FONDAZIONE PER LA RICERCA FARMACOLOGICA GIANNI BENZI ONLUS

The manufacturing and control of medical devices in the perspective of the new regulation

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XIth FORESIGHT TRAINING COURSE

Changes in Regulatory Sciences in the EU

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For medical devices, risk management has always been a very important aspect.

Already in Directive 93/42/EEC there are several references to risk analysis; for example:

- Art. 3 specifies that DM must not compromise the safety and health of patients.
- Annex 1 "Essential Requirements" it is required that risks are eliminated or reduced as far as possible and that measures are taken to control risks that cannot be eliminated.
  It is also required that DMs are designed and manufactured so as to minimize and to control the risks.
- Annex 2 "Quality System" is required to highlight the results of the risk analysis.

Europe's Medical Device Regulation (MDR) and In Vitro Diagnostic Regulation (IVDR)

In the new European Regulation for Medical Devices (2017/745) the aspects related to Risk Analysis are described in more detailed way.
These elements are present in different parts of the Regulation and are very important aspects to consider for the reorganization planned for the Technical File.

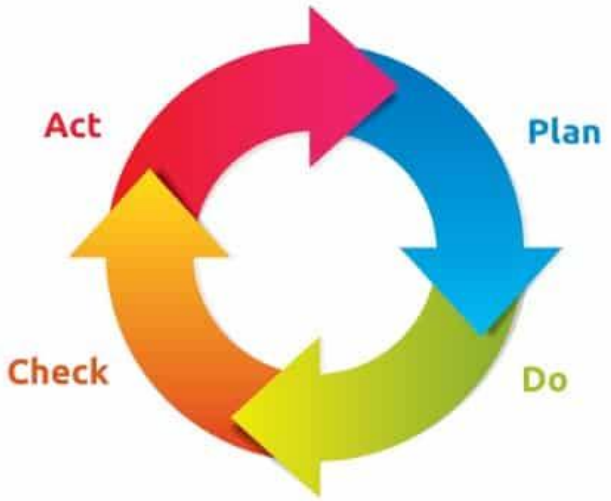
Here are some of the most important aspects of the new Regulation:

- ANNEX I "General Safety Requirements ":
CHAPT. I "General Requirements"; in points 1 to 9 for manufacturers are required:

- to reduce the risks as far as possible, always taking into account the risk-benefit ratio of the product
- to establish, implement, document and maintain an appropriate risk management system for each device

Since risk management is intended as a life-cycle/iterative process, throughout the entire life cycle of each device and requires constant and systematic updating, the manufacturers must:

- to establish and document a risk management plan for each device
- to identify and analyze the known and foreseeable risks associated with each device
- to estimate and assess the risks associated which may occur during the intended use and during foreseeable misuse
- to eliminate and/or control/mitigate these risks.



In order to eliminate or reduce these risks so that they become acceptable, manufacturers shall:

- take appropriate action to eliminate or reduce the risks, starting with the design and manufacturing aspects- take, where possible, appropriate control measures for risks which cannot be eliminated and document such residual risks
- to provide appropriate information for users on residual risks.

All known and foreseeable risks, and their undesirable effects, shall be mitigated/controlled and become acceptable in relation to the benefits assessed for users. Any residual risk must not exceed the maximum acceptable risk in relation to the benefits arising from the performance of the device.

CHAPT. II "Requirements related to design and manufacture: in points 10 to 22 important activities, documentation and controls are required, including:

- the chemical, physical and microbiological characteristics of the materials and substances of the individual devices, with particular attention to possible toxic elements with carcinogenic, mutagenic or toxic for reproduction effect
- the need to eliminate or reduce the risk of infection or microbial contamination for patients/users
- For sterile medical devices, sterility must be guaranteed until the packaging is opened in the place of use.
- sterile devices must be handled, manufactured, packaged and sterilized by appropriate validated methods
- special attention shall be paid to devices containing substances considered to be medicinal products or substances which are absorbed or found in the human body, and devices containing materials of biological origin.

The need for devices to be designed and manufactured in way to eliminate or reduce:

- the risk of injury associated with their physical characteristics

- the risk of fire or explosion

the risk of radiation emissions.

- CHAPT. III "Requirements concerning the information to be provided for each device".

- ANNEX II "Technical Documentation", Point 5, "Risk-benefit analysis and risk management" :

Appropriate documents must be provided in relation to:

- Annex 1, Sections 1 and 8, "Risk and benefit analysis".
- Annex 1, Section 3, "Solutions adopted and results of risk management".

- CHAPT. VII, "Post-market surveillance", Section 2, "Supervision", in Art. 94 and 95, is required:
an assessment of devices for which unacceptable risks are suspected and a procedure for devices presenting unacceptable risks to the health and safety of the user.

EU Regulation 2017/745

Annex II

Technical Documentation

1. DESCRIPTION AND SPECIFICATIONS OF THE DEVICE, INCLUDING ACCESSORIES AND VARIANTS

2. INFORMATION TO BE PROVIDED BY THE MANUFACTURER

3. DESIGN AND MANUFACTURING INFORMATIONS

4. GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

5. RISK-BENEFIT ANALYSIS AND RISK MANAGEMENT

6. PRODUCT VERIFICATION AND VALIDATION

EU Regulation 2017/745

Annex II

Technical Documentation

GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

Directive 93/42/EC Annex I	EU Regulation 2017/745 Annex I
1 Safe and effective devices	1 Safe and effective devices
2 Risk management	2 - 5 Risk management
4 Characteristics and performance over the lifetime	6 Characteristics and performance over the lifetime
5 Conveyance and storage	7 Conveyance and storage
6 Risks / benefits under normal conditions of use / Clinical data (6.bis)	8-9 Risks / benefits under normal conditions of use / Machinery Directive. NEW

EU Regulation 2017/745
Annex II
Technical Documentation

DESIGN AND MANUFACTURING INFORMATIONS

Directive 93/42/EC Annex I	EU Regulation 2017/745 Annex I
7 Chemical, physical and biological characteristics	10 Chemical, physical and biological characteristics (including absorption, metabolism, excretion/mechanical properties of materials/wear debris-degrading products / more details on the topic of 'phthalates/nanomaterials')
8 Infection and microbial contamination	11 Infection and microbial contamination
	12 Devices containing a substance considered as a medicinal product and devices consisting of substances absorbed by the human body/dispersed. NEW

EU Regulation 2017/745

Annex II

Technical Documentation

DESIGN AND MANUFACTURING INFORMATIONS

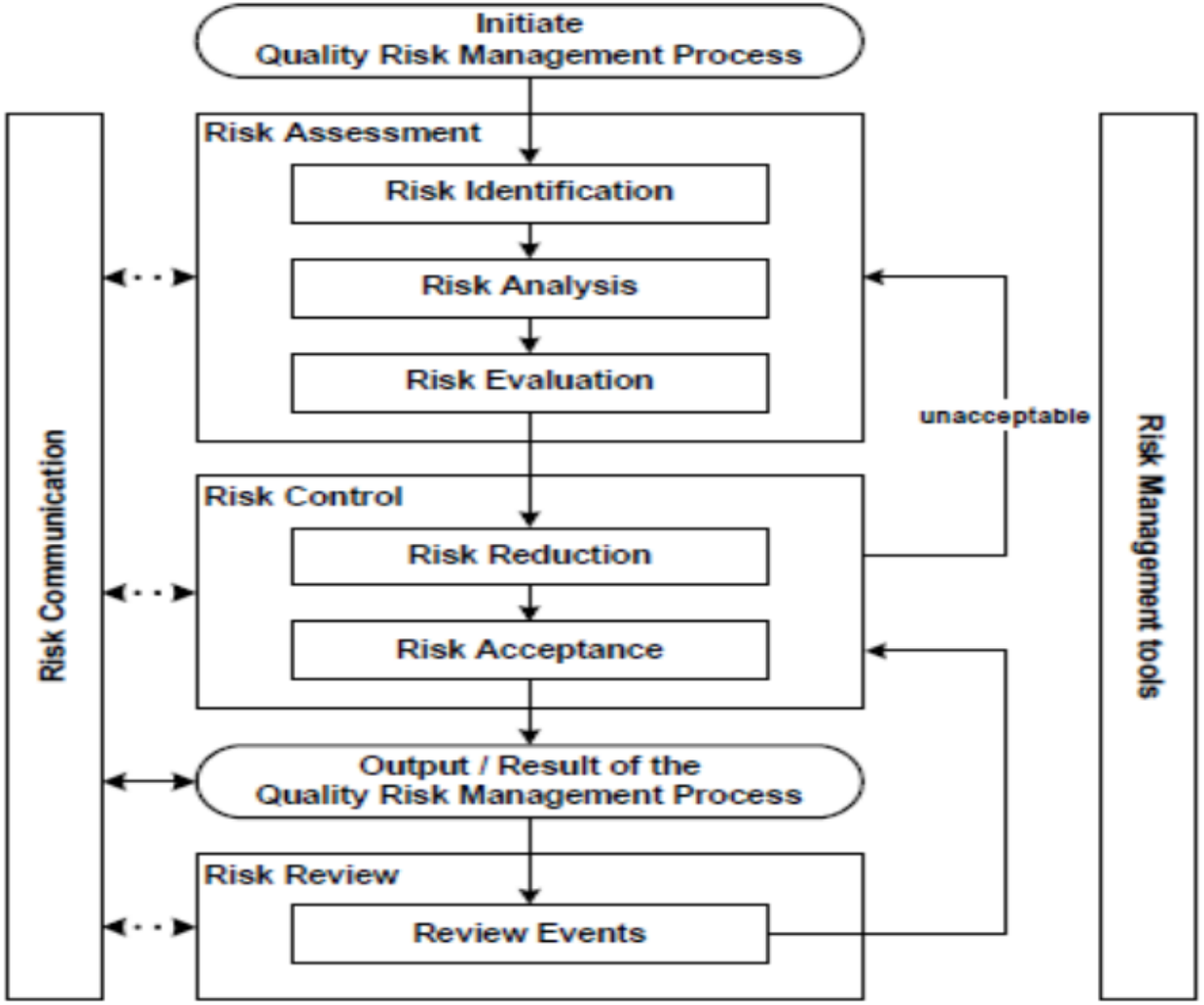
Directive 93/42/EC Annex I	EU Regulation 2017/745 Annex I
	13 Devices containing materials of biological origin (tissues or cells of human origin, tissues or cells of animal origin). NEW
9 Manufacturing and environmental characteristics	14 Construction and interaction with the operating environment
10 Measurement function	15 Devices with diagnostic or measuring function
11 Radiation protection	16 Radiation protection
12 Requirements for medical devices connected to or having an energy source	18 Active devices and devices connected to them

EU Regulation 2017/745
Annex II
Technical Documentation

DESIGN AND MANUFACTURING INFORMATIONS

Directive 93/42/EC Annex I	EU Regulation 2017/745 Annex I
n.a. in Directive 93/42/EC -> Directive 90/385/EC	19 Special requirements for active implantable devices. NEW
(12) Requirements for medical devices connected to or having an energy source	20 Protection against mechanical and thermal risks NEW
	21 Protection against the risks posed by the administration of energy or substances to the patient and the user NEW
	22 Protection against the risks posed by medical devices which the manufacturer has intended for NON-professional users
13 Labelling / IFU	23 Requirements regarding the information provided with the device

ICH Q9 "Quality Risk Management"



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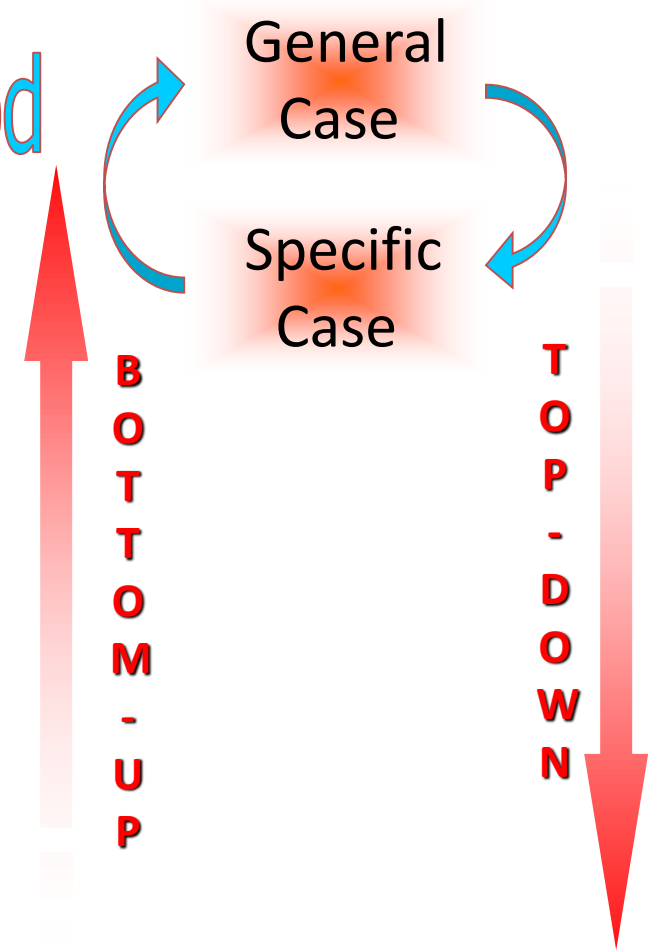
Inductive Method

One postulates a particular condition of the system or part of it and tries to imagine the effect that such a condition would have on the functionality of the system itself.

Which

system failure conditions are possible?



Deductive Method

It is postulated that the system itself has failed in a certain way, and it is attempted to understand which components of the system have contributed to this failure.

HOW

a given system failure condition may occur

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FMEA	Failure Modes and Effects Analysis
FTA	Fault tree Analysis
HAZOP	Hazard and Operability study
HACCP	Hazards Analysis and Critical Control Points

HAZOP	FMEA		FTA
Approach "SYSTEM-CENTERED"	Approach "COMPONENT-CENTERED"	Inductive method BOTTOM -UP	Deductive method TOP-DOWN
		Expects new problems	Predicts the causes of commonly known problems
Bidirectional Survey	**Unidirectional investigation**	Consider the failure of a component	Consider the failure of the system functionality
Causes ↑ Deviation from the project ↓ Effect	Component failure ↓ Cause ↓ Effect	Functional failure= result of failure of a component	Failure of a component = cause of functional failure

Risk = criticality of each hazardous situation

RISK PRIORITY INDEX

RPI = (severity) x (probability) x (detectability)

SEVERITY	
High	3
Media	2
Low	1

PROBABILITY	
High	3
Media	2
Low	1

DETECTABILITY	
High	1
Media	2
Low	3

1<RPI<27

(Different scales can also be used: 1-5 o 1-10)

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Severity

Probability

	Low	Media	High
High			
Media			
Low			

Level 1

Level 2

Level 3

Detectability

Levels

	Low	Media	High
Lev. 1			
Lev. 2			
Lev. 3			

High risk

Medium risk

Low risk

Probability

Severity

	1	2	3
3	3	12	27
2	2	8	18
1	1	4	9
	1	2	3

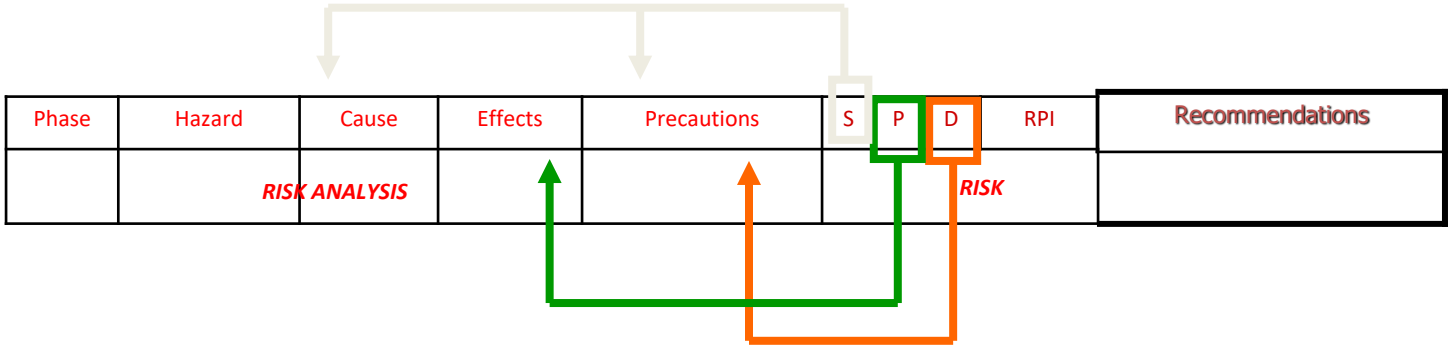
Detectability

High risk

Medium risk

Low risk

FMEA


Phase
Hazard
Cause
Effects
Precautions
S
P
D
RPI
Recommendations
RISK ANALYSIS
RISK


EXAMPLE

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RISK ASSESSMENT BEFORE THE MITIGATION AND CONTROL PHASES					RISK ASSESSMENT AFTER THE MITIGATION AND CONTROL PHASES				
HAZARD AND RISK IDENTIFICATION	**S**	**P**	**D**	**RPI**	**REMEDIATION ACTION**	**S**	**P**	**D**	**RPI**
1) What is the intended use and how the medical device should be used?									
2) Is the device intended to be implanted?									
3) Is the device designed to come into contact with the patient or other persons?									
4) What materials or components are incorporated into or used with the medical device, or are in contact with the medical device?									
5) Is there any supply of energy to the patient or extraction of energy from the patient?									
6) Are there any substances supplied to the patient and/or extracted from the patient?									
7) Are there any biological materials processed by the medical device for subsequent reuse, transfusion or transplantation?									
8) Is the medical device delivered sterile or if such medical device is required to be sterilized by user or are other microbiological controls applied?									

RISK ASSESSMENT BEFORE THE MITIGATION AND CONTROL PHASES					RISK ASSESSMENT AFTER THE MITIGATION AND CONTROL PHASES				
HAZARD AND RISK IDENTIFICATION	S	P	D	RPI	REMEDIATION ACTION	S	P	D	RPI
9) Is there a requirement for the medical device to be regularly cleaned and disinfected by the user?									
10) Is the medical device intended to change the patient's environment?									
11) Are measurements performed?									
12) Does the medical device provide interpreted data?									
13) Is the medical device intended for use with medicines or other medical technologies?									
14) Are there any unwanted releases of energy or substances?									
15) Is the medical device subject to environmental influences?									
16) Does the medical device affect the environment?									

RISK ASSESSMENT BEFORE THE MITIGATION AND CONTROL PHASES					RISK ASSESSMENT AFTER THE MITIGATION AND CONTROL PHASES				
HAZARD AND RISK IDENTIFICATION	**S**	**P**	**D**	**RPI**	**REMEDIATION ACTION**	**S**	**P**	**D**	**RPI**
17) Are essential consumables or accessories associated with the medical device?									
18) Is maintenance and/or calibration necessary?									
19) Does the medical device contain software?									
20) Does the medical device have a limited life time?									
21) Are there any delayed and/or long-term effects of use?									
22) What mechanical forces is the medical device subjected?									
23) What determines the lifetime of the medical device?									
24) Is the medical device intended for single use?									

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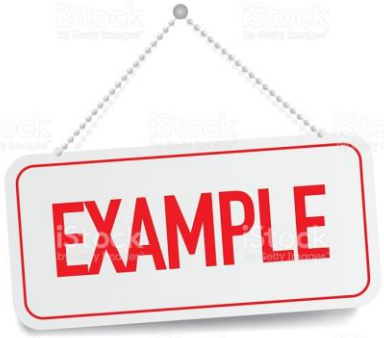

RISK ASSESSMENT BEFORE THE MITIGATION AND CONTROL PHASES					RISK ASSESSMENT AFTER THE MITIGATION AND CONTROL PHASES				
HAZARD AND RISK IDENTIFICATION	S	P	D	RPI	REMEDIATION ACTION	S	P	D	RPI
25) Is there a need for deactivation or disposal safe of the device?									
26) Does the installation or use of the medical device require special training or skill?									
27) How should information for safe use be provided?									
28) Should new manufacturing processes be established or introduced?									
29) Does the successful application of the medical device depend critically on human factors such as the user interface?									
29.1) Can the design features of the user interface contribute to misuse?									
29.2) Is the medical device used in an environment where distractions can cause misuse?									
29.3) Does the medical device have connection parts or accessories?									

RISK ASSESSMENT BEFORE THE MITIGATION AND CONTROL PHASES					RISK ASSESSMENT AFTER THE MITIGATION AND CONTROL PHASES				
HAZARD AND RISK IDENTIFICATION	S	P	D	RPI	REMEDIATION ACTION	S	P	D	RPI
29.4) Does the medical device have a control interface?									
29.5) Does the medical device display information?									
29.6) Is the medical device controlled from a menu?									
29.7) Is the medical device used by people with special needs?									
29.8) Can the user interface be used to initiate user actions?									
30) Does the medical device use an alarm system?									
31) How could the medical device be deliberately misused?									
32) Does the medical device contain critical data for patient care?									
33) Is the medical device intended to be mobile or portable?									
34) Does the use of the medical device depend on essential performance?									

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