

Risk management activity at Afssaps : Organisation, functioning, partnerships and developments

In 2005, the Afssaps implemented a program for reinforcement of post-marketing authorisation surveillance, particularly taking into account the requirements of the new Community legal framework, the reflexions conducted on the current system, and the need for interactions with other partners within the healthcare system.

Within the Afssaps, this approach has led to establish a new organisation enabling a **global and coordinated approach, mobilising the wide range of available tools in the management of medicinal product risks**, whether involving reinforced pharmacovigilance activities based on reporting of adverse effects, post-marketing authorisation studies (pharmacoepidemiological studies) or risk minimisation activities. This organisation also allows coordination with other Afssaps sectors/units that are likely to contribute to the necessary follow up, in particular with regard to inspections of companies' pharmacovigilance systems of and advertising control.

Three years of functioning of the "Risk Management Plan" (RMP) unit confirm:

- the increasing workload triggered by the submission of RMPs with marketing authorisation dossiers, their assessment, set up and follow-up.
- the need for early cross-disciplinary management, and early coordination with the pharmaceutical companies in order to have a coherent and adapted plan of follow-up measures and risk minimisation at the time of marketing of the products.
- the major role of the pharmacovigilance and addictovigilance networks, responsible for safety monitoring after the marketing.
- the need to integrate other partners, notably health professionals, patients' associations and knowledgeable companies.
- the importance of the pharmacoepidemiological studies performed with the objective of assessing safety and use of products, and the need for coordination of the requests from the French National Authority for Health (HAS), the General Health Directorate (DGS) and the Health Products Economic Committee (CEPS).
- the need to create an **expert group responsible for assessment of protocols and results of post-marketing authorisation safety studies**, in the context of the regulatory evolutions of the status of observational studies concerning authorised medicinal products, and the objectives of which are to assess, quantify and characterise the risks. This approach, initiated mid-2008, is concluded by the **first meeting of the expert group at the beginning of April 2009**.

A. Regulatory framework of RMPs

1. Situations when a RMP is required

An RMP may need to be submitted at any time of a product's life-cycle – i.e. during both the pre-authorisation and post-authorisation phases. In particular a RMP should be submitted:

- with the application for a new marketing authorisation for:
 - * any product containing a new active substance,
 - * a similar biological medicinal product,
 - * a generic/hybrid medicinal product where a safety concern requiring additional risk minimisation activities have been identified with the reference medicinal product,
 - * advanced medicinal therapies,
- with an application involving a significant change in marketing authorisation (e.g. new dosage form, new route of administration, new manufacturing process of a biotechnologically-derived product, significant change in indication/patient population (i.e. paediatric extension), unless it has been agreed with the Competent Authority that submission is not required.
- on request from Competent Authority (both pre- and post- authorisation).

- on the initiative of a MAA/MAH when they identify a safety concern with a medicinal product at any stage of its life cycle.

When not mandatory and when the MAA/MAH thinks it is not necessary to submit a RMP, the latter should submit a brief justification of this along with the application which will form part of the formal assessment.

The RMP forms an integral part of the marketing authorisation dossier within the module 1.8.2 "Risk Management Plan". Thus, in the same way as the other parts of the marketing authorisation dossier, if the RMP is not satisfactory it may be an obstruction to obtain the marketing authorisation. It also appears in the opinion of the CHMP and the public evaluation report (EPAR) published on the EMEA website.

2. Legislation in force

a. European and international legislation

- * Regulation (EC) n° 726/2004 - Art. 6 / Directive 2004/27/CE - Art. 8 (3)

In accordance with article 8-3 of the Directive 2004/27/CE and article 6 of the regulation (EC) n° 726/2004, the applicant must attach, where appropriate, a risk management plan (RMP) to each new marketing authorisation (AMM) dossier.

- * "Volume 9A" Guidelines on Pharmacovigilance for Medicinal Products for Human Use (March 2007)

1/ Part I chap 3 - Requirement for Risks Management systems

This Chapter aims to provide guidance to companies in the European Union on how to meet the requirements for a "detailed description of the risk management system" and the circumstances when it is appropriate to provide it. It keeps some elements of the Guideline on Risk Management System for Medicinal Products for Human Use (EMEA/CHMP/96268/2005) that is being updated, notably in order to integrate the situations for which RMPs will be mandatory in the case of generics. The criteria to be taken into account and which will justify providing a risk minimisation plan are currently under consideration.

2/ Annexes 5.1.1 Template for EU Risk Management Plan (EU-RMP)

3/ Part I chap 7 - Company-Sponsored Post Authorisation Safety Studies (PASS)

In addition to chapter 1.3 specifying the conditions in which a RMP must be submitted, Volume 9A integrates a specific chapter (chapter 7) relative to the recommendations on the conducting of post-marketing authorisation studies (ethical considerations, respective roles of the authorities, declaration of adverse effects and final report) by the pharmaceutical laboratories. Since 2007, non-interventional safety studies have been integrated.

It should be noted that the Review and Learning Group (R&L Project) put in place by the EMEA for the purpose to evaluate the completeness, quality and value of the submitted and finalised RMPs, together with the EMEA, is currently reviewing the different approaches for handling EU RMPs within the EU in order to share and recommend best practices.

- * ICH E2E: note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)

b. French requirements

- * Decree n°2008-435 of 6 May 2008 relative to marketing/launch of medicinal products for human use:

The article R.5121-25 of the Public Health Code transposes notably the provisions provided by the Directive 2004/27/CE - Art. 8 (3).

- * Decision of 7 May 2008 relative to the standard risk management plan template and taken pursuant to article R. 5121-25 of the Public Health Code stating the terms of submission of RMPs:

This decision aims to describe how a RMP can be presented to the Afssaps.

This template must also be followed for medicinal products registered according to a centralised procedure or a mutual recognition or decentralised procedure, for which the Afssaps may request additional specific measures, such as intensive surveillance or risk minimisation activities (e.g. monitoring of pharmacovigilance, pharmacodependence, etc.).

For a medicinal product registered according to a purely national procedure, the content of the risk management plan *can be adapted on a case-by-case basis*. Nevertheless, it must as a minimum include the following information:

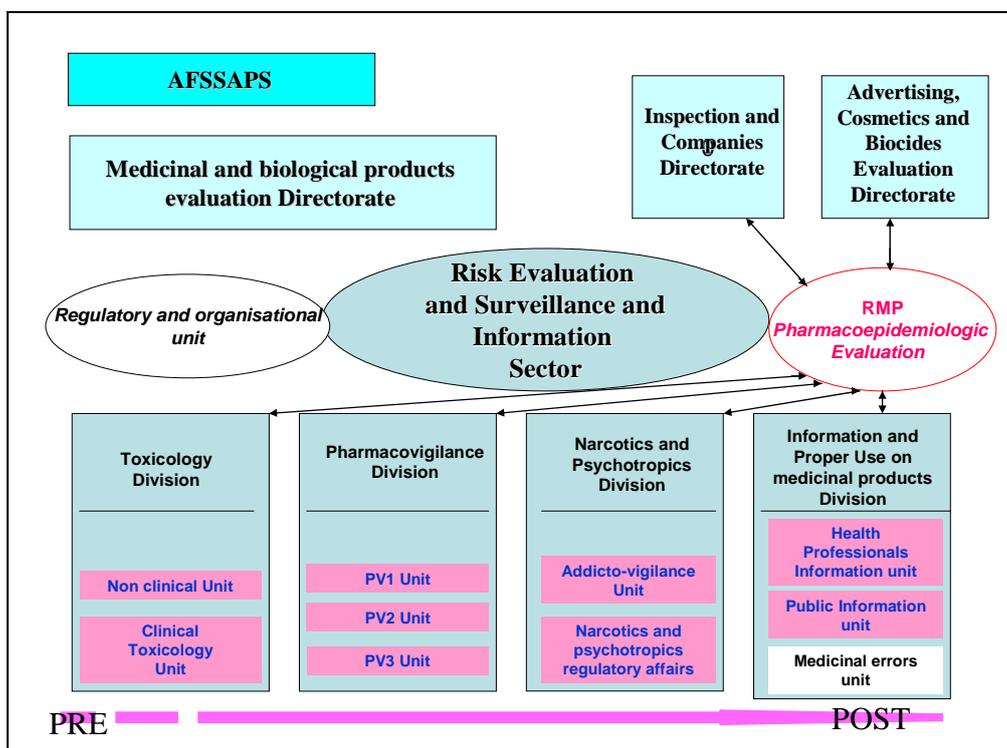
- information on the product (name, dosage, pharmaceutical form, description, indication, dosage, etc.);
- description of the safety data and presentation of exposure data: profile of safety of use under normal conditions of use and outside of the conditions of the marketing authorisation;
- pharmacovigilance plan and, if appropriate, risk minimisation plan.

B. Risk management activity at the AFSSAPS

1. Organisation

a. The RMP-Pharmacoepidemiology unit

The RMP/pharmacoepidemiology unit is located within the Risk Evaluation and Surveillance and Information Sector.



To date, 3 pharmacoepidemiologists are responsible for assessing European and national RMPs (expert consultation on studies and proposed minimisation plans), identifying the need to establish additional measures (notably at national level in addition to the EU-RMP), and coordinating the activity of follow-up on medicinal products for which a RMP is required or requested. Besides, one other assessor is specifically in charge of the risk minimisation activities.

b. The expert group

A group of experts, attached to the National Pharmacovigilance Commission and the National Narcotics and Psychotropic Drugs Commission, is currently being established. The multidisciplinary group will be constituted of experts recruited for their skills in risk management and pharmacoepidemiology/biostatistics, pharmacovigilance, addictovigilance, medicine and pharmacology.

The group will support the RMP/pharmacoepidemiology unit and will be sought to assess the relevance of performing pharmacoepidemiological studies for products for which a EU-RMP is required, and in particular to review the study protocols.

The expert group will consider the need to conduct additional studies to the European RMPs according to the specificities of the French health system. It will validate the study protocols and

evaluate the results and their impact on the public health plan. It will also consider the need to implement additional risk reduction measures.

Beyond their expertise on the methodology and the choice of statistical methods, the members of the working group will investigate the availability in France of methodological tools and sources of data in pharmacoepidemiology in collaboration with the other health authorities.

2. Modalities of the risk management activity

a. Organisation of the activity within the Agency

The activity of the RMP/pharmacoepidemiology unit requires close collaboration with the units or division responsible for the continuing evaluation of the Benefit/Risk ratio, whether pre- or post-marketing authorisation phase, i.e. the pharmaco-toxico-clinical units, the pharmacovigilance division, the narcotics and psychotropic Drugs division, the pre-clinical evaluation unit, and the methodology and biostatistics unit.

For centrally products, when France is (co)rapporteur, the pharmacoepidemiologists have close interaction with other assessors in charge of the dossier. The aim is to assess the RMP, in the perspective of the evaluation performed with other part of the dossier. The RMP assessors attend clinical expert working group together with clinical and PV assessors in order to get the opinion of physicians on the interest of the product in the therapeutic strategy, on the quality of data submitted and to discuss and define adequately the limitation of the safety profile, the important risks that need to be further assessed and the need for requiring additional PV and minimisation activities.

Agreement on the requirement for additional PV and minimisation activities is reached together with PV assessor. A close collaboration with regional pharmacovigilance centers may also be needed during the MA procedure and after the grant of the MA.

For RMP national activities, a collaboration has been also formalised with other structures:

- *With the Advertising and Proper Use of Healthcare Products Division*

Relations are established with the Advertising and Proper Use of Healthcare Products Division which is systematically informed of requests for european or national risk minimisation plans (information/training documents sent to healthcare professionals and/or patients).

A procedure sets down exchanges modalities between both structures. A joint validation of patient documents is necessary before their release. Documents intended for healthcare professionals are only validated by the RMP/pharmacoepidemiology unit, which sends to the Advertising and Good usage of Healthcare Products Department, where appropriate, a list of key elements that the promotional documents should or should not contain.

- *With the Temporary Authorisation Unit (compassionate access programme to medicinal products) - ATU Unit*

The circular DGS/SD.3A/DSS/FSS/DHOS/E2/n°2007-143 of 11 April 2007 stipulates that the Afssaps must guarantee a maximum period of 3 months for the cessation of the compassionate access programme to medicinal products from the marketing authorisation notification date.

In some cases, the RMP includes measures to be adapted at national level and that are mandatory to the product launch, according to commitments of the companies and conditions relative to the marketing authorisation. Therefore, the RMP/pharmacoepidemiology unit has a period of 3 months after notification of the marketing authorisation to validate the RMP measures.

Respecting this short timeframe requires a close and regular collaboration between the RMP/pharmacoepidemiology unit and the Temporary Authorisation Unit in order to identify the products as early as possible. Companies are also requested to contact RMP/pharmacoepidemiology in order to initiate an early collaboration upstream the launch for these medicinal products.

The procedure standardising the interaction between the RMP/pharmacoepidemiology unit and the ATU unit will be published soon, on the Afssaps website.

- *With the Generics Unit*

Identification of the generic products that might be involved in a RMP is of importance in order to apply similar measures of surveillance and risk minimisation as those requested for the innovator.

- *With the Inspection of Clinical and Non-Clinical Trials Division*

Relations have been established with the Inspection of Clinical and Non-Clinical Trials Division, which is informed of projects of post-marketing authorisation studies particularly at a national level. This

collaboration makes it possible to identify the regulatory status of the studies, and thus to ensure appropriate monitoring and control.

b. Consultation and follow-up meetings with pharmaceutical companies

Meetings are run with pharmaceutical companies, on their request or on the initiative of the Afssaps. They particularly take place in the following cases:

a) if appropriate, consultation meeting for scientific advice before submission of a marketing authorisation dossier in European procedure, particularly when France is planned to be (co)rapporteur or reference Member State.

b) in order to identify actions to be followed by the company at a national level in accordance with the European RMP when the product is close to marketing authorisation. In some cases, scientific advice meetings are an opportunity to exchange in advance about the content of the RMP and activities to be put in place. Where the application dossier has already been submitted, meetings with companies should be planned just after the opinion of the CHMP for centralised procedures (D180), around D-50 for mutual recognition procedures and D-100 for decentralised procedures. With regard to European procedures, it is of importance that early discussions between corporates and affiliates take place.

The objectives of these meetings are to consider the relevance of:

- adapting the risk minimisation plan based on key elements of the European RMP and identifying the European post-marketing authorisation studies in which France is involved (number of sites, number of patients, etc.).
- defining the specific national measures to be considered when the medicinal product or its indication meet one of the criteria listed in appendix 1. These measures may comprise national pharmacovigilance surveys, post-marketing authorisation safety studies, studies on prescription or drug use, and risk minimisation actions.

c) to define the content of the RMP for products registered in national procedures, whether pre- or post-marketing authorisation. In such a case, the RMP/pharmacoepidemiology unit encourages companies to liaise it before submitting the dossier of authorisation or just after.

d) following an alert identified in France with a national authorised product with the aim of setting up surveillance and minimisation measures.

The experience of the first three years shows that there is great interest in meeting the companies as early as possible before the marketing authorisation; if necessary, participation of other divisions/units of the Afssaps is required.

The agenda of the consultation meetings generally includes:

- a review of the current or future regulatory status,
- the provisional schedule for examination by the Transparency Committee,
- measures to put in place in agreement with the European RMP, particularly in France, and a discussion on the additional measures proposed on a national level (national pharmacovigilance/addictovigilance monitoring, additional safety study, etc.),
- the population exposed in France (clinical Trials, compassionate access programme, post-marketing authorisation studies and estimated target population),
- minimisation tools, with a copy of the documents validated in other Member States where they are available, and the validation time schedule.

c. National pharmacovigilance monitoring and interaction with the pharmacovigilance/pharmacodependence network and National Toxicovigilance System (Poison control centres)

To date, the assessment of additional pharmacovigilance activities is performed on an in-house basis at the Afssaps by RMP assessor in collaboration with PV unit. Some experts may be punctually solicited. Setting up a national pharmacovigilance survey is planned insofar as possible with the Pharmacovigilance Regional Center (CRPV) participating in the development and national adaptation of the European RMP. This national monitoring may depend on the expected use of the product, which is also depending on the indications for reimbursement.

National intensive monitoring conducted by CRPV is put in place for innovative products when an important risk is identified, where the data on safety of use are insufficient or when the use is expected to be extensive. The goal is to share safety data between the center responsible for monitoring, the

company and the Afssaps. Beyond transmissions of serious adverse effects occurring on the territory, any significant information that could modify the product's safety profile is communicated to each other. Regular updates on pharmacovigilance and prescription data, and on the progress of post-marketing authorisation studies may be planned for high sensitive products during monthly teleconferences associating the RMP/pharmacoepidemiology unit, the pharmacovigilance division, the CRPV responsible for national monitoring, and the company.

It is sometimes appropriate to contact the *National Toxicovigilance System* (Poison control centers) in the event of potential or identified risk of overdose, and thus to establish reinforced monitoring.

d. An Internet portal and a database

Information on the organisation and contents of the RMP activity intended for the general public and pharmaceutical companies are published on the Afssaps website.

Since February 2007, “**Public summary RMP**” for informing healthcare professionals and patients have been released on the Agency website. The priority of drawing up such reports is guided by the need for additional pharmacovigilance and/or minimisation activities at national level.

3. Statement of activities after three years of functioning

a. Statement as at 31 December 2008 of the RMP activity since October 2005

Type of procedure	Pre-marketing authorisation dossiers evaluated	Post-marketing authorisation dossiers evaluated	Total dossiers evaluated
European centralised procedure	53 dossiers Fr Rapporteur / Co-Rapporteur	5 dossiers Fr Rapporteur / Co-Rapporteur	58
	118 dossiers Fr Recipient	10 dossiers Fr Recipient	128
European mutual recognition procedure	9 dossiers Fr Reference MS	1 dossier Fr Reference MS	10
	15 dossiers Fr concerned MS	3 dossiers Fr concerned MS	18
National procedure	6 dossiers	2 dossiers	8
Total	201 dossiers	21 dossiers	222

From October 2005 to the end of December 2008, 222 RMPs were examined by the unit. Most were evaluated at pre-marketing authorisation stage and fell within a centralised procedure.

b. National activities set up within the framework of the RMPs since October 2005

	Centralised procedures (n=186)	National / MR / DC procedures (n=36)
National monitoring of Pharmacovigilance / Addictovigilance	20	8
Utilisation studies	4	3
National post authorisation safety studies	2	8
Risk minimisation activities = adaptation of the EU minimisation plan	30	9

c. Statement as at 31 December 2008 of intensive monitoring of pharmacovigilance (PV) / addictovigilance (AV) since 2005

Medicinal products	CRPV/CEIP
Centralised procedures	
Acomplia® (Withdrawn MA)	Grenoble (PV)
Arixtra®	Paris HEGP (PV)
Byetta®	Montpellier (PV)
Cervarix®	Bordeaux (PV)
Champix®	Paris Pitié-Salpêtrière(PV)
Cymbalta®	Paris Saint-Antoine (PV)
Efient®	Poitiers (PV)

Exjade®	Paris HEGP (PV)
Galvus®	Henri-Mondor (PV)
Gardasil®	Bordeaux (PV) / Lyon (Pregnancy)
Intrinsa®	Poitiers (PV)
Isentress®	Besançon (PV)
Januvia®	Montpellier (PV)
Lyrica®	Toulouse (PV)
Orencia®	Nancy (PV)
Procoralan®	Lille (PV)
Protopic®	Toulouse (PV)
Revlimid®	Nice (PV)
Tysabri®	Nice (PV)
Xyrem®	Bordeaux (PV-AV)
Other procedures	
Alendronates	Limoges (PV)
BCG SSI® Vaccine	St-Etienne (PV)
Benfluorex	Besançon (PV)
Buflomedil	Lyon (PV)
Buprenorphine	Grenoble (PV- AV)
Methadone	Marseille (PV- AV)
Methylphenidate	Reims (PV) / Paris Fernand Widal (AV)
Desmopressin	Caen (PV)

At 31 December 2008, 28 national pharmacovigilance monitoring programmes are currently ongoing or about to start, of which 20 in addition to the European RMP in centralised procedure and 8 for national or mutually procedure.

d. Statement as 31 December 2008 of intensive monitoring of toxicovigilance or solicitation of the National Toxicovigilance System since 2005

Medicinal products	Poison control centers
Centralised procedures	
Acomplia® (Withdrawn MA)	Grenoble (TV)
Champix®	Grenoble(TV)
Other procedures	
Buflomedil	Lyon (TV)
Méthadone	Marseille (TV)

4. Institutional partnerships established as part of post-marketing authorisation monitoring

The monitoring activities planned by the RMPs mainly lead to the establishment of post-marketing authorisation studies. Insofar as additional studies may be requested by other French authorities, coordinated activities have been undertaken with the DGS and the HAS in order to share information, avoid duplicates and clarify the objectives assigned to the post-marketing authorisation studies.

a. Exchanges with the Secretariat of Transparency Committee of the HAS

The EU-RMP serves as a basis for developing additional activities, for medico-economic evaluation, and for defining the place of medicinal products in the therapeutic strategy. That means that at the moment of the opinion, Afssaps exchanges data with the Secretariat of the Transparency Committee of the French National Authority for Health. This approach makes it possible to ensure that studies requested by the Afssaps as part of RMPs for evaluation and risk management purpose are complementary (and no duplicates) to those requested by the Transparency Committee. Bimonthly exchanges have been developed since mid-2005. The DGS has been invited to participate in this operational coordination since January 2006.

In addition to these exchanges, an assessor from the RMP/pharmacoepidemiology unit participates in the Public Health Interest (ISP) group attached to the Transparency Committee, in charge of reviewing post-registration study protocols, asked by this committee. The goal of these studies is mainly medico-economic.

However, despite the establishment of this Afssaps/HAS coordination committee, some difficulties are persisting. In fact, study the protocol to be led within the framework of the RMP are often not finalised at the time of examination by the Transparency Committee. To avoid redundant studies, necessary to meet the requirements of both the RMP and the Transparency Committee, this latter may include, in the opinion of the Transparency Committee, the following mention relative to the RMP: *“In the event where the studies planned or underway, notably within the framework of the European Risk Management Plan, cannot answer the questions asked by the Transparency Committee, a specific study must be performed.”*

b. Participation in the “liaison committee of post-marketing authorisation studies” under responsibility of the DGS

A liaison committee for post-marketing authorisation, led by the DGS, meets in principle once per quarter and includes as participants the Afssaps, the HAS, and also CEPS, the Social Security Department (DSS) and the *Caisse Nationale d’Assurance Maladie des Travailleurs Salariés* (CNAMTS). It defines policies for post-marketing authorisation studies and examines the most sensitive projects.

5. Inventory of tools and databases available

The Afssaps is also strengthening its capacity for access to databases in order to be able to integrate into the risk surveillance approach relevant and up-to-date elements on the prescription and dispensing of medicinal products.

a. SNIIR-AM (CNAMTS)

The consultation of the *Système National d’Information Inter-Régimes de l’Assurance Maladie* (SNIIR-AM), particularly data on reimbursement of medicinal products of the General Health Insurance Scheme and data from the *Échantillon Généraliste de Bénéficiaires* [General Sample of Beneficiaries] is now possible for Afssaps pharmacoepidemiologists who have been trained. The *Échantillon Généraliste de Bénéficiaires*, at 1/100, enables monitoring of the subjects included for up to 20 years.

Furthermore, in 2007, the Afssaps obtained the agreement of the CNAMTS to extract individual data at a national level on the female population aged 14 to 23, which is a cohort of around 3.7 million subjects for the first year of surveillance, with the aim of monitoring the onset of any auto-immune complications following anti-HPV vaccination. The transmission of these data to the Afssaps has started during the second quarter of 2008 and the first results of the analyses will be presented to the national reference group of anti-HPV vaccines before the end of 2009.

b. RSI (formerly CANAM)

The conditions of partnership between the Afssaps and the *Régime Social des Indépendants* (RSI) within the framework of management of the risks of medicinal products were defined in 2007; various types of collaboration were identified. The RSI database could make it possible, notably in the context of an alert, to characterise the population of patients exposed to a suspect medicinal product, or to monitor prospectively or retrospectively, as part of a RMP, a certain number of indicators, or even to envisage cross-disciplinary projects.

c. IMS Health data

The Afssaps has data from two IMS databases, information of which is complementary. The Xponent database allows the extraction of sales figures of community pharmacies, and the EPPM database provides prescription data extrapolated from a panel of doctors.

6. New developments

a. Collaboration with patients’ associations

As part of the AFSSAPS/Patients' Associations partnerships established in 2005, a discussion on the involvement of the associations in risk management plans was initiated. It appears that the associations could contribute to the establishment of risk surveillance activities and the development of minimisation tools.

In addition to making it possible to collect information in real conditions of prescription, such a collaboration could also offer a significant added value in certain situations, such as the marketing of an active substance of a new therapeutic class or that of a medicinal product not having been studied in certain at-risk populations. Furthermore, associations already participate widely in the readability testing of information documents intended for patients; this activity logically falls within their purpose.

A pilot phase is planned, on the basis of the desire of the associations and their members, with the first eligible RMPs. It must nevertheless be noted that the network constituted by the AFSSAPS currently only comprises some forty associations, which obviously does not cover the whole therapeutic areas.

b. Reinforcement of relationship with healthcare professionals

A partnership with learning societies and representation of healthcare professionals is under development. The objectives are to enhance participation of healthcare professionals in the process of the evaluation and information.

c. Management of observational safety studies in partnership with the Directorate of Inspections and Institutions

In the context of the guideline on post-marketing authorisation studies (Volume 9A Guideline on Pharmacovigilance for Medicinal Products for Human Use), and the need felt to give them a regulatory framework, a procedure is also planned for management of safety non-interventional pharmacoepidemiological studies requested by the authorities or desired by the laboratories.

APPENDIX

List of criteria and situations to be considered to analyse the need for a national RMP

Beyond the necessary adaptation of the risk minimisation plan of the EU RMP, there are a certain number of situations in which a RMP may be developed at a national level. This RMP may be composed of a national pharmacovigilance plan and a risk minimisation plan

Three categories of situations have been identified:

1. Situations related to the organisation of the healthcare system and Medical Practice (prescription / dispensing / administration / patient monitoring)

- Conditions of access to the product (e.g. narcotics)
- Prescription practices specific to the French situation (e.g. prescription of hypnotics, anxiolytics, antibiotics, etc)
- Prescription recommendations defined by the French authorities (e.g. recommendations for vaccination)
- Risk of off-label use
- Potential risks related to the conditions of use of the product (risk of medical errors)

2. Situations related to the product

- Different therapeutic range / profile of drug interactions
- Risk of pharmacodependence (abusive use or misuse)
- Special perception of risk: product class for which issues have already arisen in France

3. Situations related to the pathology

- Particular epidemiological situation (e.g. microbial resistance)