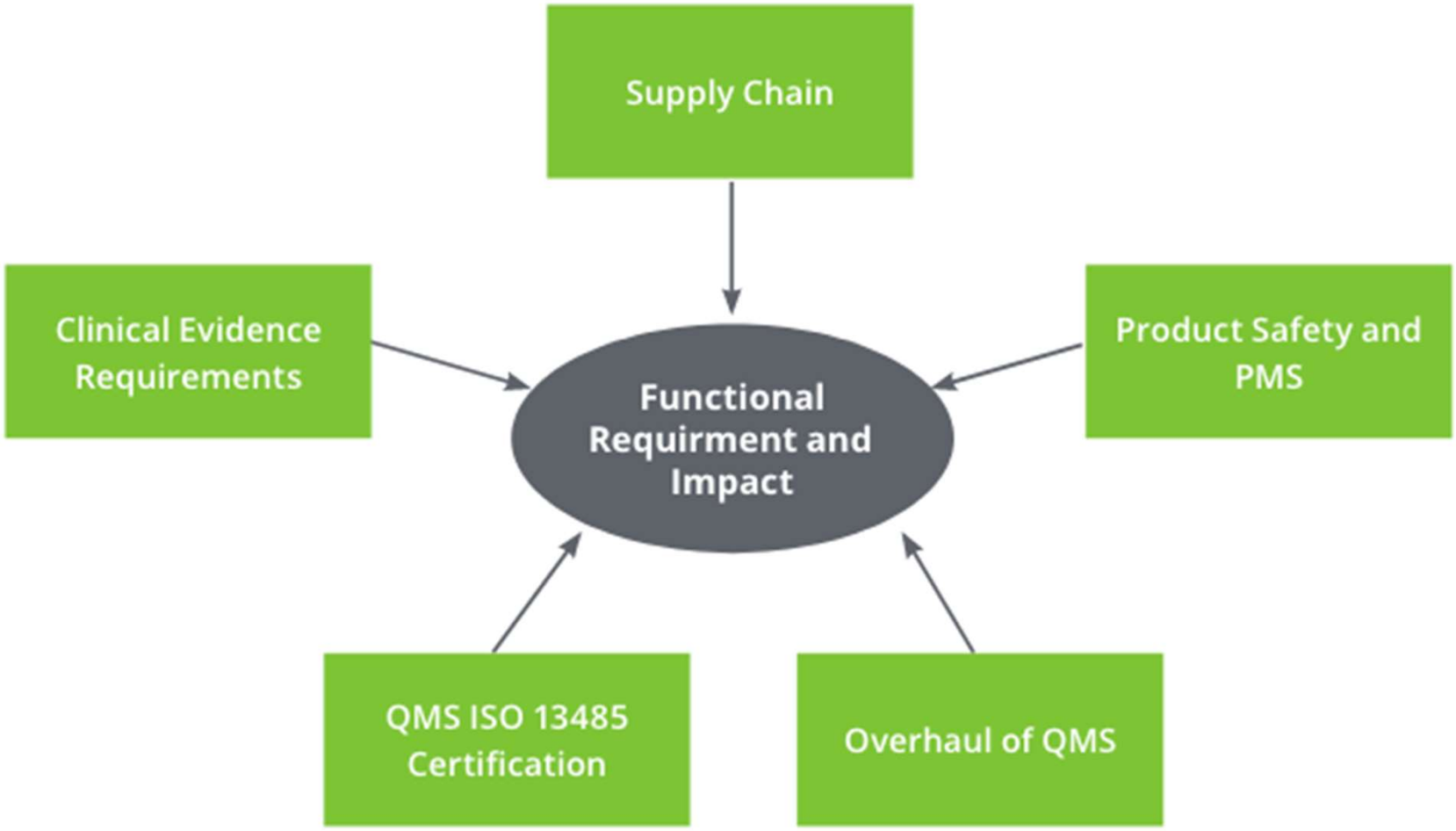
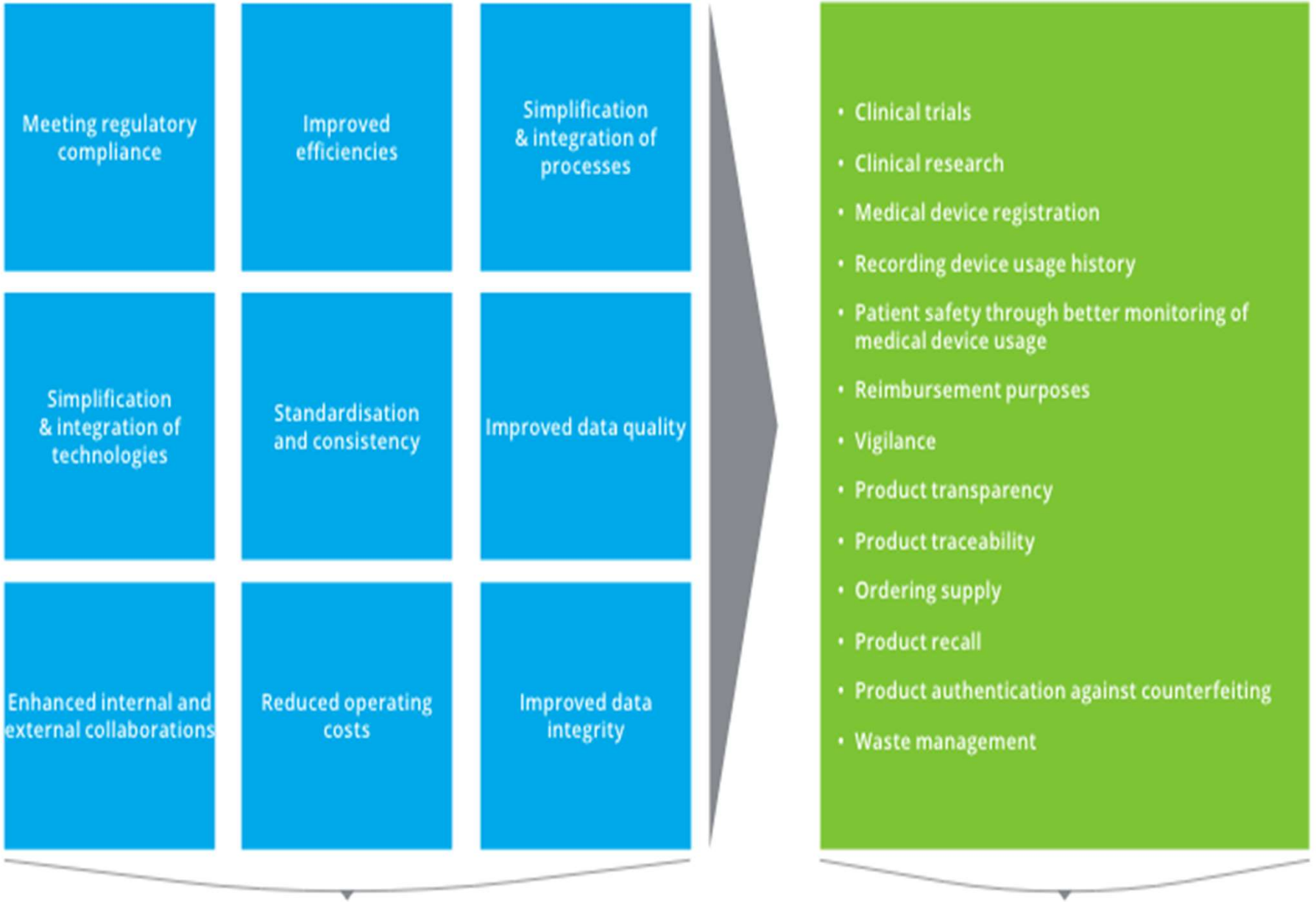
TRACEABILITY
SIMPLIFICATION
COLLABORATION
MEDICAL DEVICES REGULATIONS
IN-VITRO DIAGNOSTICS REGULATION
ISO IDMP STANDARDS
PHARMACO-VIGILANCE ICH ISO STANDARDS
CLINICAL TRAIL REGULATION
QUALITY METRICS AND ICH Q12
PATIENT SAFETY PUBLIC HEALTHCARE


Increased unannounced Inspections
Increased Vigilance
Notified Bodies
Heightened Scrutiny
Dossier/Technical File Reviews


SUPPLY CHAIN FLOW
MONITOR COMPLIANCE
IMPACT ON SUPPLIER AGREEMENTS
INCREASED SCRUTINY OF SUPPLY CHAIN
UNANNOUNCED AUDITS
MANUFACTURER
IMPORTER
DISTRIBUTOR
PATIENTS
REPORT NON-COMPLIANCE
REGULATORY AUTHORITIES


Supply Chain
Clinical Evidence Requirements
Functional Requirment and Impact
Product Safety and PMS
QMS ISO 13485 Certification
Overhaul of QMS


Meeting regulatory compliance
Improved efficiencies
Simplification & integration of processes
Simplification & integration of technologies
Standardisation and consistency
Improved data quality
Enhanced internal and external collaborations
Reduced operating costs
Improved data integrity
• Clinical trials
• Clinical research
• Medical device registration
• Recording device usage history
• Patient safety through better monitoring of medical device usage
• Reimbursement purposes
• Vigilance
• Product transparency
• Product traceability
• Ordering supply
• Product recall
• Product authentication against counterfeiting
• Waste management
Benefits of data outcomes from regulation changes
Use of medical devices data

Rule 3

"All non-invasive devices consisting of a substance or a misture of substances intended to be used in vitro in direct contact with human body or with human embryos before their implantation or administration in to the body are in class III"

Rule 8

added in class III

"Active implantable devices or their accessories"

"surgical meshes"

Rule 9

"All active devices that are intended for controlling, monitoring or directly influencing the performance of active implantable devices are in class III"

Rule 10

sub-rule 10a added as follows, "Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes, is in clas IIa, except if such decisions have an impact that may directly or indirectly cause: the death or an irreversible deterioration of the state of health, in which case it is in class III"

Rule 19

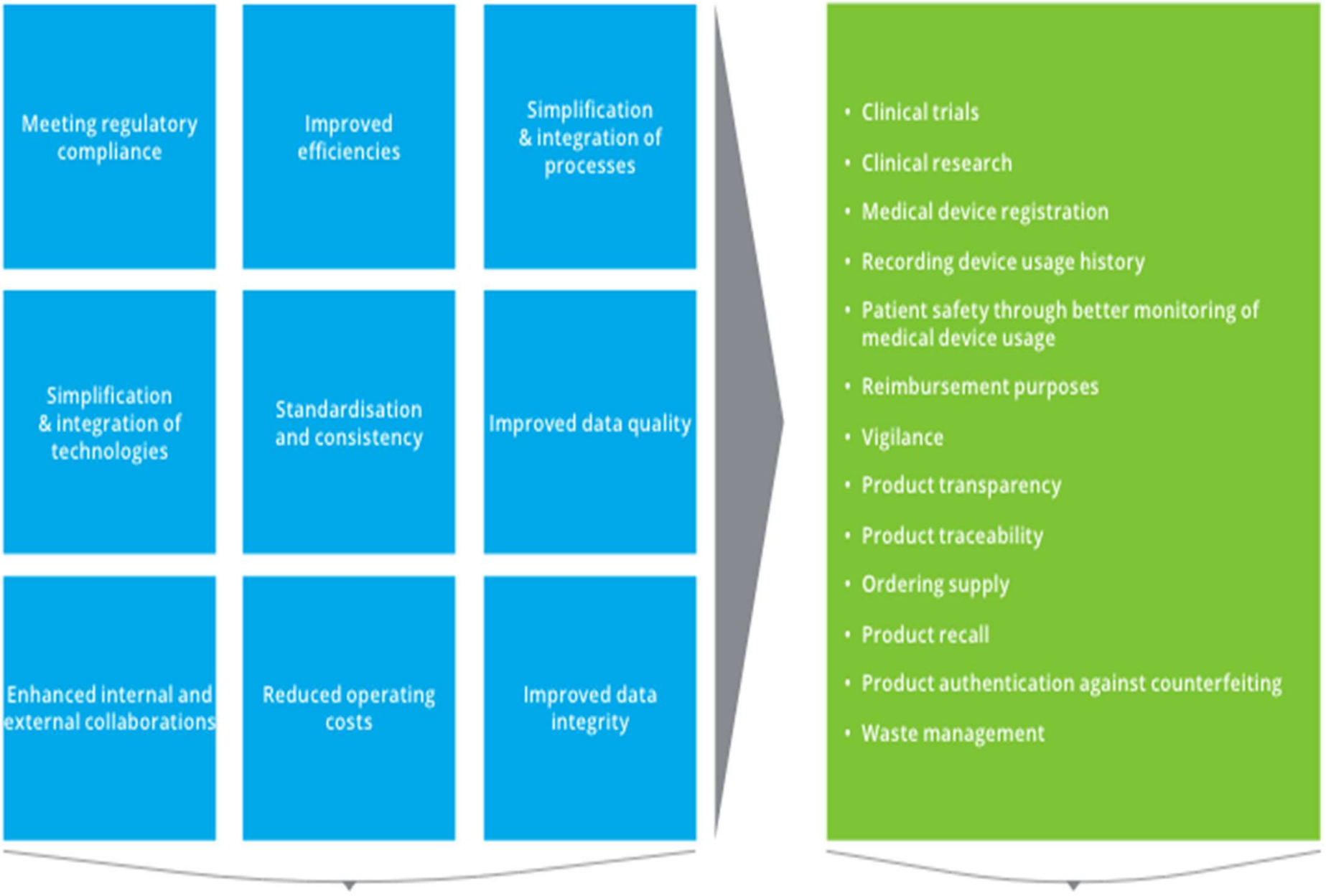
All devies incorporating or consisting of nanomaterial are in class III if they present a high or medium potential for internal exposure

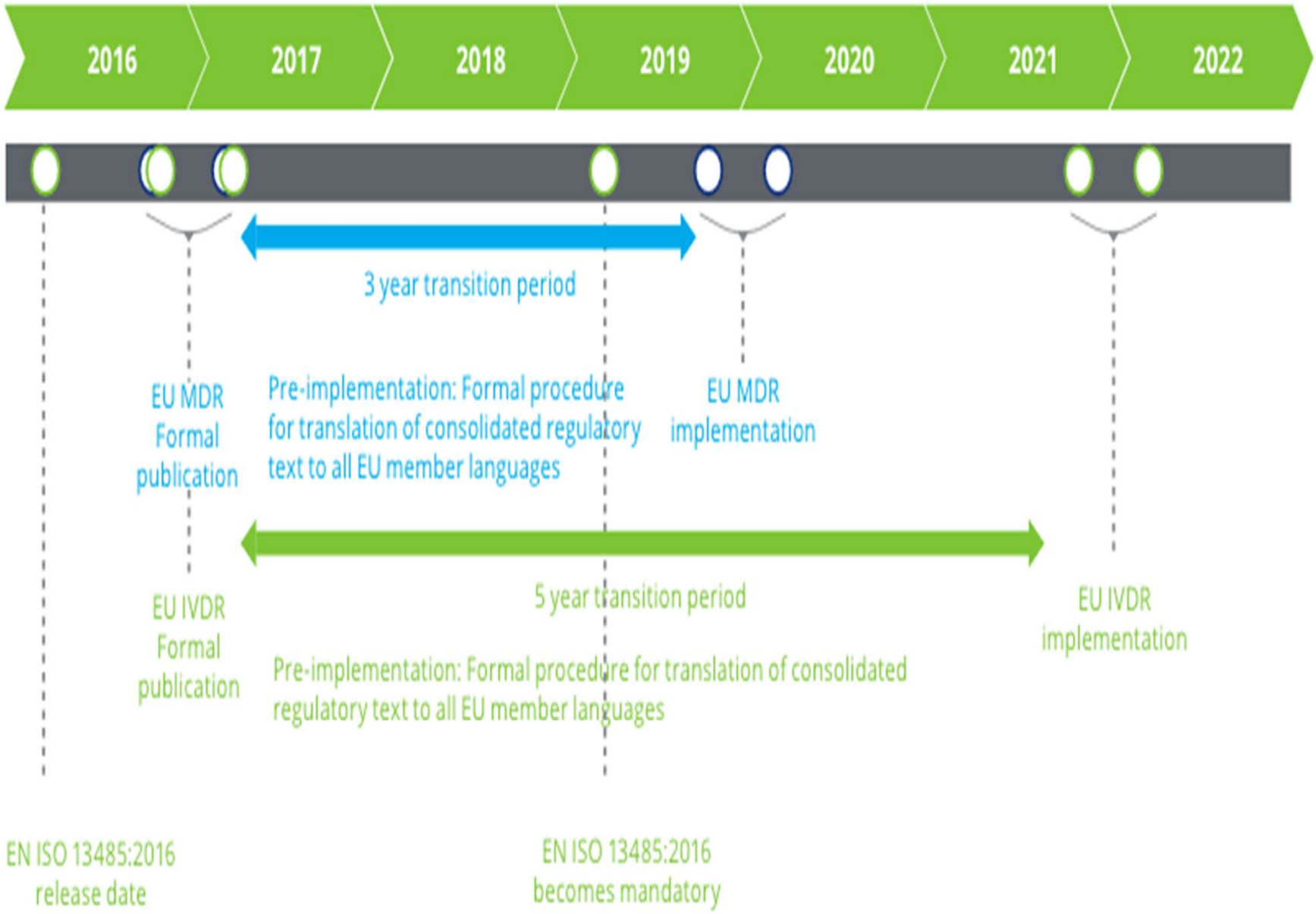
Rule 21

Devices that are composed of substances or combinations of substances that are intended to be introduced in to the human body via a body orifice, or applied on skin and that absorbed by or locally dispersed in the human body are: in class III if they, or their products of metabolism, are systemically absorbed by the human body in order to achieve their intended purpose; in calls III if they achieve their intended purpose in the stomach or lower gastrointestinaltract and they, or their products of metabolism, are systemically absorbed by the human body

Rule 10 ➡

Active therapeutic devices with an integrated or incorporated diagnostic function, which significantly determinated the patient management by the device are in class III, such as closed loop systems or automated external defibrillators


Meeting regulatory compliance
Improved efficiencies
Simplification & integration of processes
Simplification & integration of technologies
Standardisation and consistency
Improved data quality
Enhanced internal and external collaborations
Reduced operating costs
Improved data integrity
• Clinical trials
• Clinical research
• Medical device registration
• Recording device usage history
• Patient safety through better monitoring of medical device usage
• Reimbursement purposes
• Vigilance
• Product transparency
• Product traceability
• Ordering supply
• Product recall
• Product authentication against counterfeiting
• Waste management
Benefits of data outcomes from regulation changes
Use of medical devices data


2016
2017
2018
2019
2020
2021
2022
3 year transition period
EU MDR
Formal
publication
Pre-implementation: Formal procedure
for translation of consolidated regulatory
text to all EU member languages
EU MDR
implementation
5 year transition period
EU IVDR
Formal
publication
Pre-implementation: Formal procedure for translation of consolidated
regulatory text to all EU member languages
EU IVDR
implementation
EN ISO 13485:2016
release date
EN ISO 13485:2016
becomes mandatory

- The new Regulations on in vitro diagnostics: ather real revolution?

The IVSs are devided in 4 classes, depending on the risks associatet to their use. Thei are classified from A (low risk) up to the D High risk)

The conformity assessment procedures (Article 40) are linked to the risk classes:

- Class A IVDs can use self-certification (NB not required)
- Class IV sterile IVDs require an assessment of the NB of the aspects related to sterilization, according to Annex VIII (or Annex X).
- Class B IVDs require the implementation of a quality management system with the sampling, by the NB, of at least one of the technical files per group / category of generic devices as part of the on-site controls, unless these devices are for self-test or for proximity test (near patient test - POCT), in which case the technical documentation of all the devices must be evaluated.

When the current system of "generic" IVDs or self-checks, listed in Annex II, List B and in Annex II, List A, is confronted with the proposed system, there is clearly no direct relationship between the "old" and the new system. A "generic" IVD can occur in all four risk classes, while an Annex II, List A IVD can only end up in Class C or D. Also the "in-house tests" must be classified, because the class devices D may require additional requirements.

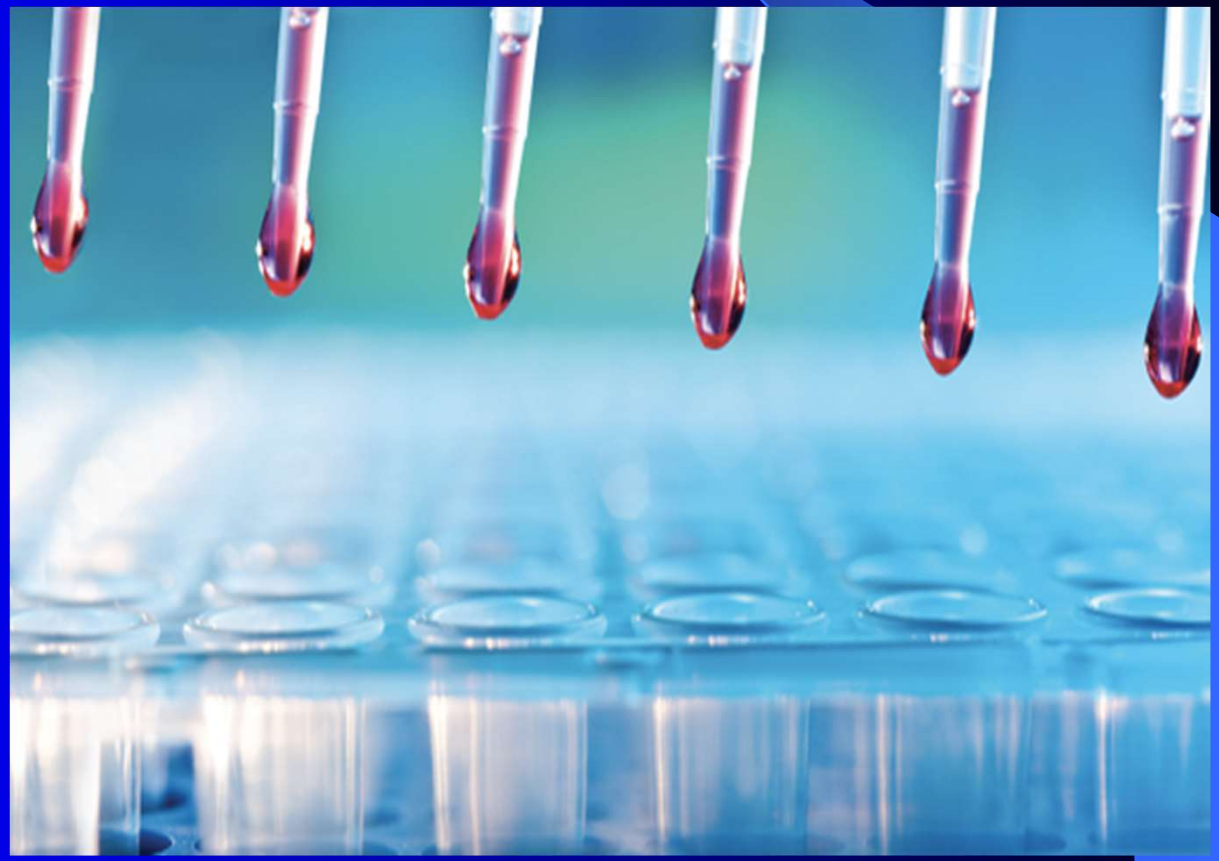
When the current system of "generic" IVDs or self-checks, listed in Annex II, List B and in Annex II, List A, is confronted with the proposed system, there is clearly no direct relationship between the "old" and the new system.

• Class C devices require a complete quality management system combined with a review of the technical documentation of at least one device per group / category of generic products (Annex VIII except for Chapter II) or an EC type examination (Annex IX) , together with production quality assurance or EC type verification (Annex X). • Class D requires The same procedure as the class C, plus verification of the lot and the involvement of the reference labo-ratory of (Annex VIII), for the execution of the evidence. (Alternatively, certification as provided for in Annex IX and Annex X is possible).

- Internal tests require laboratory compliance to EN ISO 15189: 2012 (Requirements for the quality and competence of medical laboratories) and a statement that the general safety and performance requirements are met; for class D devices, a quality management system is required (ISO 13485: 2016).
  In the interest of public health or the health of an individual patient, an NB may decide to allow the placing on the market of an IVD without applying a conformity assessment procedure. Annex II lists the requirements that the technical documentation must have. There is a detailed list of items to be reported in the technical documentation. Although the basic concept of the STED format (Summary Technical Documentation) can still be considered, Annex II provides additional details and additional additional requirements.

The classification must always be carried out by checking all the rules. As already mentioned, the rule that leads to the highest risk class must be applied. For devices with multiple intended purposes, (intended use), all purposes must be classified and the highest risk class must be applied. The strain shown in the following table is short and synthesized.

This table,
it should be
used only as
quick reference;
for the purpose of
classifying
cation must
the
original rules



Classification Quick Reference		
Rule	**Text of Rule**	**Class**
1	• Transmissible agents in substances, cells, tissues, organs, etc. intended for donation • Transmissible life-threatening agent with high risk of propagation • Monitoring infectious load of life-threatening disease	D
2a	• Blood grouping, or tissue typing as part transfusion, transplantation or administration	C
2b	• Except for certain high risk blood groups and tissue types	D
3	• Infectious diseases, including sexually transmitted agents • Pre-natal screening, congenital disorders in embryo, fetus, or new-born • Companion diagnostics • Disease staging • Screening, diagnostics, and staging of cancer • Genetic testing	C

4a	• Self-testing, except uses as noted in rules 4b below*:	C
4b	• Self-testing for detection of pregnancy, fertility testing, cholesterol level determination • Self-testing for glucose, erythrocytes, and bacteria in urine	B
5	• Product for general laboratory use, accessories with no critical characteristics, buffer solutions etc. • Instruments intended for IVD procedures • Specimen receptacles	A
6	• Devices not covered by the above-mentioned classification rules	B
7	• Controls without a quantitative or qualitative assigned value	B

Classification Quick Reference	
Class	**Procedure**
A	Self-declare conformity: • Technical documentation (including risk/benefit analysis, risk management, product verification & validation, etc.)
A sterile	Notified Body (NB) intervention by: • Quality management system of sterile aspects (Annex VIII, except Chapter II), or • Production quality assurance of sterile aspects (Annex X)
B	NB intervention by: • Quality management system (Annex VIII, except Chapter II), or • Review of technical documentation of at least one device per generic device group • Additional: all self-testing and near-patient testing need technical documentation assessment
C	NB intervention by: • Quality management system audit (Annex VIII, except Chapter II), and • Review of technical documentation of at least one device per generic device group, or • EC type-examination (Annex IX), and • Production quality assurance (Annex X) • Additional: all self-testing and near-patient testing need technical documentation assessment

D	NB intervention by: • Full quality management system audit (Annex VIII), and • Assessment of technical documentation, and • Batch verification, or • EC type-examination (Annex IX), and • Production quality assurance (Annex X), and • Batch verification • Additional: all self-testing and near-patient testing need technical documentation assessment, and • A reference laboratory will be requested by the notified body to verify the performance
In-house, A, B, and C	Self-declare: • Appropriate quality management system • EN ISO 15189 compliant • Documentation according to Article 4.5
In-house D	Self-declare: • Appropriate quality management system • EN ISO 15189 compliant • Documentation according to Article 4.5 • Additional documentation re. quality system, performance data etc.

Art. 4.5 dell'ALLEGATO *IX* **VALUTAZIONE DELLA CONFORMITÀ BASATA SUL SISTEMA DI GESTIONE DELLA QUALITÀ E SULLA VALUTAZIONE DELLA DOCUMENTAZIONE TECNICA** - CAPO I **SISTEMA DI GESTIONE DELLA QUALITÀ**

- Chapter VI of the IVDR
  Clinical evidence, performance evaluation and performance studies
  Annexes XII-XIII
  Clinical trials and post-market follow-ups are introduced as new concepts for IVDs.
  Clinical evidence consists of the evaluation of analytical performance, scientific validity and clinical performance, including their relationship / mutual interaction. The clinical evidence is based on clinical data and on the assessment of the clinical performance of an IVD, to ensure that it meets the expected benefits and clinical safety. the clinical benefit is the positive impact of a device or its functionality in patient management
  Of public health. Clinical evidence must support the intended use, and is based on a continuous process of performance evaluation. This must be programmed into a performance evaluation plan (Article 47 (2)). This requirement will ensure the identification of obsolete and less performing devices for non-compliance, which can stimulate innovation.

- The performance evaluation plan should describe how to demonstrate the following characteristics:
  - Scientific validity ("Scientific Validity Report");
  - Analytical performance ("Analytical performance analysis");
  - Clinical performance ("Clinical Performance Report");
  - Performance evaluation ("Performance evaluation report").

  Performance studies may have different risk profiles, depending on their study projects:
  - Studies with "residual" samples: these studies do not need to be authorized, although many of the requirements for other studies can also be applied to these studies (Article 48, paragraph 2a).
  - Studies with a high risk (Article 48aa): these studies include requirements such as those relating to informed consent, with additional requirements if the subject is minor, incapable, etc. Ethical reviews are required as well as the authorization of the Member States concerned. These studies are

Studies that require sampling invasive surgical;
Studies that involve further invasive procedures or other risks for the subjects of the studies;
Intervention performance studies clinical trials (definition 37), when test results can influence the decisions of patient management or the guide treatment;
Performance study of th companion devices

Companion diagnostic test: "an essential device for the safe and effective use of a corresponding medicine in order to:
a) identify, before and / or during treatment, patients who are most likely to benefit from the corresponding medicine; or
b) identify, before and / or during treatment, patients who are likely to see increased risk of serious adverse reactions following treatment with the corresponding medicinal product ".

- Member States may request that tests be carried out by an EU reference laboratory; it remains unclear whether the individual Member State may require the use of a specific (national) reference laboratory.
  For Class C and D IVDs, performance appraisal reports must be updated annually as part of their post-market surveillance plans. These relationships are also necessary for Class A and B IVDs, but without the requirement of the annual update.
  Chapter VII and XI of the IVDR
  Post-market surveillance, supervision, market surveillance and confidentiality
  Annex IIa - Technical documentation on post-market surveillance
  An IVD manufacturer must develop a post-market surveillance plan that monitors specific elements of safety, clinical performance and risk / benefit ratios. For manufacturers it is also mandatory to develop post-market surveillance reports, in accordance with Annex II bis of the IVDR.

Manufacturers of Class C and Class D devices must also draw up periodic updated safety reports
with at least annual updates (Article 58c). Finally, the manufacturers of IVD products of the class
D must submit these annual updates to Eudamed and have them reviewed by their NBs.
Accidents and field safety corrective actions must be reported via Eudamed.
Manufacturers must investigate incidents and report their results. Serious accidents (definition
52) must be reported directly to the Member State concerned.
Eudamed will have specific sections to load incidents and post-market surveillance data
To facilitate all reporting requirements.

And more , and more……

THANKS FOR THE ATTENTION