From clinical trials to routine uses: the example of Lu177 (Plenary Session 6)

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The new BSS

Article 55 -2.

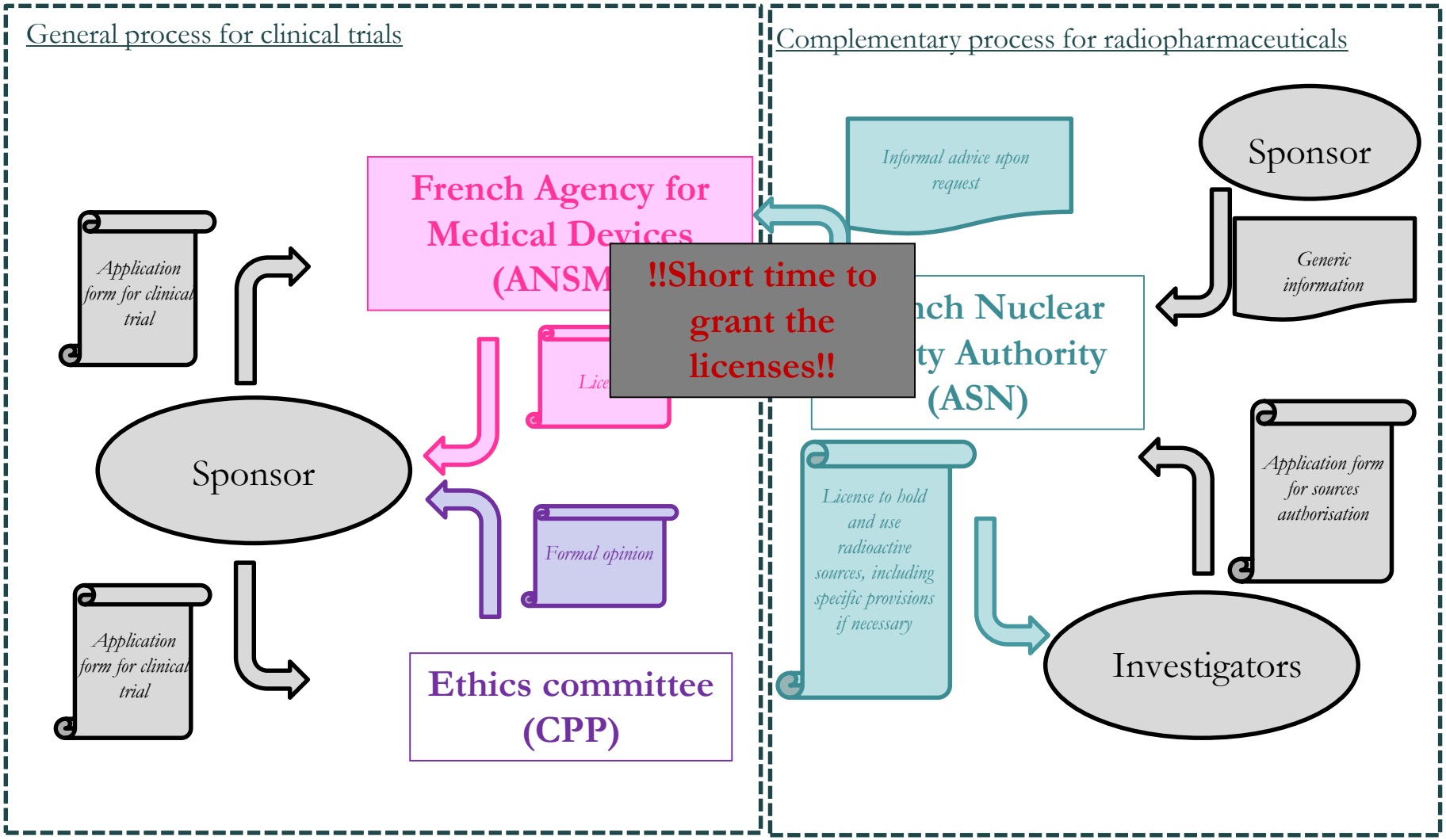
(a) new types of practices involving medical exposure are justified in advance before being generally adopted;

- Are the clinical trials on radiopharmaceuticals subjected to justification ***in advance***?

(e) medical exposure for medical or biomedical research are examined by an ethics committee, set up in accordance with national procedures and/or by the competent authority;

- Already implemented in the French process

French process for biomedical research, before introducing new radiopharmaceuticals



Detailed duties of the stakeholders

Ethics committee (CPP)	French Agency for Medical Devices (ANSM)	French Nuclear Safety Authority (ASN)
- Protection of volunteers: information, agreement… - Relevance of the trial, - Assessment of the balance benefits/risks, including radiological aspects - Material and financial resources	- Quality and safety of the products - Safety of the patients during the tests, including the assessment of patient exposure	Assessment of the radiations protection arrangements: - for patients - for workers - and for the environment

What's about Justification?

- **Current French PUBLIC HEALTH CODE article R. 1333-26: Provisions to grant specific licence for the biomedical research and to define a dose constraint.**

In practice….

Ethics committee (CPP)	French Agency for Medical Devices (ANSM)	French Nuclear Safety Authority (ASN)
Assessment of the balance benefits/risks, including radiological aspects	Safety of the patients, including the assessment of patient exposure	Assessment of the radiations protection arrangements: - (for patients) - for workers - and for the environment
➢ ***no particular skills relative to the ionizing radiations risks.***	➢ ***no consideration of the occupational or the public exposure.***	➢ ***Specification of particular conditions of use, taking into account occupational and public exposure***

Lutetium 177

Half-life: 6,65 days

Emissions:

β- (max energy 497 keV)

γ (113 keV and 208 keV)

Contaminated by Lu177m (half-life: 160 days)

Products available:

Name	Type	European marketing authorization
Lumark®	radiopharmaceutical precursor	granted
Endolucin beta®	radiopharmaceutical precursor	granted
Lutathera®	radiopharmaceutical medicine	application received

- Used for radionuclide therapy in nuclear medicine department, for the treatment of mid-gut neuroendocrine tumors (orphan disease).
- Also currently tested for others indications:
  - the treatment of pancreatic neuroendocrine tumors
  - the treatment of prostatic tumors
  - the treatment of pulmonary tumors

The case of Lu177 in France (1)

2012 - First step: clinical trials

Ethics committee (CPP)

Positive opinion issued in july 2012

NETTER-1
- International clinical trial, sponsored by AAA
- 20 patients included in France

French Agency for Medical Devices (ANSM)

Clinical trial licence granted in july 2012

French Nuclear Safety Authority (ASN)

Due to the contamination by Lu177m, ASN required the sponsor to carry out an EIA which was then assessed by IRSN (TSO)

Considering the workers exposure, the public exposure and the potential environmental impacts, licences are granted under the following specific conditions:

- Urines shall be collected in storage tanks for radioactive decay, in the same conditions than I131, so the treated patients shall be hospitalized in a shielded room for 24 h

Licences to hold and use Lu177 for the NETTER-1 trial granted to 6 investigating centres, since December 2012

Respect of the regulatory process

What's about Justification?

The case of Lu177 in France (2)

2012/2015 - Second step: new trials and compassionate uses

- 2 others trials started in 2012 and 2015, respectively involving 4 and 10 investigating centres.

- Considering the preliminary results of the study NETTER-1 (benefits +++ for the patients), ANSM started to grant licences for compassionate use in 2015.

  - **Increase of the number of treated patients expected (Sponsor's projection: 100 patients in 2015; 500 patients in 2017)**

  - **ASN Experts Committee was assigned to re-assess the specific conditions of use, taking into account the increasing number of treated patients; a working group has been set up and started in September 2016.**

2016 – MA Application sent to EMA in April

What's about Justification?

The case of Lu177 in France (3)

Next step: routine uses

French Agency for Medical Devices (ANSM)	French Nuclear Safety Authority (ASN)
➢ **Granting Marketing Authorizations.**	➢ **Granting Use Authorizations.**
According to the EU directive 2001/83/CE, MA application includes data relative to: - the radiological risk for the patient - the occupational risk - the environmental risk	Considering the number of patients, the practices… update of the specific licence conditions.

➢ Two independent and parallel processes, potentially divergent
(i.e.: disagreement about patients hospitalization)

➡ **What's about "transparency" on Justification?**

➢ **Usually considered as achieved by the Market Authorisation**
➢ **Not really achieved from the radiation protection point of view**

Perspectives

National level

- **Project of MoU between ASN and ANSM to coordinate the assessment of the generic justification before the marketing authorisation being granted.**

This assessment should be based on sponsor's data such as:

- Benefits for the patient
- Risks fort the patient and the comforters
- Environmental impact…

European level

- **Implementation of the EU regulation 536/2014 on clinical trials on medicinal products for human use**

Article 37 **"…**within one year from the end of a clinical trial in all Member States concerned, **the sponsor shall submit to the EU database a summary of the results of the clinical trial**. **[…]** However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year, the summary of results shall be submitted as soon as it is available."

Attention: the results of the clinical trial could be available after the MA delivery….

☞ **In this context, the French draft decree makes provisions for the supervision of the new radiopharmaceuticals use, after the MA delivery, if needed, depending of the stakes (MSW justification/PS5).**