RÉPARER L'HUMAIN

LES DISPOSITIFS MÉDICAUX : DE L'ASPECT RÉGLEMENTAIRE À LA MISE SUR LE MARCHÉ

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GdR B2i

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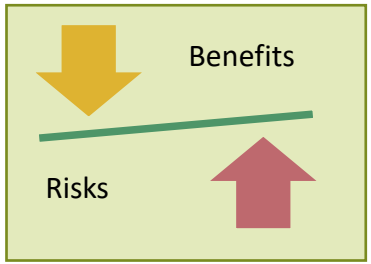
LE DISPOSITIF MÉDICAL

Snitem

Pour faire avancer la santé

GENERAL SAFETY AND PERFORMANCE REQUIREMENTS : FOR ALL MEDICAL DEVICES !



+

Design / Manufacture

- Chemical, physical and biological properties
- Infection and microbial contamination
- Presence of substances (medicinal product, biological origin)
- Construction of devices and interaction with their environment
- Protection against radiation
- Softwares
- Active devices (incl. implantable)
- Protection against mechanical and thermal risks
- Protection against the risks posed by devices supplying energy or substances
- Protection against the risks posed by medical devices intended by the manufacturer for use by lay persons

Information provided with the MD (labeling and instructions)

Pre-clinical and clinical evaluation

Risk management

1

PRE-CLINICAL AND CLINICAL EVALUATION :

SPECIFICITIES FOR MEDICAL DEVICES

PRE-CLINICAL EVALUATION

Conditions :

- Finished products
- Harmonized standards and other references
- Performance of tests (in vitro, ex vivo, animal testing, mechanical, electrical…)
- Analysis report of the tests and relevant and documented justifications in the absence of tests
- Characteristics maintained over time (stability)

CLINICAL EVALUATION

- **For all devices, the technical documentation includes a clinical evaluation and a post-market clinical follow-up plan**
- The Clinical Evaluation is based on a combination of:
  - Critical evaluation of the literature
  - Critical evaluation of the results of all available clinical investigations
  - Consideration of alternative treatment options
- The objective of the clinical evaluation is to:
  - Define the benefit/risk balance
  - Define the clinical benefit(s): significant, measurable, results in terms of benefit for the patient: benefit in terms of survival rate, functional benefit...
- **The manufacturer may not make any claim that is not based on clinical evaluation**

CLINICAL INVESTIGATION

- **Any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device**

- The results of clinical investigations are one of the foundations of clinical evaluation

For **Class III** and **implantable** devices:

- Clinical investigation is the rule for clinical evaluation
- And its absence is the exception!

POST MARKETING CLINICAL FOLLOW-UP (PMCF)

POST MARKETING CLINICAL EVALUATION

- **Ongoing process of updating clinical assessment**
- **Proactive process of clinical data collection and analysis to :**
  - Confirm safety & performance of the device throughout its life cycle
  - Detect unknown side effects and emerging risks
  - Identifie systematic misuse (suitablility of destination)

- PMCF is mandatory
- PMCF evaluation report included in technical documentation
- Encouragement by the Commission and the Member States of the setting up of registries
- PMCF plan is documented (annex XIV part B - MDR)

- Reflects the MD in real life…
  - Planned
  - Customer surveys
  - Clinical investigations
  - Extension of pre-market investigations …

THE SCRUTINY PROCESS IN CLINICAL EVALUATION (ARTICLE 54) : SUMMARY

+ Voluntary consultation of experts panels on clinical strategy (art 61 point 2 MDR)

Which Medical Devices?

Class III implantables devices

Class IIb actives MD intended to administer and/or withdraw drugs to/from body

Which circonstances?

Novelty

Significative → of B/R

Significative → of incidents

Exclusions (renewal of MDR certificate, range evolution/MDD or MDR*, conformity to common specifications)

Which process?

ON sends its clinical evaluation report (+ manufacturer data)

Expert panel seizes (or not)

Expert panel delivers a non-binding opinion (in theory)

*MDCG 2019-3 rev1

WHO MAKES AND VERIFIES THESE CLINICAL ASSESSMENTS?

- Manufacturer:
  - The clinical assessment must be validated and signed by persons with clinical expertise
  - The competence and the updating of the competence of these persons are documented in the manufacturer's QMS (CV + trainings followed)

- Notified bodies:
  - The presence of employees with clinical expertise is mandatory, and is verified by the competent authorities (ANSM) during notification and follow-up inspections of the NB
  - The NB shall verify the competence of the persons who have performed and signed the manufacturer's clinical assessments
  - The NB shall verify / validate the clinical results presented by the manufacturer as part of the certification

SPECIFICITIES OF MD CLINICAL EVALUATION

- Must necessarily be adapted to the DM concerned
- Takes into account the pre-clinical evaluation
- Methodology applicable to drugs not adapted in many cases (placebo, blind, etc.)
- Long implementation times and short life cycles
- Target populations are often very small and do not enable large-scale trials
- Clinical evaluation criteria: survival rate, functional benefit, "diagnostic utility", quality of life, etc.
- Very strong link with the medical-surgical act or the use by lay person
- Learning curve and possible variations in practice
- Organizational impact

2

CLINICAL INVESTIGATIONS ON MEDICAL DEVICES :

REGULATORY APPROVAL PROCESS

WHAT REGULATION ?

Since may 26, 2021 : EU 2017/745 Regulation

- New classification of clinical investigations
- New rules for prior approval (what CI need ethical / scientific approval ?)
- New authorization deadlines
- Implementation of an EU electronic system : “Eudamed”
- …

+ national legislation -> France : code de la santé publique

- Subjects not covered by the European regulation (contracts between companies as sponsor and hospitals or health professionals)
- National positions called for by the European regulation (e.g. organization of ethics committees or sanctions)

MDR MAIN PRINCIPLES : IDENTICAL TO THE PREVIOUS REGULATION

- Protection of subjects' rights, safety, dignity and well-being
- Expected benefits > risks and inconveniences for subjects
- Informed consent of subjects (exceptions: disability, emergency, etc.)
- Scientific and ethical review of the clinical investigation project
- EU legal representative required for non-EU sponsors
- Medical care provided by a doctor, dentist or authorized person
- No indue influence, including financial, on subjects
- Withdrawal of the clinical investigation possible at any time without justification
- Appropriate health facilities
- Sponsor's insurance
- …

NEW CATEGORIZATION OF CLINICAL INVESTIGATIONS

Previous regime → categorization according to the **degree of intervention on the subject** :

- intervention on the subjects not justified by usual practice
- minimal risk and burden to subjects
- without risks or constraints for the subjects

New regulation → categorization according to the **status of the device** :

- CE-marked / non CE-marked device (or CE-marked but used outside the scope of its intended purpose)
- risk class of the device

+ the **intervention on the subject** :

- additional invasive or burdensome procedure for subjects

NEW CATEGORIZATION OF CLINICAL INVESTIGATIONS

Sources : MDR + MDCG guidance 2021-6 + **french legislation**

<table>
<tr><th colspan="3">IC conduites pour établir la conformité du DM
(art. 62.1 RDM)</th><th>Autres IC
(art. 82 RDM)</th></tr>
<tr><td colspan="2">IC portant sur :
- DM non marqué CE (y compris les DM sur mesure ou DM en interne dits « in house »[2] même s'ils ne font pas l'objet d'un marquage CE) quand l'IC vise à établir la conformité
- DM marqué CE, utilisé hors destination</td><td rowspan="2">IC SCAC :
- DM marqué CE, utilisé dans sa destination
- et comportant des procédures additionnelles invasives/lourdes

(toute classe de DM)</td><td rowspan="2">Cas 4.1. IC SCAC (DM marqué CE, toute classe, utilisé dans sa destination) avec des procédures additionnelles non lourdes et non invasives

Cas 4.2. IC sur DM marqué CE (toute classe), utilisé dans sa destination sans objectif d'établissement de la conformité, et avec procédure additionnelle invasive ou lourde ou avec procédure additionnelle non invasive et non lourde (par exemple par des équipes d'établissement de santé avec un promoteur institutionnel)

Cas 4.3. IC sur DM marqué CE (toute classe), utilisé hors destination sans objectif de marquage CE ou d'établissement de la conformité (par exemple par des équipes d'établissement de santé avec un promoteur institutionnel)

Cas 4.4. IC sur DM non marqué CE (toute classe y compris DM sur mesure / DM en interne dits « in house »), sans objectif de marquage CE ou d'établissement de la conformité (par exemple par des équipes d'établissement de santé avec un promoteur institutionnel)</td></tr>
<tr><td>Classe I
Classe IIa non invasif</td><td>Classe IIb non invasif
Classe IIa et IIb invasifs
Classe III</td></tr>
<tr><td>Art. 62, 70, 70.7.a et 74.2</td><td>Art. 62, 70, 70.7.b et 74.2</td><td>Art. 74.1 et art 62 (certaines dispositions mentionnées dans l'art.74.1)</td><td>Art 82 et art. 62 (certaines dispositions mentionnées dans l'art. 82.1)</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td></tr>
</table>

FORMALITIES AND DEADLINES (FRANCE) : PRE-CE

Clinical investigation regarding non CE-marked device*

class I, class IIa non invasive	**class III, class IIb, class IIa invasive**
1	2

12 days of clock-stop for sponsors' answers

Admissibility examination by ANSM :
10 days (+ 15 days if incomplete file)

Ethical review by CPP :**
45 days

Admissibility examination by ANSM :
10 days (+ 15 days if incomplete file)

Scientifique review by ANSM :
45 days (+ 20 jours if consulting experts)

Ethical review by CPP :
45 days

*or CE-marked device used outside the scope of its intended purpose

**CPP : comité de protection des personnes (ethic committee)

FORMALITIES AND DEADLINES (FRANCE) : POST-CE

Post market clinical follow-up (PMCF) :

+ **additional invasive or burdensome procedure** for subjects

3

Admissibility examination by ANSM :
10 days (+ 15 days if incomplete file)

Ethical review by CPP (taking into account the ANSM opinion on the safety of the additional procedure) :
30 days

Post market clinical follow-up (PMCF) :

+ **additional non-invasive or non-burdensome procedure** for subjects

4.1

Admissibility examination by ANSM :
10 days (+ 15 days if incomplete file)

Ethical review by CPP :
45 days

12 days of clock-stop for sponsors' answers

FORMALITIES AND DEADLINES (FRANCE) : ACADEMIC RESEARCHES

CE-marked device :

+ additional procedure (invasive/burdensome or not) for subjects

4.2

Admissibility examination by ANSM :
10 days (+ 15 days if incomplete file)

Ethical review by CPP (taking into account the ANSM opinion on the safety of the additional procedure if invasive/burdensome) :
30 days

Non CE-marked device

4.3

Or CE-marked device used outside the scope of its intended purpose

4.4

Admissibility examination by ANSM :
10 days (+ 15 days if incomplete file)

Scientifique review by ANSM :
45 days (+ 20 jours if consulting experts)

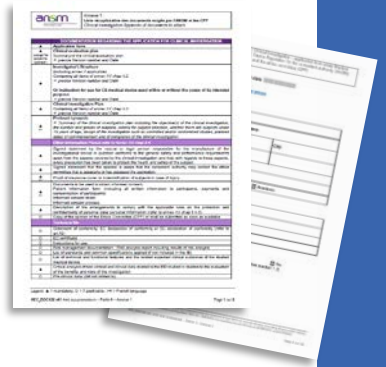
Ethical review by CPP :
45 days

12 days of clock-stop for sponsors' answers

SUBMISSION IN PRACTICE

- **Content of the file: Annex XV, chapter 2 of the MDR**
  - Regardless of the clinical investigation category (content to be adapted according to the CI)
  - A single file submitted to ANSM and to the CPP

- **Avis aux promoteurs ANSM**
  - Guide for submission in rance
  - List of documents to be provided, language of these documents, filing form, …

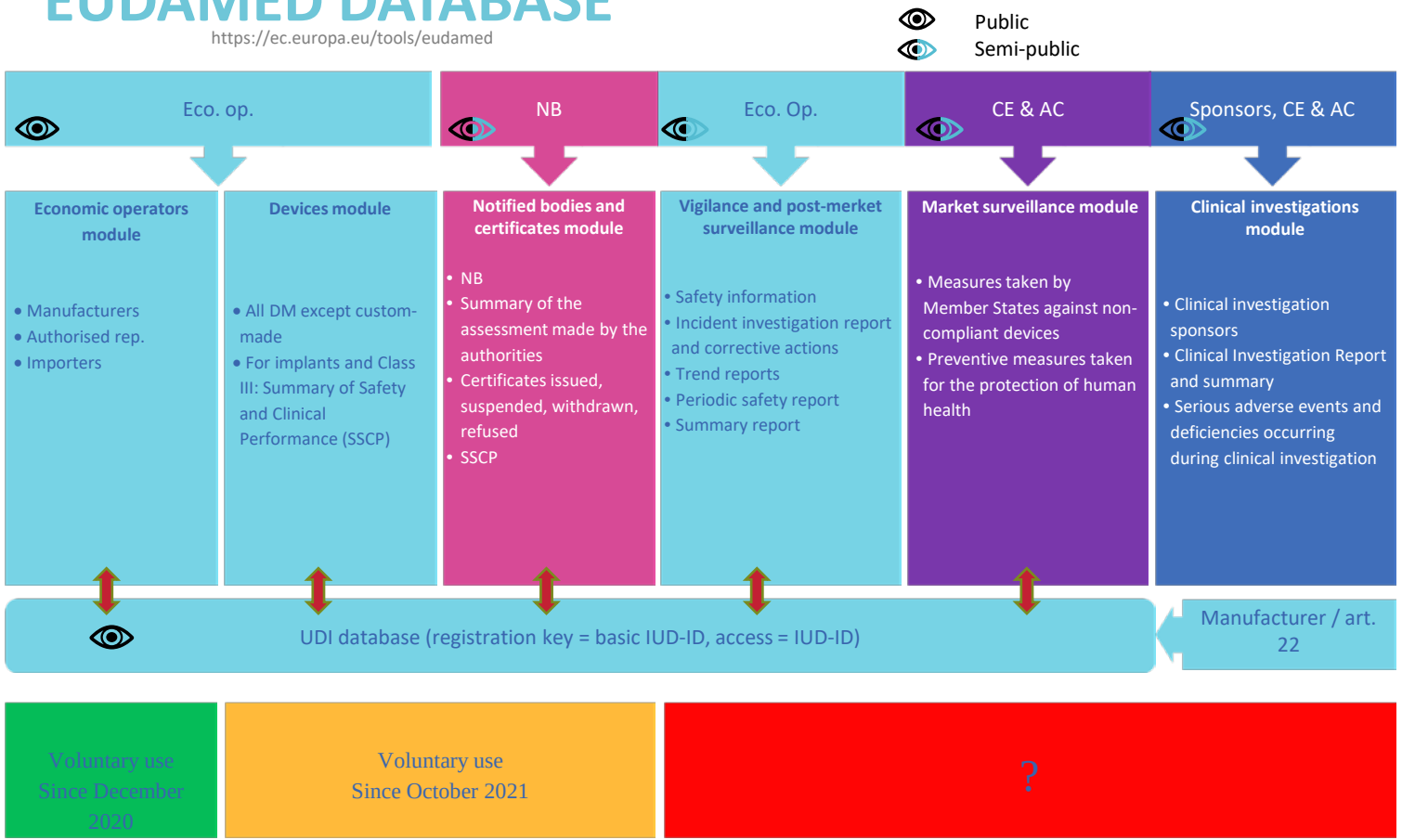


- Submission of the file: the same day to ANSM and to the CPP
  - CPP : SI RIPH 2G
  - ANSM : EC.DM-COS@ansm.sante.fr or Eudralink

will be replaced by the EUDAMED database

EUDAMED DATABASE

https://ec.europa.eu/tools/eudamed



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SUBSTANTIAL MODIFICATIONS

SUBSTANCIAL MODIFICATIONS (ANNEX VII 4.9 AND IX 2.4/4.10 AND X.5)

Compulsory Information by manufacturer

- QMS modification or range of products
- Design, indication or any item that can question safety, performance or conditions of use

Evaluation by NB

- Change control management
- Verification of continued compliance (audit or assessment necessary?)
- Notification of the conclusion (additional document to the certificate)

NO PUTTING ON THE MARKET WITHOUT PRIOR APPROVAL

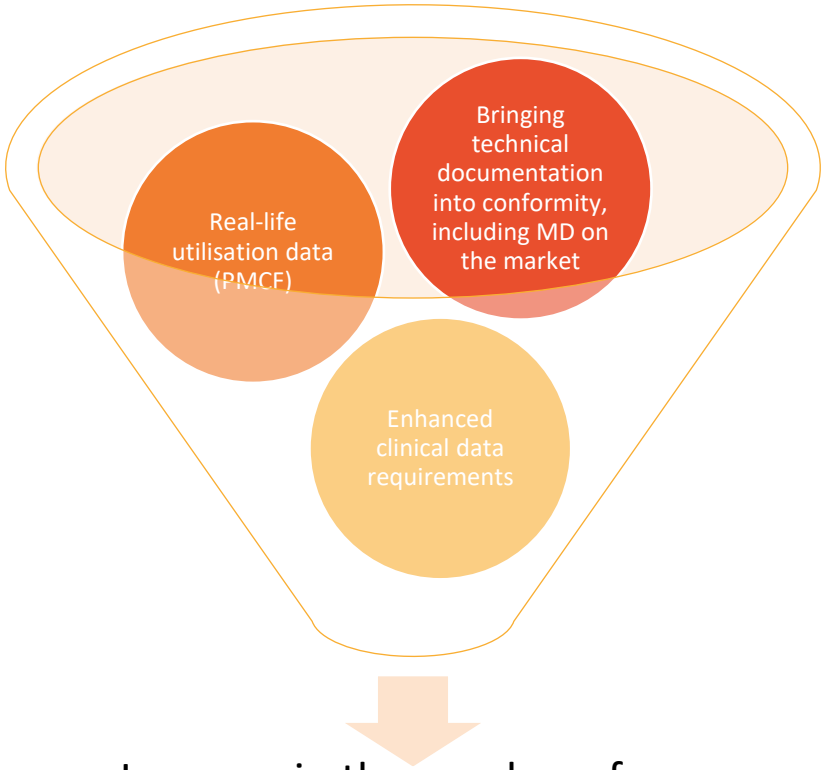
CONCLUSION

Regulation 2017/745 will:

- increase **European harmonization** in terms of clinical investigation authorization modalities,
- improve **transparency and information** (EUDAMED database, summary of safety characteristics and clinical performance)
- to strengthen the demonstration of **clinical evaluation**
- Provide a **centralized evaluation** for the most risky DMs

A panel of European experts will develop **common specifications** by device category for clinical evaluation

CONCLUSION



Increase in the number of pre and post CE clinical investigations

DOCUMENTS DEVELOPED BY THE SNITEM (IN FRENCH):

Fiches & synthèses

Guides & docs de référence

www.snitem.fr

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