Agence nationale de sécurité du médicament et des produits de santé

The compassionate use of medicinal products.

The French ATU system

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ECRD 23 May 2012

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- Employee of ANSM (State operator).

  Nothing to disclose
- This speech is made under strict compliance with the independence and impartiality of ANSM as regards other speakers.

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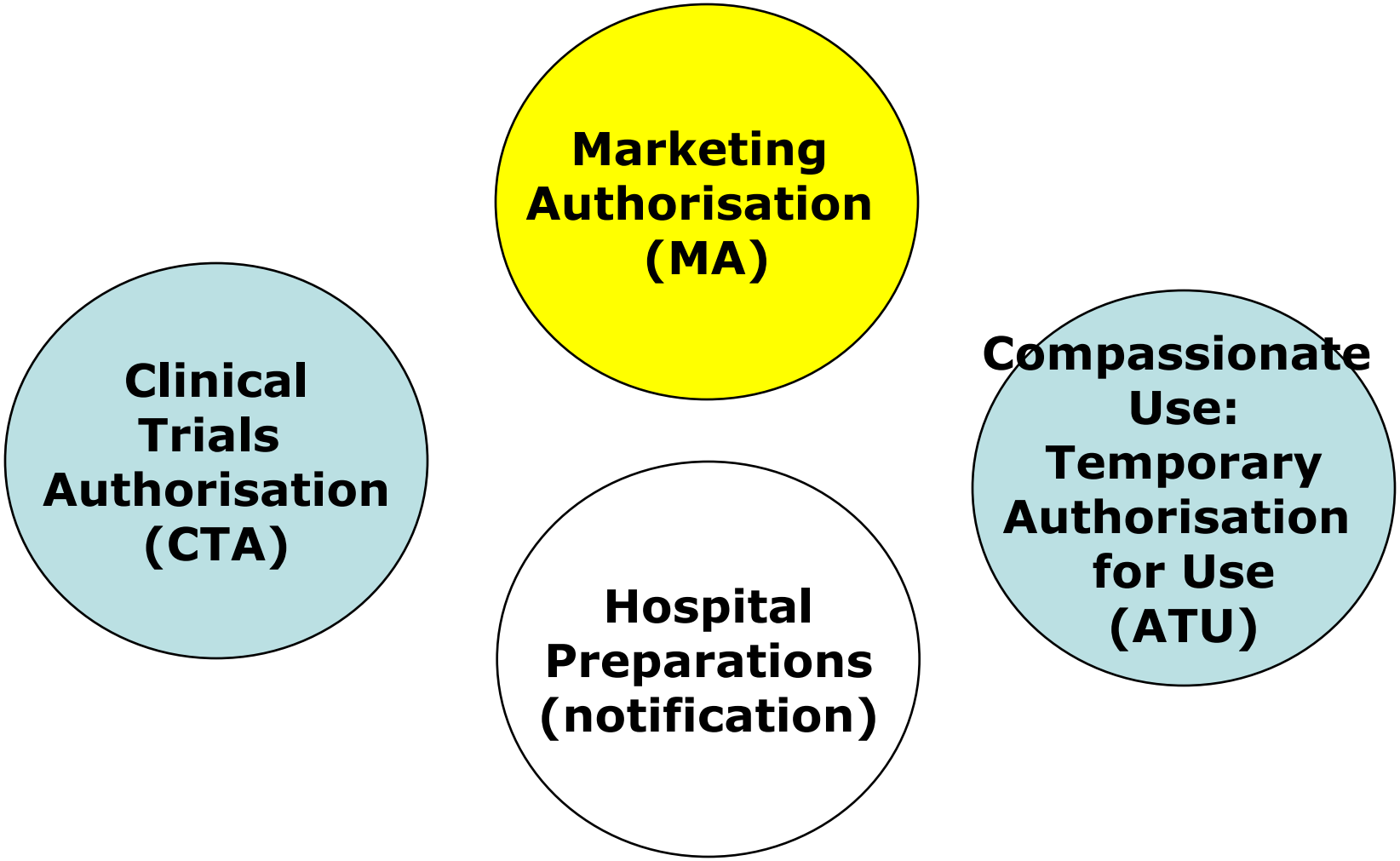
Outline

- The French system of compassionate use: a15-year experience
- Perspectives
- Off label use

In France: how to make a MP available to patients ?



Compassionate use: legal basis

In EU, exemptions of marketing Authorisation to place a medicinal product (MP) on the market :

1. **Individual use** (Article 5 - Directive 2001/83/CE)

A member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order formulated in accordance with the specifications of an authorized health care professional and for use by his individual patients on his direct personal responsibility.

→ nominative ATU in France

Compassionate use: legal basis (2)

- **Use for a group of patients** (Article 83 – Regulation (EC) n°726/2004)
  - The European compassionate use program
    - Scope :
      - For MP entering in the scope of centralised MA
      - For a group/cohort of patients,
      - with chronically – seriously debilitating of life threatening disease,
      - with no therapeutic alternative
      - CTs are running or there is a MAA
    - CHMP may give an opinion but the competence (responsability) is still of MS
    - Only 2 experiences

→ cohort ATU in France

General principles of the ATU

- **Legal provision laid down in France in 1994**
- **Exceptional derogation to the MA**

- **This provision allows**
  - (early) access to new promising drugs or to old drugs
  - not covered by a MA/not available in France (approved abroad or being developed)
  - when there is an unmet need.

- **This use is controlled by the competent authority :**

Any use of a MP not holding a MA and not used within a clinical trial is subject to prior authorisation (ATU), granted by ANSM

Criteria for granting ATU

- it is a MP *(not a preparation),*
- with no MA in France *(whatever the indication)*
- for treatment, prevention or diagnosis (*not for investigation)*
- of a rare or serious disease
- no satisfactory alternative method is available in France (*with a MA*)
- efficacy and safety are presumed
- benefit is expected for the patient
- the patient cannot be included in a clinical trial (CT)
- ATU is granted for a limited period of time (*Temporary authorisation*)

ATU are not clinical trials !

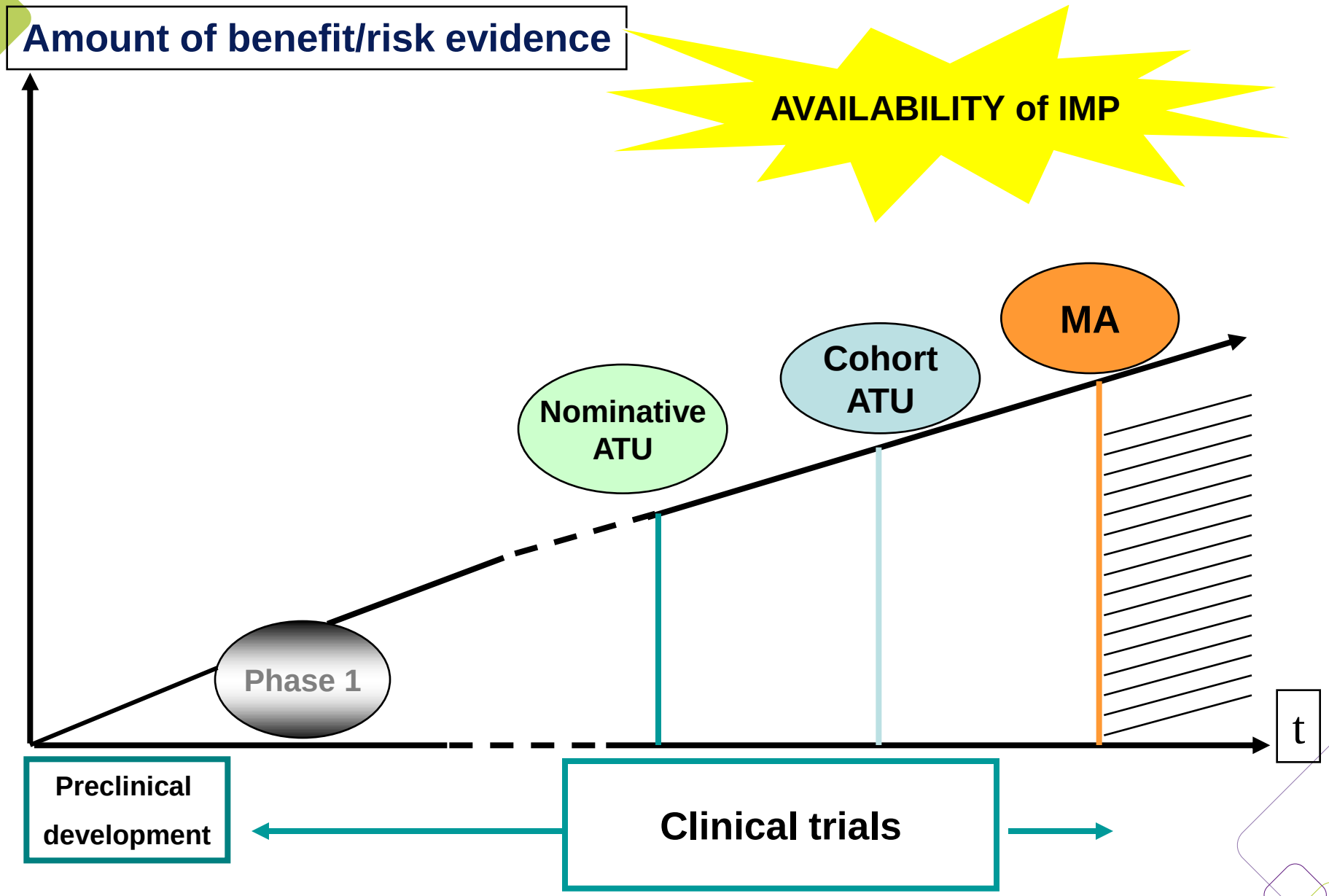
ATU	Clinical trials
◆ The objective is to treat ◆ Efficacy/Safety data are yet available ◆ Benefit/risk is presumed positive ◆ Patient is informed by the physician	◆ Objective is to investigate ◆ Collect essential information on benefit/risk balance for MA ◆ Directive 2001/20/EC - Signed informed consent - CT authorisation + Ethics Committee opinion - CT insurance - GCP…

Patients should always be considered for inclusion in CTs before being offered ATU

- Off label use : not ATU (other provisions in France)
- ATUs are not clinical trials, even to continue treatment at the end of a CT
- ATUs must not replace or slow down CTs
- Expanded access through clinical trial process is possible/preferred

2 types of ATU

Cohort ATU	Nominative ATU
◆for a group of patients, for one indication, ◆applied by the company, commitment to submit a MA ◆safety and efficacy of the MP are highly presumed, close to the MA ◆ATU for one-year duration, renewal possible ◆SmPC, patient information leaflet, labelling ◆always follow up of all patients and data collection according to a protocol for therapeutic use (PTU) ◆periodic data-reporting to ANSM	◆one patient, on a named patient basis ◆provided the patient cannot enter a CT ◆on the request and responsibility of the physician ◆ safety and efficacy of the MP are presumed ◆ATU for the duration of treatment ◆usually, follow up of patients and data collection according to a protocol for therapeutic use (ANSM decision)


Amount of benefit/risk evidence
AVAILABILITY of IMP
MA
Cohort ATU
Nominative ATU
Phase 1
t
Preclinical development
Clinical trials

Assessment

What is assessed by Afssaps ?

- The MP
  - Quality
  - Safety
  - Efficacy
- The medical context :
  - disease
  - therapeutic alternatives
- The need to mitigate risks

The protocol for therapeutic use and data collection (PTU)

- Established by ANSM with the Company

- Purpose (1) : providing physicians and pharmacists with information on the MP and conditions for using the MP :
  - Criteria for use (SmPC)
  - Patients information process (leaflet and procedure)
  - Conditions of prescription and supply of the MP.

- Purpose (2) : describing and organising pharmacovigilance
  - Procedures of safety monitoring of patients,
  - Procedures of ADR reporting and CRFs.

- Purpose (3) : organising data collection and analysis :
  - Description of the treated patients and the real conditions of use of the MP
  - Sometimes some efficacy data and always safety data
  - Conditions for the periodic data reporting to ANSM.

Pharmacovigilance

Cohort ATU or nominative ATU with PTU	Nominative ATU with no PTU
Described in the protocol of therapeutic use (PTU) : ◆ Monitoring of each patient ◆ Data collection ● from physician to company ● from company to ANSM ◆ One dedicated regional center of pharmacovigilance ◆ Periodic data analysis reported by the Company to ANSM and assessed ◆ Summary of collected data ● circulated to concerned physicians/pharmacists ● published on ANSM website	◆Same pharmacovigilance rules as marketed MPs (spontaneous reporting + PSUR) if no PTU

Other provisions

- GMP
- Only hospital physicians can prescribe the MP
- Prescription may be restricted to certain specialists
- Only hospital pharmacists can supply the MP
- Committment of physician to give information to patients
- No advertising allowed
- Information materials for physicians on the MP, to be validated by ANSM

Metrics (1)

- ATU implemented in 1994
- More than 1000 MPs assessed since 1994
- ~230 MPs subject to ATU in 2011 ; several indications
- Availability 10-12 months on average before MA
- Therapeutic areas :
  - **Oncology-haematology**
  - **CNS**
  - **Infectious diseases including AIDS**
  - **Metabolism (rare diseases)**

Metrics (2)

- Nominative ATU in 2011
  - ~ 25 000 ATU (initial + renewal) ; 460 refusals
  - ~ 18 000 patients (30% children)
  - 53 new MPs

- Cohort ATU
  - Since 1994 : more than 130 active substances
  - From several months to years before MA (now ~1 year)
  - 7 new cohort ATU in 2011 (18 applications) :
    - Vemurafenib, Paser®, Tafamidis, Vimpat®, Jevtana®, Ipilimumab, Abiraterone
  - 5 new cohort ATU in May 2012 (14 applications) :
    - Crizotinib, Ruxolitinib, Propanol, Pomalidomide, Brentixumab;

Innovations are available several months before MA….

- Rare diseases :
  - 72% of the 64 authorised OMP were available in France through ATU
  - 35 months before MA (average)
  - 2011 : tafamidis. ATU 23 months before MA (transthyretin amylosis)
  - Significant examples: Fabrazyme (14 mths), Carbaglu (22), Pedea (45), Wilzin (64), Orfadin (123), Diacomit (145), Thalidomide (152)…
- Cancer :
  - In 2011, 31 medicinal products, 3000 patients with nATU
  - including new personalised medicines
    - Metastatic melanoma (2011)
    - Lung cancer (2011)
    - Myelofibrosis (2012)
- C Hepatitis :
  - ribavirine then bitherapy and now tritherapy (protease inhibitors /2011)
- All new AIDS medicines…

To sum up,

- The system is extremely useful to cover public health needs
  - Supported by patients and physicians
  - Controlled by the competent authority

- But, a risk to slow down CTs and MA

- And, regarding nominative ATU,
  - Too many
  - Complex system
  - No strong regulatory long term status (no mandatory MAA)
  - Patients monitoring and data collection to be improved.

What is going to change

Objectives

1. Avoid temporary situations that last too long (improve the end of ATU)

- MA as the gold standard
- Develop clinical trials
- Favor Cohort ATU (✓ 75% in 2012)
- Nominative ATU as the very last option for patients

2. Improve safety-efficacy management of compassionate use

→ Optimise patients monitoring

3. Improve Transparency

→ New rules, new law (December 2011)

Clarification of criteria for ATU

- If MA abroad : have a MAA in France
- Applications for nominative ATU should not be considered :
  - If there is no MAA or cohort ATU application (or commitment to do so)
  - Or if there is no CT or CTA in France
- Otherwise, exceptional nominative ATU (derogation to the rule)
  - e.g. if serious complications are very likely

Enlarge patients follow-up and data collection

- Protocol of therapeutic use, as the rule ;
- For Cohort ATU and nominative ATU ;
- Not only safety but also efficacy data collection.

Improved transparency

- Information of ANSM by the Company on any new data that could impact patients' safety
- Enlarged publication of information by ANSM

Another new and interesting legal provision, just for information

- Off label use
- New system laid down in the December 2011 law.
- “RTU” : Recommendations for Temporary Use
  - Established by ANSM
  - If no therapeutic alternative (with MA or Cohort ATU)
  - Based on evidence
  - In case of rare diseases, collaboration with centres of reference
  - For 3 years
  - Published by ANSM.
- RTU includes
  - Follow up of patients/protocol of RTU.
  - Data collection and transmission to ANSM for surveillance

www.ansm.sante.fr

- **Notice to applicants for ATU and templates (ATU request form, templates for PTU, periodic report …)**
- **Updated list of cohort ATU**
  - **SmPC and PIL**
  - **PTU**
  - **Summary of ATU periodic reports**
- **Updated list of refusals of cohort ATU**
- **List of medicinal products available through nominative ATUs (on a monthly and annual basis), PTU and summary of ATU periodic reports.**
- **List of hospital preparations that can be replaced by ATU medicinal products**

Abreviations

- ANSM: Agence nationale de sécurité du médicament et des produits de santé
- ATU : Temporary Authorisation for Use
- CHMP: Committee for human medicinal products
- CNS : Central nervous system
- CRFs : Case report forms
- CT : Clinical Trial
- CTA : Clinical Trial Authorisation
- EMA: European Medicines Agency
- MA : Marketing Authorisation
- MAA : marketing authorisation application
- MP : medicinal product
- MS: member state
- PIL : patient information leaflet
- PTU : protocol of therapeutic use
- PSUR : periodic safety update report
- RTU: recommendations for therapeutic use
- SmPC: summary of product characteristics

Thank you!