The compassionate use of medicinal products.
The French ATU system

C. Bélongey
Head of Department of evaluation of Clinical Trials and Medicinal products of special status

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Outline

- The French system of compassionate use: a 15-year experience
- Perspectives
- Off label use
In France: how to make a MP available to patients?

- Marketing Authorisation (MA)
- Clinical Trials Authorisation (CTA)
- Hospital Preparations (notification)
- Compassionate Use: Temporary Authorisation for Use (ATU)
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!

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

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

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

AVAILABILITY of IMP

Preclinical development

Clinical trials

Phase 1

Nominative ATU

Cohort ATU

MA
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

**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

## Nominative ATU with no PTU

- 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

- Commitment 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 amyloidosis)
  - Significant examples: Fabrazyme (14 mths), Carbaglu (22), Pedea (45), Wilzin (64), Orfadin (123), Diacomet (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
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!