

AFSSAPS Partnership with patients'  
and consumers' organisations

Outcome of discussion and key  
recommendations

march 2006

Agence française  
de sécurité sanitaire  
des produits de santé



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143-147 boulevard Anatole France  
F - 93285 Saint-Denis Cedex

[www.afssaps.sante.fr](http://www.afssaps.sante.fr)

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## INTRODUCTION

The French Agency for the Safety of Health Products (AFSSAPS) is permanently acting to ensure that health products can be used in the safest possible conditions, according to current knowledge. Meant for the patient, this mission confronts two ongoing demands that AFSSAPS is facing:

- The goal to help relieving pain, illness and death, leading AFSSAPS to continuously evaluate the impact of decisions on patients' access to treatments and their chances of recovery;
- The need to control and minimise as much as possible risks which people are increasingly reluctant to admit, in particular when these are avoidable or insufficiently identified.

Today these requirements cannot be reconciled without the patients' active participation. Patients must have sufficient information to exercise their freedom of choice and increase the level of safety by respecting the rules of proper use.

However, the optimisation of therapeutic treatment cannot be achieved one-sidedly: in order to adhere to it, in a trusting dialogue with the health professionals, patients are entitled to expect a high level of transparency, or even, to some extent, the possibility of asserting their own opinions.

With this in mind, the conditions for a genuine "healthcare democracy" are gradually being set up, in which patients' associations play an important role; they have gained credibility with both patients and consumers and the status of partner of health professionals and healthcare institutions.

In their common objectives, aimed at promoting the safe use of health products and ensuring access to therapeutic innovation, while providing adequate information to patients AFSSAPS and the patients' and consumer's organisations have built up over the last year a constructive dialogue based on an exchange of experiences and ideas in several working groups dealing with specific areas. This report sets out the results of this joint study and highlights the proposals it has provided. AFSSAPS is determined to continue the dialogue on the basis of these promising results and the quality of the human relations forged over a year between those who accepted to participate in this process.

Jean Marimbert

## **THE ROLE OF THE ASSOCIATIONS: AN EVOLUTIVE CONCEPT IN FRANCE AND EUROPE**

At a time when citizens, particularly users of the health system and their relatives, have high expectations in terms of information and participation in healthcare processes, it is vital to strengthen the existing networks and allow exchanges and consultation.

Sick or healthy, every citizen must be able to be involved in the individual and collective issues concerning health. Associations have been working for many years to achieve this goal. In 1998, the "Etats Généraux de la Santé" made this requirement of healthcare democracy heard, which was then put into law: the law of 15 April 2000 on citizens' rights in their relations with the administrations, the law of 4 March 2002 on patients' rights and the quality of the health system, and lastly the law of 9 August 2004 on the public health policy, which encourage the active participation of representatives and users by enhancing the official framework of their activity.

This new orientation confirms the position of the French Agency for Sanitary Safety of Health Products, which for several months, even years, has increasingly included patients in the decision-making process, for specific diseases. Thus AFSSAPS, from its inception, has created a policy of dynamic communication in order to make reference information on health products available to health professionals, the press, institutions as well as the general public.

In parallel, a discussion was set up at European level on the position patient associations should occupy within health bodies. The European Agency for the Evaluation of Medicinal Products (EMA) encourages national authorities like AFSSAPS to take similar initiatives to make it possible to promote active participation by patients and the associations which represent them. Furthermore, at the beginning of 2005 EMA defined criteria of acceptance which patients must meet in order to participate in its activities (EMA/14610/04).

In this context AFSSAPS wished to open a wide-ranging consultation with the associations, groups of associations and representative structures concerned by health products, whether for reasons of access to new products, prevention of risk, optimisation of therapeutic treatment or patient education. On 2 December 2004 the Agency held the first meeting.

The aim of this meeting was to outline everyone's expectations and identify means of setting up a mechanism for consultation and knowledge sharing. Four important topics were identified and led to the setting up of four AFSSAPS/associations working groups:

- Transparency and dissemination of information
- Vigilance on health products
- Early access to medicinal products
- Procedures for exchanges between AFSSAPS and patients' and consumers' associations.

## **WORKING PROGRAMM CONDUCTED BY THE AFSSAPS/PATIENTS' AND CONSUMERS' ASSOCIATIONS WORKING GROUPS AND METHODOLOGY**

The associations which participated in this study have a common interest: they have all acquired experience, if not expertise, in terms of health products. However, their audience is often different, both in terms of number of people concerned and in terms of level of involvement vis a vis health products. These are associations, unions of associations or representative structures, which include sick people, patients, victims, disabled persons, their relatives or family and, more generally, all current or potential users of health products. With a view to simplification, the terms "patients or consumers" have been adopted by agreement in this document, since they cover very diverse human realities, which should nonetheless all be taken equally into account.

AFSSAPS is in charge of four main missions: evaluation, control, inspection and information. In order for the working groups to include all these activities in their study, the five technical and scientific divisions of the Agency (evaluation of medicinal products and biological products, evaluation of medical devices, evaluation of advertising and cosmetic products and biocides, laboratories and controls, inspection of laboratories and establishments), as well as the legal and European affairs unit, are represented.

Under the coordination of the unit for risk monitoring, proper use and information on medicinal products, four working groups met several times in 2005.

### **Group 1: Transparency and dissemination of information**

Associative pilot: Christophe DEMONFAUCON – Association Française des Troubles Obsessionnels Compulsifs

AFSSAPS pilots: Bernard DELORME (Patient and public information unit) and Laurent FLEURY (Internet unit)

#### **ASSOCIATIONS**

- Jacques BERNARD - Alliance Maladies Rares
- Jean-Pierre ESCANDE - Ligue contre le cancer
- Gilles GAEBEL - Collectif Inter-associatif Autour de la Naissance / Associations d'aide aux Victimes d'Accidents Médicaux et à leur famille.
- Denise LESŒUR - Association pour la lutte contre le psoriasis
- Evelyne ROLLAND - Association Nationale de Défense contre l'Arthrite Rhumatoïde

#### **AFSSAPS**

- Brigitte BRIAND (Safety alerts unit)
- Régine LANFRANCHI (Marketing Authorisation and European regulation procedures management unit)
- Carole LE SAULNIER (Legal and European affairs unit)
- Marie-Laurence GOURLAY (Department of advertising and proper use)
- Nathalie MARLIAC (Medical device vigilance unit)
- France ROUSSELLE (Regulatory affairs unit)

This group endeavoured to define a mechanism which would enable the implementation of clear information adapted to the general public. Several proposals were made in order

to make AFSSAPS information more accessible and were subsequently ranked by order of relevance and feasibility.

### **Group 2: Vigilance system for health products**

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Associative pilot: Georges-Alexandre IMBERT - Association d'Aide Aux Victimes d'Accidents Médicamenteux

AFSSAPS pilots: Anne CASTOT (Department of risk monitoring, proper use and information on medicinal products) and Carmen KREFT-JAIS (pharmacovigilance unit)

#### ASSOCIATIONS

- Marie AUZANNEAU et Thomas SANNIE - Association Française des Hémophiles
- Franck BARBIER - AIDES/TRT5
- Jean et Jany BATAILLE - Fédération Française des Groupements de Parkinsoniens
- Laurence CARTON - Association Française de Lutte Anti-Rhumatismale
- Sophie LE PALLEC et Karine PAYEN - Amalyste
- Sandrine ROLLOT - Association Française des Polyarthritiques

#### AFSSAPS

- Nedjwa ABBADI (Cosmetovigilance unit)
- Christiane ANGOT (Department of medical devices)
- Nadine DEMARE (Department of safety alerts)
- Charlotte HAZAK (Department of risk monitoring, proper use and information on medicinal products)
- Nadra OUNOUGHENE (Haemovigilance unit)
- Nathalie RICHARD (Narcotics and psychotropics unit)

This second group focused on procedures which would enable patients' experience to be taken into account and information to be exchanged on safety data relating to health products. It also considered the relevance and feasibility of having patients participate in the vigilance system.

### **Group 3: Information to patients on early access to some medicinal products**

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Associative pilot: Elise BOURGEOIS-FISSON - TRT-5 (inter-associative group on therapeutic treatment and research)

AFSSAPS pilot: Chantal BELORGEY (Department of evaluation of clinical trials and special status medicinal products)

#### ASSOCIATIONS

- Françoise BERGIER - Union Nationale des Amis et Familles de Malades psychiques
- Dominique CHARRIER - Association Française contre les Myopathies
- François HOUÏEZ - Eurordis (European Organisation for Rare Diseases)
- Marie LANTA - Ligue contre le cancer
- Evelyne LE ROUX - Vaincre la mucoviscidose
- René-Joseph MOREL - Fédération Nationale d'Aide aux Insuffisants Rénaux
- Nathalie ZACCOMER - Association des Paralysés de France

## AFSSAPS

- Julie CAVALIER (regulatory affairs unit)
- Elisabeth HERAIL (legal and European legal affairs unit)
- Annie LORENCE (orphan medicinal products unit)
- Françoise MANCEL (temporary use authorisations unit)
- Philippe VELLA (clinical trials unit)

This working group was devoted to information to patients on early access to some medicinal products, which led it to consider:

- Clinical trials
- Medicinal products accessible with an ATU (temporary authorisation for use)
- Hospital preparations
- Medicinal products for paediatric use.

### **Group 4: Exchange procedures between AFSSAPS and patient associations**

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Associative pilot: Françoise NICOLE KREMER - Femmes pour toujours

AFSSAPS pilots: Ophélie BROCA (Department of risk monitoring, proper use and information on medicinal products) and Irène BIDAULT (Pharmacovigilance unit)

## ASSOCIATIONS

- Christian DE THUIN - Institut National de la Consommation
- Francis GRANGER - Association Française du Syndrome de Marfan
- Alain OLYMPIE - Association François Aupetit (Crohn's disease and ulcerative colitis)
- Nadine PLACET-PIETRI - Association Entraide aux Malades de Myofasciite à Macrophages

## AFSSAPS

- Christine GRASMICK (laboratories and controls division)
- Pascale MAISONNEUVE (unit for coordination of information on vigilance systems, risks and public health actions)
- Dominique MASSET (toxicological watch and non clinical evaluation unit)
- Ventizlava PETROV-SANCHEZ (pharmaco-toxico-clinical unit 4)
- Catherine REY-QUINIO (pharmaco-toxico-clinical unit 2)

The participation of patients' and consumers' representatives in the Agency's Commissions and working groups was the first issue of interaction discussed by this working group. Proposals were also made for regular, organised exchanges to be set up between AFSSAPS and the associations.

On 16 December 2005, the department of risk monitoring , proper use and information on medicinal products organised a meeting, in the presence of the Head of Agency and the associations which had already participated in the meeting of 2 December 2004. Details of the content of this work are set out below.

## **DEVELOPING THE INFORMATION TO THE GENERAL PUBLIC ON HEALTH PRODUCTS**

The working group considered two main issues:

- What should be the content of the information which AFSSAPS makes available to patients and associations?
- What form should it take in order to meet their needs?

### **Creation of a permanent structure in charge of reviewing information**

During the last few years, whenever a question on the safety of use of health products affecting a wide public was raised, AFSSAPS has developed information documents for patients, in the form of "Questions / answers", "You and your treatment", etc. It dealt with topics as diverse as mercury in dental fillings, stopping sales of local antibiotics for nose, throat and mouthwashes, prevention of adverse effects from medicinal products in the elderly, labelling of solar products, treating fever in children, etc. In September 2005, a document on proper use of medicinal products and driving was also published and distributed to the public by pharmacists.

Patients' and consumers' organisations are in favour of these information documents and would like them to be developed. In order to meet the public needs, it would be useful to set up an ongoing mechanism involving the associations. Therefore it has been proposed to create a review group comprising associations of patients, families, victims and consumers, whose aim would be to give an opinion on and validate the different documents which the Agency produces specifically for patients.

In order to determine pragmatically the benefits and limits of such a "review system", tests were carried out between April and December 2005 concerning various information documents which AFSSAPS then put on line on its internet site. It transpired that the contribution of patients' organisations is of added value, but needs rapid communication means (e-mail) for exchanges. Furthermore, the specificity of some subjects suggested the necessity of having a multidisciplinary view, or of occasionally contacting associations specifically concerned.

The reflection is therefore orientated towards the creation of a permanent group of twenty organisations' representatives, complemented by a list of representatives with special skills who would be consulted as and when needed. The "Transparency and dissemination of information" working group drafted a document formalising the mode of operation and the obligations of the members of this reference group, in particular with regard to respect for confidentiality and independence (see annex 1).

## **Improvement of patient information leaflets**

Special attention was paid to patient information leaflets. Indeed, in many cases it is the first source of information on the treatment they are taking.

During the nineties and under the effect of the regulations (article R. 5143 of the Public Health Code), an information leaflet that often gave little information, in which as a rule only contra-indications, precautions for use and main adverse effects were mentioned, developed into a document which is a complete reflection of the summary of product characteristics (RCP), as known to the prescribing doctor.

This development in favour of more exhaustive information is indisputably positive, even though it is sometimes detrimental to easily understandable text, as advocated in the recommendations issued by AFSSAPS in 1996. The patient may, for example, be disorientated by the long list of therapeutic indications, in which he fails to find the disorder for which he is being treated; likewise, faced with an unstructured list of adverse effects, he will have difficulty identifying the problems he may have experienced after taking the medicine. What is more, little investment is allotted to the graphic layout of the leaflet, especially as regards packaging. Thus it can be noted that many products would benefit from being more readable, by means of a simple improvement in layout. A similar study was conducted at European level, leading to two measures: firstly, the inclusion in the Marketing Authorisation dossier of readability tests carried out with groups of patients (directive 2004/27/EC), in the evaluation of which the reference group proposed above could be associated; followed by the drafting of guidelines, whose publication is scheduled by the middle of 2006.

The patient associations which participate in the working groups expressed their wish to contribute as much as possible in the evaluation of the readability tests which are beginning to be set up during the Marketing Authorisation procedures. An evaluation of leaflet quality could also be envisaged between the granting of the Marketing Authorisation and the launch of medicinal products, or even be accompanied by an evaluation of packaging quality.

They would also like new recommendations for manufacturers, setting out the European guidelines, to be drawn up jointly with the Agency.

It is also important for the public to know that as part of the development of the "Répertoire des Spécialités Pharmaceutiques" available on the AFSSAPS website (<http://AFSSAPS.sante.fr/htm/1/amm/amm0.htm>), they already have the updated text of a large number of medicinal products at their disposal.

Finally, a link on the AFSSAPS Internet site to patient information leaflets (or to that of EMEA for medicinal products pertaining to a centralised procedure) is an opportunity worth exploring.

These different proposals for improvement are compatible with the current regulatory framework on patient information leaflets. However, they will not compensate for the lack of certain information useful to the patient, and other complementary actions have been envisaged. For example, the patient also requires information on the disease for which he is taking this medicinal product, the nature of the adverse effects for which he must be

alerted (what is an allergic reaction?), the role of excipients (lactose intolerance), the compliance, accompanying measures, (diet, hygienic lifestyle, etc.). Solutions have been proposed, such as the drafting of a "double leaflet" common to all medicinal products of the same therapeutic class. The study should therefore be pursued more thoroughly and needs to be extended; this can be done by involving the Marketing Authorisation study group "Médicaments de prescription médicale facultative" as well as, on a broader basis, manufacturers, health professionals, sickness funds, etc

## **Public access to reference information**

AFSSAPS is already providing a large amount of information available, especially on its website. However, on the one hand the search for information should be made easier for the general public, and on the other hand, the wording should be widely comprehensible. With that in mind, several actions were proposed by the working groups:

- optimise the website: this involves a so-called "contents" site which is particularly extensive. The downside of such rich information is that an Internet user may have difficulty finding what he is looking for rapidly, even if he is a health professional. It was proposed, firstly, to set up more efficient search engine, which would for example enable access by disease, medicinal product, etc. It was also proposed that the information should be structured by different levels of complexity under suitable headings, which presents the advantage of maintaining the principle of free access to all the documents on the site.

It should be noted that these proposals link up with the actions scheduled by the AFSSAPS establishment plan, which defined the development of the Internet site as one of its priorities. As from the middle of 2005, an inventory has been drawn up by an external audit, to which the proposals of the AFSSAPS/associations working groups were retransmitted. This audit has been consolidated since December 2005 with plans for restructuring the site.

- develop a glossary: The objective is to provide patients with definitions, worded in simple language, of the main technical terms used in the documents published by the Agency, as well as an explanation of initials and acronyms. On the AFSSAPS website, this will enable the insertion of hypertext links, in particular in documents intended for patients. For a single definition, it will sometimes be necessary to give different levels of detail, according to the diversity of the areas concerned.

The compilation of this glossary also entails major writing and validation work, as well as regular updates. In order for this project to see the light of day as soon as possible, the working group "Transparency, comprehension and dissemination of information" carried out a preliminary census of some sixty priority definitions, as a function of the scientific, technical, medical, administrative terms, abbreviations and initials frequently used in AFSSAPS documents. The needs expressed by the working group devoted to informing the public on clinical trials will also be taken into account.

- promote Public Evaluation Reports (RapPE) tailored to patients' expectations: The RapPE sets out over a few pages, a summary of the Marketing Authorisation

dossiers for every new medicinal product (new active ingredient, fixed combination or new form giving rise to a specific indication, indication extension, etc. which makes it possible in particular to know the methodology of the clinical trials carried out and the conclusions which led to the issuing of the Marketing Authorisation. It constitutes a compilation of essential and relevant data which therefore attracted the attention of the patient association representatives, but whose current form makes it more accessible to health professionals than to patients. A recent proposal of simplified wording was made by EMEA, which it will be worth applying to the RapPEs already carried out (around thirty to date).

## **ASSOCIATING PATIENTS AND CONSUMERS IN THE MONITORING OF RISKS ASSOCIATED WITH HEALTH PRODUCTS**

Within the framework of health vigilance, mechanisms for risk evaluation and monitoring, in which health professionals participate, have been set up. Thus AFSSAPS coordinates the systems relating to its field of competence: pharmacovigilance, dependency on medication, haemovigilance, biovigilance, materiovigilance, reactovigilance and cosmetovigilance.

These different vigilance systems contribute in a vital way to knowledge of products for therapeutic use. When the marketing authorisation is issued, some adverse reactions are in fact underestimated or not identified, since the clinical trials conducted during the initial evaluation relate by definition to targeted and/or restricted populations and often for short periods of treatment.

The purpose of health vigilance systems is therefore to identify and reduce risks related to health products after they have been marketed. In practice, this is an ongoing process of collecting, recording, identifying, analysing and evaluating adverse events or incidents linked to the use of a health product with the aim of optimising their safety of use.

### **Notification of adverse events by the patient**

At present, the vigilance systems mainly rely on the notification of adverse events by health professionals. The working group "Health product vigilance" considered the possibility of extending the notification to the people concerned as well as to patients and consumers association, which would make it possible to access additional data on the risk of health products, particularly in terms of impact on patients' quality of life and lifestyle. Moreover, such direct notification may partly compensate for the under-notification currently observed.

To date, there is no provision, either from a legal or a regulatory aspect, which enables patients or patient associations to report adverse events from health products directly. However, pilot studies, in particular in pharmacovigilance and cosmetovigilance, have been carried out in order to evaluate their possible participation in the risk monitoring system. For several years it has been noted that patients sometimes contact the regional pharmacovigilance centres (CRPV) or industry directly in order to report the onset of an adverse event.

The opening up to patients of notification of adverse events therefore appears as a logical development of the system. Its implementation should be considered and stipulated, not as questioning the capacity of analysis and alert of the current system, but rather as a complementary source of information.

In the long term, allowing the public to consult the databases of adverse events could also be envisaged with a view to transparency.

## **Tools for patients' notification**

The working group "Health product vigilance" has drawn up a patient notification form (see annex 2). This form can apply regardless of the nature of the adverse event described and whatever the health product involved and can therefore be used by all the associations. It is simple and easily comprehensible, whilst being sufficiently detailed to enable an analysis of the case.

In the first instance, the reporting form can be sent to AFSSAPS by fax or post. Subsequently, the notification could be made via the Internet, or even by telephone. In the longer term, the creation of a specific "entrance door" to the databases of the vigilance systems could be envisaged.

An important point covered by the group was respect for confidentiality. This is why the "Data Processing and Freedoms" law is mentioned in the notification form and a box informs patients that transmitting the data to AFSSAPS may, if necessary, give rise to a direct request for information to the health professional with whom they have been in contact.

To help this direct notification form, a user guide intended for patients has been drawn up (see annex 3). Its purpose is to explain to patients and consumers the importance and usefulness of each field of the form.

## **Benefit of the associative support**

Direct notification does however have its limits: the lack of medical validation and the risk of receiving meaningless notifications. However, an evaluation between identified signals and other sources on the one hand, and appropriation of the form by patients on the other, will help to optimise such notification.

Due to their proximity to patients, the associations can play an important role by helping and educating patients for these reportings. The active participation of some associations in direct notification following withdrawals of medicinal products from the market for safety reasons has already proved to be effective.

In order to allow associations to fulfil their role as best as possible, the working group produced a memorandum on the reporting of adverse events likely to be due to health products (see annex 4). Its aim is to help the associations in evaluating the patients' reports to be transmitted to AFSSAPS.

Furthermore, a list of representatives more concerned by vigilance issues within the patients' and consumer's organisations is currently being established. It should facilitate exchanges between the Agency and each organisation.

## **Pilot study**

Before allowing patients' reporting, the working group "Health product vigilance" proposes to conduct a pilot study whose purpose is as follows:

- to test the tools:
  - notification form
  - user guide
  - memorandum;
- to test notification channels;
- to evaluate the quality of patient reports:
  - have the patients understood the questions properly?
  - have key data elements been completed correctly?
  - does the information enable an analysis of the adverse event?

This study will be conducted from June to December 2006 with the participation of volunteer patients' and consumer's organisations and should also make possible a comparative analysis of patient notifications with those of health professionals. It will mainly be focused on the unusual nature and severity of the event described, the impact on quality of life and the frequency of the various adverse events reported.

## **DEVELOPING INFORMATION ON EARLY ACCESS TO SOME MEDICINAL PRODUCTS**

It is up to AFSSAPS to ensure that each treated patient receives a product whose pharmaceutical quality, safety of use and effectiveness are proven and validated. To that end, AFSSAPS plays a determining role in terms of encouraging the development of medicinal products and constitutes a watchdog for new products with regard to medicinal products used within the framework of clinical trials, medicinal products available with an authorisation for temporary use (ATU), paediatric medicinal products and hospital preparations.

### **Improving information on clinical trials**

AFSSAPS is responsible for all the activities concerning clinical trials of medicinal products.

Since 2002, the Agency has put a list of clinical trials on rare diseases and some serious diseases on its website (<http://afssaps.sante.fr/htm/5/essclin/indesscl.htm>). In order to comply with the new provisions of the public health code (article L. 1121-15), this list will be extended to all authorised biomedical research relating to health products, except in the case of a justified refusal by the promoter.

In order to make this list easier to use for patients' and/or consumers' organisations and patients themselves, the drafting of a glossary is envisaged. This proposal is therefore in line with that of the working group "Transparency, comprehension and dissemination of information".

Furthermore, in order to extend the information on clinical trials, the group proposes to draw up a general information and promotion document on biomedical research and then to develop texts on target themes.

Lastly, it is proposed that the list of Ethics Committees be released on the Agency's Internet site.

### **Improving information on ATUs**

AFSSAPS issues Temporary Authorisations for Use (ATUs) on an exceptional basis, pursuant to article L.5121-12 of the public health code, for medicinal products which do not benefit from a Marketing Authorisation in France. These are medicinal products authorised in foreign countries or still under development.

A guideline on the ATU mechanism for applicants is available on the Agency's internet site and is currently being translated in French. Furthermore, the list of medicinal products which have been the subject of a cohort ATU since 1994, as well as that of the ATUs currently concerned, have also been put on line.

In order to pursue the development of information on ATUs, the working group "development of information on early access to some medicinal products" has elaborated

a thesaurus of nominal medicinal products with an ATU. This is already accessible on the Agency's Internet site (<http://AFSSAPS.sante.fr/htm/5/atu/indatu.htm>). The group also recommends the publication of negative opinions for cohort ATUs and the validation of the patient information note by the patients' organisations.

### **Information on hospital preparations**

The Agency's "hospital preparations" unit has the responsibility of determining whether hospital preparations are indispensable or not in order to encourage the use of medicinal products as a replacement or on the contrary of promoting the Marketing Authorisation process. The group proposes that a registry of essential hospital preparations be developed.

### **Paediatric medicines**

Many medicinal products are poorly or not adapted to children. In paediatrics, a large number of medicines are prescribed outside of marketing authorisations (AMM) and are therefore not subject to an evaluation of effectiveness and safety of use for children.

A paediatric unit and a committee of paediatric experts have been set up at AFSSAPS in order to establish, with external experts, an inventory of practices and needs concerning the use of medicines for children: the need for suitable pharmaceutical forms, the need for paediatric clinics.

As part of this evaluation work, the working group "development of information on early access to some medicinal products" propose that a comparison be made of paediatric medicinal products with a Marketing Authorisation in the United States with products currently available in France, in terms of the needs identified by the Agency. The drafting of a paediatric drugs dictionary, ranged by disease, is also planned.

## **ASSOCIATING PATIENTS AND CONSUMERS IN THE AGENCY'S WORK**

### **What contribution?**

The patients' and consumer's organisations are currently represented in four commissions: National Pharmacovigilance Commission, Cosmetics Commission, Commission in charge of controlling advertising and diffusion of recommendations on the proper use of medicines and Commission in charge of controlling advertising in favour of objects, equipment and methods presented as beneficial to health (see annex 7). Furthermore, some of them are present in the working groups or take part in regular meetings on specific subjects.

The patients' and consumers' organisations have expertise in the use of health products which is different while complementary to the scientific expertise normally used by the Agency in its evaluation processes. Due to their direct interaction with patients, they have access to their experience, understanding of information and an idea of their quality of life. The working group "Exchange procedures" has therefore envisaged more systematic and extensive involvement of the associations in the Agency's work. This study should be carried out more thoroughly both at scientific and at regulatory level.

On the other hand, there are converging fields of interest for the Agency and the associations, where a concerted action would be fully justified.

Likewise, AFSSAPS and the associations are interested in the impact of the information produced by the Agency for patients, which should be measured in terms of:

- visibility,
- understanding,
- and above all, changes in behaviour, since most of this information is linked to use of health products.

To do so it is necessary to have tools which enable the qualitative and quantitative monitoring of the use of health products, as well as measurement points before and after the release of the information. Given the difficulty in fulfilling these conditions, it has not yet been possible to formulate more concrete proposals, and here again, it is desirable to continue the study by selecting subjects in whom it is relatively easy to evaluate a change in behaviour, or organising a follow-up of documents published for patients (evaluation of the number of consultations and setting up of a satisfaction questionnaire).

### **On what bases should this partnership be built?**

The participation of the patients' and consumer's organisations in the Agency's work requires a reciprocal commitment, based on responsibility, which implies a certain amount of availability on the part of the patients' and consumer's organisations, the training of participants and most importantly, the ability to share information.

In this respect, the working group "Exchange procedures" has drawn up a "Charter of representatives of patients and consumers associations" which defines the conditions for participation in AFSSAPS' work. It stipulates in particular the qualification of the patients'

and consumer's organisations and representatives, the need for independence and the duties of transmission of information while complying with confidentiality (see annex 5).

The group also proposed a "Framework agreement" aimed at defining future collaborations which will be developed between AFSSAPS and the patients' and consumers' organisations. It will enable the terms and conditions to be stipulated according to a specifications sheet drawn up in advance (see annex 6).

Furthermore, the group proposes the creation of an "associations' desk" in order to facilitate exchanges and enable the organisations to have a single point of contact at AFSSAPS. This point of contact between the patients' and consumer's organisations and the Agency will provide a link with the correspondents of the different divisions concerned.

Finally, the restructuring of AFSSAPS' website will be an opportunity to open up a specific portal dedicated to the associations. They will find the whole information intended for them and will have a "mailbox" enabling them to contact the Agency more easily.

### **What exchanges?**

The partnership between AFSSAPS and the patients' and consumers' organisations requires regular exchanges organised over the long term. It is essential for the associations to have access to targeted information on health products but also to the programmes and reports of the commissions and working groups. This will be set up gradually, within the framework of European harmonisation during 2006. Thus AFSSAPS will make available the internal regulations of the commissions, their agendas, the reports and, for decisions taken, details of votes and explanations, including minority opinions. In the first phase, this will apply to the national pharmacovigilance commission, the national narcotics commission, the marketing authorisation commission and its working groups.

It is also important to consider the distribution of information to other patients' and consumer's organisations or to non-represented patients. The associations, which collaborate with AFSSAPS, have a transversal vision of the associative world which may contribute to this. Again with the aim of providing regular diffusion of AFSSAPS information adapted to patients' understanding and knowledge, the group "Exchange procedures" proposed to develop an electronic newsletter. Initially, a census of the associations is necessary in order to draw up a diffusion list reserved for those associations. A page of "briefs", produced by a mixed editorial committee (representatives of AFSSAPS and the associations), could be a suitable way for maintaining a periodic link between the Agency and the associations.

## IMPLEMENTATION AND TIMETABLE

Among the proposals of each working group, some are actions which are either immediately operational or achievable in the short term, or requiring an additional study or regulatory modifications. In all cases, it is proposed that working groups be set up around the following missions:

- The "review group" will be in charge of improving the information documents intended for the general public. It will participate in particular in the drafting, validation and distribution of documents such as recommendations, clarifications, information on clinical research, etc., but will also contribute to the leaflet validation process;
- The "risk monitoring" group will deal with vigilance problems and will be in charge of setting up and monitoring the pilot study; it will also have to discuss patients' access to the databases;
- The group "Involvement of the patients' and consumers' organisations in the Agency's work" will carry out various studies on their participation in the commissions and working groups, the actions to be undertaken with the other patients' and consumer's organisations and non represented patients, as well as on exchanges with other potential partners.

In order to set up these groups as rapidly as possible, the department for risk monitoring, using proper information on medicinal products, has requested all the patients' and consumer's organisations which participated in the first day of exchanges on 2 December 2004 to appoint a possible representative for each of these groups. All the proposals described in this summary will then be implemented or studied, according to the following timetable:

### 1<sup>ST</sup> SEMESTER 2006

- **Concerning information to the general public,**
  - Publication of an information note on cohort authorisations for temporary use (ATU)
  - Publication of a text setting out AFSSAPS' objectives concerning hospital preparations
  - Appointment of the review group
  - Creation of the "patient desk"
- **Concerning risk monitoring,**
  - Completion of the "Memorandum of notification of adverse events"
  - Completion of the notification form and its user guide of the notification form
  - Setting up and launch of the pilot study (June -> December)

- **Concerning participation in the evaluation processes,**
  - Constitution of a list of correspondents of patients' and consumer's organisations
  - Creation of a registry of medicinal products with a nominative ATU

#### REMAINDER OF 2006 – BEGINNING OF 2007

- **Concerning information to the general public,**
  - Publication of the Commissions mandate as well as timetables and reports.
  - Compilation of the glossary
  - Publication of an information document for people volunteering for biomedical research
  - Publication of the clinical trials registry
  - Publication of the hospital preparations registry

And more specifically for the patients' and consumers' organisations:

- Creation of an "associations' portal" on the Internet site
  - Setting up of an editorial committee in order to produce the "Letter" to the associations
- **Concerning risk monitoring,**
    - Making the notification form available to the general public
    - Approaching industry and health professionals
  - **Concerning participation in the evaluation process,**
    - Setting up "phase points" in the evaluation of a risk
    - Publication of the list of cohort ATU rejections
    - Setting up a "Patient Leaflet" working group

#### IN THE LONGER TERM

- **Concerning information to the general public,**
  - Publication of an information document for the general public on clinical research
  - Study on actions to be carried out vis a vis "non represented" patients
- **Concerning risk monitoring,**
  - Developing a public access to databases on adverse effects.
- **Concerning participation in the evaluation processes,**
  - Study on the associations' participation in the Agency's commissions and working groups
  - Study on the information networks between duly represented associations and the others
  - Defining procedure of information exchange on a product-related issue, still under evaluation

## **ANNEXES**

**ANNEX 1:**  
CREATION OF A REVIEW GROUP PARTICIPATING IN THE APPROVAL OF INFORMATION DOCUMENTS FOR THE PUBLIC

**ANNEX 2:**  
PATIENT REPORTING FORM

**ANNEX 3:**  
USER GUIDE FOR THE REPORTING OF ADVERSE EVENTS

**ANNEX 4:**  
MEMORANDUM ON REPORTING OF ADVERSE EVENTS WHICH MAY BE ASSOCIATED WITH A HEALTH PRODUCT

**ANNEX 5:**  
PROPOSAL OF POLICY FOR REPRESENTATIVES OF PATIENTS OR CONSUMERS ORGANISATIONS, WITHIN THE FRAMEWORK OF AFSSAPS' WORK

**ANNEX 6:**  
PROPOSAL OF FRAMEWORK AGREEMENT

**ANNEX 7:**  
AFSSAPS COMMISSIONS IN WHICH THE ORGANISATIONS ARE REPRESENTED

## **ANNEX 1: CREATION OF A REVIEW GROUP PARTICIPATING IN THE APPROVAL OF INFORMATION DOCUMENTS FOR THE PUBLIC**

### 1°) Objective

To promote the distribution by AFSSAPS of suitable and useful information on health products intended for a non specialist public.

### 2°) Composition

The head of the "patients/public information" unit of AFSSAPS, or his representative, coordinates the group's work.

The group will comprise:

- Representatives of patients' organisations,
- Representatives of patients' families' organisations,
- Representatives of organisations representing consumers,
- Nursing staff qualified to administer health products.

The group will mainly be composed of representatives of patients' organisations; however, it will comprise at least two representatives of patients' families' organisations, two representatives of consumers' organisations and two nurses.

The group will also include, in view of the purpose of the documents submitted for its examination, the manager of the division(s) of AFSSAPS concerned, or his representative.

### 3°) Missions

The group will have the mission of giving an opinion, in particular, on:

- Draft information documents prepared by the different divisions of AFSSAPS, prior to their release to the public:
  - By evaluating their relevance and suitability for the needs of potential users,
  - By proposing possible improvements,
- The French version of the patient information leaflets, which may be submitted to it as part of a procedure for a European marketing authorisation or via mutual recognition.

### 4°) Operation

The "Patients/Public Information" unit of AFSSAPS will systematically communicate the draft documents to the members of the group, unless this is impossible due to the urgency,,indicating the required deadline for response, and will organise the collection of their opinions.

In view of the sometimes very short publication deadlines for the documents concerned, the consultations of the members of the group and the return of their opinions to AFSSAPS will normally take place by rapid communication means such as e-mail, fax or a telephone call. For purposes of transparency, each member of the group may have access to the opinions formulated by the other members of the group.

.../...

.../...

The work of the group will be subject of an annual report. The draft annual report will be prepared by the "Patients/Public Information" cell of AFSSAPS; it will be adopted by a majority of members, then made public.

#### 5°) Additional expertise

Within the framework of its mission, the group may call on qualified persons chosen from a list drawn up by the managing director of AFSSAPS.

#### 6°) Obligations

The members of the group undertake individually:

- To respect confidentiality concerning the work of the group and the documents they have received,
- To comply with the rules of professional ethics of AFSSAPS, in particular that of the public declaration of interests indicating the absence or existence of any interest which could be considered as prejudicial to their independence,
- To be duly commissioned by the organisation they represent,
- Not to take part in the work of the group if they have a direct or indirect interest in the dossier examined.

If any member should fail to comply with his obligation, they may be replaced.

#### 7°) Criteria of eligibility of the organisations represented

they must:

- Supply a copy of their memorandum and articles of organisation and the receipt of registration at the prefecture;
- Be in a position to prove:
  - A clearly defined effective and public activity, part of which directly concerns the use of health products,
  - Their representativeness vis a vis a wide audience with the persons they intend to represent,
  - A Management Board appointed according to clearly defined clauses, the majority of whose members are not health professionals,
  - Their independence; in particular, the articles of association, financing and conditions of organisation and operation of the association must not be such as to limit this independence, particularly vis a vis producers, users and suppliers of health products.

#### 8°) Allowances

Members of the group are entitled to allowances for travel and accommodation expenses under the terms and conditions laid down by amended decree No. 90-147 of 28 May 1990.

The members of the group are appointed by decision of the managing Director of AFSSAPS, for a period of two years renewable.

**ANNEX 2:**

**PATIENT REPORTING FORM ON ADVERSE EVENTS WHICH MAY BE ASSOCIATED  
WITH A HEALTH PRODUCT**



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**ADVERSE EVENT(S)**

Date of appearance: |\_|\_|\_|\_|\_|\_|\_|\_|\_|\_| (corresponds to the date of the 1<sup>st</sup> symptoms)

Time of appearance in respect of:

The 1<sup>st</sup> use:.....seconds / minutes / hour(s) / day(s) / month(s) / year(s)  
(Cross out what does not apply)

or the last use:..... seconds / minutes / hour(s) / day(s) / month(s) / year(s)  
(Cross out what does not apply)

Development of the adverse event:

Recovered without lasting effects    Recovered with some lasting effects    Not recovered    Death

Have you received any treatment for the adverse event?

YES    NO

**Description of the adverse event and its development:**

[Empty text box for description of the adverse event and its development]

Consequences on daily life (stopped working, unable to go out, etc.):

NO    YES; specify:.....

5

**DETAILS OF THE DOCTOR WHO NOTED THE ADVERSE EVENT OR YOUR ATTENDING PHYSICIAN OR ANY OTHER HEALTH PROFESSIONAL (optional)**

Name:..... Forename:.....  
(Complete) (Complete)

Address: .....

Post Code: |\_|\_|\_|\_|\_| Town:.....

Tl.: |\_|\_|\_|\_|\_|\_|\_|\_|\_|\_| Fax: |\_|\_|\_|\_|\_|\_|\_|\_|\_|\_|

Qualification:  General Practitioner    Specialist (specify):

6

**OTHER NOTIFICATION(S)**

Was the adverse event reported by you or a health professional to one of the following organisations:

AFSSAPS    Industry  
 Regional pharmacovigilance centre    Other organisation(s): specify .....

## ANNEX 3:

### USER GUIDE TO THE REPORTING FORM OF ADVERSE EVENTS WHICH MAY BE ASSOCIATED WITH A HEALTH PRODUCT

#### **WARNING:**

*AFSSAPS has set up a reporting form<sup>1</sup> to enable you to report adverse events<sup>2</sup> which you suspect of being linked to a health product (medicinal products and raw materials, medical devices, in vitro diagnosis medical devices, biological products of human origin (labile blood products, organs, tissues, cells, gene therapy and cellular therapy products), ancillary therapeutic products, cosmetic products, etc.). This guide is intended to help you in completing this notification form.*

*It is essential for AFSSAPS and its network of vigilance systems to have access to all the medical data concerning yourself in order to carry out an evaluation of the link between the health product and the adverse event you have noted. It would therefore be helpful if you could attach to this form any document providing complementary information (hospitalisation reports, additional examinations, etc.), on the understanding that they will be used in complete confidentiality.*

*This notification of adverse events by patients does not replace the reporting of adverse events by health professionals. It simply aims to complement the vigilance procedure and to collect notifications of adverse events which professionals do not declare for various reasons. In all cases, we encourage you to contact your doctor or any other health profession so that he can make the reporting of the adverse event himself, or to contact a patient association or a consumer representative structure.*

- 1. Why is it useful to have information about the person presenting the adverse event or, failing this, on the person declaring the adverse event (if the patient does not declare the event himself)?**

It is important to have information about the person who has suffered the adverse event or the person who declared the adverse event:

- To understand why the adverse event occurred in this person in particular (medical background, etc.);
- To be able to contact him if any important information for reaching a conclusion as to whether the health product was responsible for the onset of the adverse event is missing;
- And to detect possible duplication (the same adverse event presented by a single person notified several times)

In all cases, the confidentiality is preserved, which means his name and details are not recorded in any database.

- The details of the patient or, failing that, the declarer (if he is not the patient):

<sup>1</sup> Reporting/notification: Transmission of the presumed adverse event arising from a health product to a vigilance organisation or AFSSAPS.

<sup>2</sup> Adverse event: Any harmful and unsought event occurring in a person during a treatment, or following that treatment, whether or not it is considered as being linked to one or more drug(s).

- If the declarer is the patient who suffered the adverse event:

To notify an adverse event, you are not obliged to give your full name and forename; however, in order to enable AFSSAPS to detect any duplication (for example, if your doctor has already declared your adverse event without informing you) you must give the initials of your name and forename.

If you wish to give your full name and forename, rest assured that they will not be recorded in the database and will be considered as confidential. This information will serve solely for purposes of contacting you if need be (example: missing information).

- If the declarer is not the patient and if the patient's details are not known:

It is useful to have the declarer's details. They will be used to contact him if any additional information is necessary.

- The patient's date of birth and sex:

The date of birth and sex of the patient who suffered the adverse event are two important elements which appear in the database and make it possible to detect any duplication.

Furthermore, the age and sex are important parameters for evaluating the adverse event described. For example, elderly subjects or children are generally more fragile and adverse events are often manifested in different ways depending on the person's age and general state of health.

- The patient's department of residence:

Like the date of birth and sex, the department of residence is a tool which makes it possible to detect duplications.

In addition, if the same adverse event is found in patients from the same department, this may, for example, put the sanitary authorities on the track of a problem linked to the same batch of medicinal products or a local medical practice which does not conform to the recommendations for proper use.

## **2. Why is it necessary to give precise and detailed information on the suspected health product(s)?**

- Name of the suspected health product:

It is essential to give the exact name of the suspected health product. If the name is incomplete, wrong, illegible or unknown, it will not be possible to evaluate the link between the adverse event and the health product. The notification will not be taken into account.

The exact name of a health product gives access to a range of information such as:

- ◇ its composition: active substance(s) and excipient(s)<sup>3</sup>
- ◇ the dosage, if there exist different dosages for the same medicinal product/health product;
- ◇ the galenics, that is, the form in which the medicinal product is presented (powder for a drinking solution, tablet, syrup, suppository, etc.).

What is more, in order to evaluate an adverse event and to determine whether the health product is responsible, different elements are taken into account, in particular:

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<sup>3</sup> An excipient is understood to be any substance other than the active substance or substances of the content(s) in a medicinal product or cosmetic; it is used, in particular, to modify the taste, encourage absorption, ensure preservation or simply to facilitate manufacture. Excipients are inert in principle, but some of them may be responsible for adverse events, in which case they are called excipients with known effects.

- the administration route (oral, injection, inhalation, patch, vaginal, rectal, etc.) and the dose administered, are important items of information. The wrong use of a health product or the wrong dose may cause an adverse reaction.
- the dates of treatment: the dates of the start and end of treatment make it possible to estimate the period during which the patient was exposed to the health product. This period is an important parameter for evaluating whether the product is responsible for the onset of adverse events. For example, some adverse reactions only appear after a certain period of treatment with a medicinal product. It is therefore important to know precisely how long the patient has followed the treatment without experiencing an adverse event and if need be, the time that has elapsed since the treatment was stopped.
- The batch number<sup>4</sup>: The batch number is on the packaging of the health product. This number makes it possible to track a product from manufacture to administration. An adverse effect may also be linked to a quality defect in a health product. If the batch number is specified in the notification form, the incriminated batch can easily be found and if need be, withdrawn from the market.

### 3. Why is it necessary to indicate any other health product used?

It is important to indicate on the notification form any other health products taken during the period preceding the onset of the event. It may for example be a question of a medicinal product taken occasionally or every day, prescribed by a doctor, found in the medicine cabinet at home or bought over the counter.

Indeed, this is important for several reasons:

- The interaction between two health products is sometimes a cause of an adverse reaction.
- The suspected health product is not necessarily the product really responsible, even if it has already been suspected to cause the same adverse events.
- And lastly, identifying the treatments you follow also makes it possible to have a better knowledge of your general state of health, which is an important parameter in understanding an adverse event.

### 4. What is a contributing antecedent/factor?

Medical antecedents designate all the illnesses and disorders the patient has suffered from, as well as his close relatives. Any medical antecedent may contribute to the onset of an adverse event. The analysis of an adverse event therefore takes into account the patient's general state of health. This is why the presence of any chronic disease, such as diabetes for example, must be specified.

### 5. How can an adverse event best be described?

- description of the adverse event:

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<sup>4</sup> Batch: Defined quantity of a raw material, a packaging article or a product manufactured in a single operation or a series of operations, such that it may be considered homogeneous. For purposes of control of the finished product, the batch of a medicinal product is the set of units of a pharmaceutical form originating from the same initial mass and having been subjected to a single series of manufacturing operations.

It is important to describe the symptoms of the adverse event clearly and precisely. Try to be very descriptive (example: red spots on the skin, itching, tingling, stinging, etc.); do not designate the symptoms in medical terms or in the form of a medical diagnosis UNLESS the diagnosis was firmly made by your doctor (example: don't say that "you had an outbreak of eczema" if the doctor did not give such a diagnosis and even if you think it really is that. Simply describe the reaction observed on the skin).

In addition to the adverse event, the conditions of its onset (progressive, overnight, after a meal, etc.), the treatment used to relieve it, etc., be as precise as possible as to the time scale of the events.

You can attach to the notification form any additional element which complements the reporting (hospitalisation reports, additional tests, etc.).

- the date of onset of the event:

It is important to specify the date of appearance of the adverse event. By comparison with the dates of prescription, the delay between the administration of the health product and the onset of the event can be assessed.

- outcome:

The development of the adverse event is also a criterion enabling a health product's responsibility for the onset of an adverse event to be judged. It is therefore useful to describe how the symptoms were dealt with (treatment or otherwise) and to explain how they developed:

- persistence,
- attenuation or disappearance,
- appearance of new symptoms,

It may therefore be necessary to complete the notification form in several instalments (time of the adverse event, its disappearance, its reappearance if applicable, etc.). Furthermore, it may be necessary to adopt a detached attitude in order to assess the responsibility of a health product in the onset of an adverse event.

## **6. Why information of your health professional is necessary?**

The name and address of the health professional consulted by the patient must figure in the notification form in order to obtain additional information which is often necessary.

If the doctor who prescribed the suspected health product (medicinal product, for example) is not the same one who treated the adverse event, it is the details of the latter which should be given as a priority.

The details of the health professional are also considered confidential and are therefore not recorded in the AFSSAPS database.

## **ANNEX 4:**

### **PARTICIPATION OF PATIENTS AND CONSUMERS IN THE VIGILANCE SYSTEMS:**

#### **REPORTING OF ADVERSE EVENTS WHICH MAY BE ASSOCIATED WITH A HEALTH PRODUCT**

##### **MEMORANDUM**

This memorandum is proposed within the framework of the setting up of a partnership between AFSSAPS and the patients' associations and organisations representing consumers. It aims to undertake and follow up the implementation of the direct notification<sup>5</sup> by the associations, as well as by the patients and consumers themselves or their assigns, of information relating to adverse events from the health products<sup>6</sup> they may have in their possession.

In broader terms, it is necessary to continue and intensify the procedure of monitoring of the use and effects of health products; indeed, these, and in particular medicinal products, are the main cause of adverse events linked to health care, whether they are effects linked to the actual toxicity of the product or caused by wrong medical practices.

Thus the national survey on serious adverse reactions associated with treatment (ENEIS) conducted between April and June 2004 at 71 health establishments, shows that 3 to 5% of hospital stays are the result of a serious adverse reaction. Two-thirds of these reactions follow outpatient medical treatment, the others are the result of a previous hospital stay.

#### ***Why?***

All health products present benefits and risks. These two factors evolve over time. Not all adverse reactions are identified at the time of marketing, particularly in the case of medicinal products, since only data deriving from clinical trials are available at that point, which do not reflect exactly the conditions of use in daily practice.

It is therefore not rare for new adverse reactions to be discovered (unexpected adverse reactions) when a health product is used by a wider population in "real life" situations.

The information derived from reportings of adverse events may thus help to:

- Identify a new rare or serious adverse reaction not observed previously;
- Have a better knowledge of the safety profile of a health product;
- If need be, take the necessary corrective measures (withdrawal, stopping sale of the product, modification of the information on the product, etc.);

Thus the reporting of adverse events is essential to know and better manage the risks associated with the use of health products.

#### ***What role for the patients' organisations ?***

The associations are in possession of certain items of information relating to health products, through the intermediary of their members and/or the public. This information, which complements that of the health

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<sup>5</sup> Notification / Reporting: transmission of the presumed adverse event from a medicine or product to a vigilance organisation or to AFSSAPS.

<sup>6</sup> Health products: any substance or composition presented as having curative or preventive properties vis a vis human diseases, as well as any product administered with a view to making a medical diagnosis or to restoring, correcting or modifying an organic function.

professionals, may make it possible to increase the rate of notification of adverse events from health products and consequently to improve knowledge and data on health products, but also to identify new signs.

### **What is an adverse event?**

An adverse event designates a harmful and unintended symptom arising in a subject exposed to a health product, without making a judgement as to a causal link.

These events may arise under normal conditions of use of the product. They may be:

- observed in the space of a few minutes or several years after use of a product,
- of variable intensity: without serious consequences or, on the contrary, alter quality of life or even lead to death
- of a very diverse nature: pain in the legs, back, stomach, fever, skin reddening, itching, depression, sleep disturbances, language, motor, behavioural disturbances, nausea, vomiting, diarrhoea, etc.

### **What is the regulatory framework relating to notification of adverse effects?**

Legal requirements for the monitoring of adverse effects from health products after they have been commercialised are set out in Law No. 98-535 of 1 July 1998, "relative au renforcement de la veille sanitaire et du contrôle de la sécurité sanitaire des produits destinés à l'homme", and by the corresponding decrees.

Depending on the nature of the health product (medicinal products, medical devices, blood products, etc.), the adverse effects are governed by specific vigilance systems, which are implemented by AFSSAPS. These are:

- pharmacovigilance (medicinal products and medicinal products derived from blood),
- haemovigilance (labile blood products, that is, usable within a limited time scale), for example: immunoglobulins;
- medical devices vigilance, example: hip prostheses,
- reactivogilance (*in vitro* diagnostic medical devices), example: pregnancy tests
- dependency on medication (narcotics and psychotropics), example: Subutex®, a medicinal product used in treating patients who are drug addicts, antidepressants, anti-anxiety medicinal products, etc.
- biovigilance (organs, tissues, cells and ancillary therapeutic products),
- and cosmetovigilance (products intended for cosmetic use or body hygiene).

All the vigilance systems have the same objectives: to identify and minimise the risks associated with health products. Thanks to the reporting, recording, processing and investigation of adverse events and incidents associated with the use of health products, each vigilance system contributes to providing a health watch and safety.

Over and beyond these requirements, the AFSSAPS alert unit is developing and implementing mechanisms for the rapid dissemination of information to distributors or holders of health products which have been the subject of decisions to withdraw batches or products.

### **How are adverse reactions detected after the health product has been marketed?**

Adverse reactions are detected thanks to the spontaneous reporting by health professionals and drug manufacturers of effects which may be due to the health products, then evaluated by experts. Health professionals (doctors, pharmacists) are in fact under a legal obligation to report as rapidly as possible to the vigilance system any serious or unexpected adverse effect observed in a patient.

In parallel with this spontaneous notification by health professionals and manufacturers, follow-up studies of patients exposed to health products may be set up in order to systematically gather adverse events, reveal risk factors and estimate their incidence<sup>7</sup>.

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<sup>7</sup> Incidence : Number of new cases occurring during a given period.

Vigilance systems	Who must declare?	What?
<b>PHARMACOVIGILANCE</b>	Physician, Dental surgeon Midwife Pharmacist	<b>MANDATORY REPORTINGS</b> - Serious adverse effect - Unexpected adverse effect
	Any other health professional	<b>OPTIONAL REPORTINGS</b> - Serious adverse effect - Unexpected adverse effect
<b>Special case:</b> Pharmacovigilance of medicinal products derived from blood (MDS)	Any person qualified to prescribe, dispense, administer medicinal products derived from blood	<b>MANDATORY REPORTINGS</b> - Adverse effect
<b>DEPENDENCY ON MEDICATION</b>	Physician, Dental surgeon Midwife Pharmacist	<b>MANDATORY REPORTINGS</b> - Cases of serious dependency on medication - Cases of serious abuse
	Any other health professional or any other person as part of his function	<b>OPTIONAL REPORTINGS</b> - Cases of serious dependency on medication - Cases of serious abuse
<b>HAEMOVIGILANCE</b>	Physician, Dental surgeon Midwife Pharmacist Nurse	<b>MANDATORY REPORTINGS</b> - serious adverse effects in donors and any adverse effect in receivers; - serious incidents
<b>BIOVIGILANCE</b>	Physician, Dental surgeon Midwife Pharmacist Nurse Biologist	<b>MANDATORY REPORTINGS</b> - Incident - Adverse effect in a patient, a living donor or a receiver
<b>MATERIOVIGILANCE</b>	Health professionals who are users of medical devices	<b>MANDATORY REPORTINGS</b> - Risk of serious incident - Serious incident
	Non user health professionals	<b>OPTIONAL REPORTINGS</b> - Incident
<b>REACTOVIGILANCE</b>	Any health professional who is a user	<b>MANDATORY REPORTINGS</b> - Risk of incident - Incident
	Any other health professional (non user not operating in a health establishment or a blood transfusion establishment)	<b>OPTIONAL REPORTINGS</b> - Risk of incident - Incident
<b>COSMETOVIGILANCE</b>	Any health professional	<b>MANDATORY REPORTINGS</b> - Serious adverse event - Adverse event which although not meeting the definition of serious adverse event, appears to be of a serious nature

### **How are adverse events gathered?**

A spontaneous reporting of adverse events is made by means of a reporting form provided for that purpose. The reportings are made by health professionals and/or collected by local and regional correspondents (regional pharmacovigilance centres, regional haemovigilance centres, centre of evaluation and information on dependency on medication), charged with collecting and transmitting adverse events to AFSSAPS.

Manufacturers are also obliged to inform AFSSAPS of any important information relating to the safety of use of their product, since they also receive information from health professionals, patients, the media or their subsidiaries overseas.

Additional information on safety, effectiveness and proper use of health products can also be obtained from:

- post-marketing studies;
- publications in scientific journals;
- communications on the risks observed in other countries.

The procedure will shortly be complemented by patients being offered the possibility of reporting directly to AFSSAPS any adverse events they suspect of being associated with a health product.

### ***What types of information are collected in the reports of adverse events?***

The reportings must contain relevant and precise information on the patient, the adverse event which may be associated with a health product and the incriminated health product. Personal data relating to the patient's identity are confidential. The information supplied is protected in accordance with law No. 78-17 of 6 January 1978 "relative à l'informatique, aux fichiers et aux libertés".

The reporting must include the following information as a minimum:

- an identifiable source of information (the person who declares the adverse event);
- an identifiable patient/consumer;
- the name of the suspected product;
- the nature of the adverse event.

In practice, in order to be properly evaluated and to be usable, the reporting must contain the maximum information, in particular on the patient (sex, date of birth, weight, height, department of residence, medical antecedents, profession, etc.), the suspected health product (name, posology, method of administration/use, dates of start and end of use, pathology treated, batch number, expiry date, etc.) and the adverse event (description, date of appearance, development, severity, etc.).

The reporting must include any element which makes it possible to complete the reporting (copies of hospitalisation reports, medical letters and supplementary tests, etc.). The person who declares the adverse event may be contacted again if the observation requires any follow-up (example: has the adverse event disappeared? Has it reappeared? etc.) or whether it is necessary to obtain additional information. At any time after obtaining new data, the initial information may be complemented and modified: the dossier is evolutive (see the "guide for assistance in completing the notification form of adverse events which may be associated with exposure to a health product").

### ***How are adverse events recorded?***

Adverse events declared by means of the notification form are recorded in the national databases of the different vigilance systems (pharmacovigilance, haemovigilance, etc.), then evaluated in function of the data collected. These data will make it possible to determine, after evaluation, the causal link, if any, between the health product and the onset of the adverse event.

Local and regional correspondents of vigilance systems (depending on the vigilance system of the health product concerned) can have access to these databases, in general piloted by AFSSAPS.

### ***How are adverse events evaluated?***

The evaluation of the adverse events declared to AFSSAPS is carried out in two steps:

1) In an initial phase and on a case by case basis,

The evaluation is carried out by the experts of the vigilance system. It will be necessary to assess the causal link between the adverse event and the health product by taking into account the medical data supplied, the other health products used at the same time as the suspected product, the existence of a chronic disease or any other documents such as hospitalisation reports or analysis results. All these elements are important for a complete analysis of the signal.

2) In a second step, if necessary,

A global evaluation is carried out by a commission of experts: the analysis of aggregated events which have arisen with the same health product or the same family of health products may confirm the existence of a signal (see below). This evaluation is based on the nature, severity, frequency and consequences for the patient. This process of analysis may lead to a decision being taken.

Adverse events are characterised in function of their nature and expectedness:

- Expected adverse effects correspond to a harmful and unwanted reaction, but known and foreseeable according to the scientific data and characteristics of the health product;

- Unexpected adverse effects correspond to a harmful reaction that is unwanted and unknown, that is, not foreseeable according to the scientific data and characteristics of the health product.

The seriousness is assessed in function of the consequences of the adverse event on the person (patient, consumer, user, third party). In the case of medicinal products, it is graded according to 5 criteria:

- fatal,
- life-threatening,
- results in persistent or significant disability/incapacity,
- results in or prolongs hospitalisation,
- results in congenital abnormalities/birth defects..

The intensity of the reaction (or its severity), evaluated in function of the extent of repercussions of the effect on a patient's daily life, must also be taken into account.

Lastly, the frequency of the adverse effect must also be considered.

The analysis of all the information contained in the notification form seeks to estimate the causal link which may exist between the use of the health product and the onset of the adverse effect. This method, called imputability, is supposed to be rational and reproducible; it concerns the analysis of the data on a case by case basis. The causal link may be graded: unlikely, doubtful, possible, probable/ likely or certain.

Generally speaking, the risk of an adverse effect from health products is evaluated according to a continuous process based on notifications, data from scientific literature, studies on safety of use, etc. It needs to be updated regularly in function of new data.

### ***What is a signal?***

A signal designates an event or a series of events which may attract attention within the framework of routine monitoring of health products. In practice, one may speak of a signal when the value of a parameter (number of cases of an adverse event, rate of incidence, nature of an adverse effect, etc.) deviates from what is expected or accepted.

The detection of a signal may, after its evaluation, constitute an alert which should lead to the taking of suitable corrective measures (see below). In all cases, the occurrence of a signal calls for enhanced monitoring of the health product concerned.

### ***How many reportings are needed to constitute a signal?***

There is no minimum number of adverse events for obtaining a signal. A single adverse event or several hundred may constitute a signal. In practice, it is observed that more than one adverse event is required to constitute a signal.

### ***At what point is a measure taken?***

A measure is taken when the health product presents a potential risk for the health and health safety which requires that health professionals and patients be informed in order to modify their practices.

The level of risk is determined by an analysis of the scientific data and the characteristics of the health product, the reportings of adverse events and any alert signals, new data supplied by the laboratory, following post-commercialisation studies.

In all cases, the taking of measures follows on the continuous evaluation of risks but also of the benefits of the health product concerned.

Indeed, the risk cannot be assessed on its own, without taking into account the expected therapeutic benefits.

In function of this risk/benefit ratio, the nature of the adverse effect or the non existence of a therapeutic alternative, the risk may be considered acceptable or unacceptable, depending on its severity, frequency or the number of individuals concerned.

### ***What measures can be taken by AFSSAPS?***

According to the law, AFSSAPS may be required to re-evaluate the risk/benefit ratio "at any appropriate time, in particular when a new element is likely to call the initial evaluation into question".

Several assumptions exist depending on the importance of the new data supplied by the vigilance systems.

- Either there are no modifications to the risk/benefits ratio, but the information simply needs to be completed; for example, it is noticed that under real conditions of use, there is a precaution for use which should be particularly taken into account. This forms part of the rules of good use which must of course be communicated; they do not modify but define more accurately what was known about the medicinal product when the marketing authorisation (AMM) was obtained.
- Or there are more important modifications and it is necessary to include in the product characteristics a new contra-indication, a new adverse effect. Modifying decisions will then be taken and will also be the subject of a report to health professionals.
- Finally, AFSSAPS may have to take health policing measures, under the conditions provided for in the public health code. These policing decisions may, for example, take the form of the suspension or withdrawal (temporary or definitive) of the marketing authorisation of a medicinal product, the suspension or prohibition of manufacture and putting on the market, free of charge or for payment, of a health product not subject to authorisation (cosmetics).

### ***How is the information linked to evaluation of adverse events distributed?***

#### Feedback to doctor and patient:

At present there is no systematic feedback on each reporting transmitted to AFSSAPS, but in some cases it may be necessary to transmit the results of the evaluation of the adverse event to the doctor who made the reporting. The latter may in turn inform the patient concerned accordingly.

#### Distribution of general information:

The ongoing evaluation of the risk/benefit ratio of a health product or an entire class of health products may lead to the release of new information regarding the product or the class respectively.

The "Vigilance Bulletin", a bi-monthly publication of AFSSAPS, makes health professionals and the public aware of any signals detected during the analysis of all the data relating to the health products. This is a means of dissemination of information and raising awareness of the existence of potential risks and of the proper use of health products. A bulletin dedicated solely to haemovigilance also enables the release of more specific information. These bulletins are published on the Agency's website, [www.AFSSAPS.sante.fr](http://www.AFSSAPS.sante.fr) and are sent by e-mail to subscribers on the distribution list.

New data on the safety of use and effectiveness of health products is provided to health professionals and the public on a one-off basis, as a result of the reporting of adverse events, in the form of:

- Press releases, if need be at press conferences,
- Letters to prescribers and/or pharmacists,
- publications of studies in specialised journals,
- reports,
- updates of monographs (essential information concerning a medicinal product).

All these information media are also available on the Agency's website.

Whenever it disseminates important information to health professionals, AFSSAPS has set itself the rule of doing so in parallel to the general public. The principle being that as from the time when a new item of data on the safety of use of health products is going to affect different types of "users", everyone can have access to it in the most comparable form possible.

In future, the Agency expects to improve and enhance this procedure in order to better inform health professionals and the general public about the proper use of health products.

**ANNEX 5:  
PROPOSAL OF A CHARTER FOR PATIENTS' OR CONSUMERS' ASSOCIATIONS  
WITHIN THE FRAMEWORK OF AFSSAPS' WORK**

***“Conditions of participation of the associations in AFSSAPS' work”***

1. General considerations

The associations or representative structures mentioned may participate in AFSSAPS' work if they prove that for the three years preceding the application they carried out effective public activity with a view to upholding the rights of patients and users of the health system or of consumers.

The effective public activity of the association or representative structure is assessed on the basis of the actions it carries out:

1. in favour of the promotion of the rights of patients and users of the health system to the public authorities and within the health system;
2. for the participation of patients and users in the drawing up of health policies and for their representation at hospital or public health bodies;
3. in terms of prevention, assistance and support in favour of patients and users of the health system;
4. in protecting the interests of patients and consumers.

2. Qualifications of the representatives

The associations or representative structures must assure the training of their members (*Art. R. 1114-2*) so that they perfect their level of knowledge. The representatives of the associations should ensure adequate level of knowledge to effectively represent patients or consumers within the framework of their participation in the different working groups of AFSSAPS, complementing their associative expertise.

3. Representativity

The representativity of these associations or structures must be substantiated and attested to by a sufficient number of members (*Art. R. 1114-3.*). Otherwise, the association or structure is regarded as representative if it can prove that it has a wide audience among the people it intends to represent or defend.

4. Independence and individual freedom

The statutes, financing and conditions of organisation and operation of the association should not be such as to limit its independence. In particular, the association's independence must be guaranteed vis-à-vis health professionals, health establishments, health services and organisations in which individual acts of prevention, diagnosis or treatment are carried out as well as producers, operators and suppliers of health products. The association must also present sufficient guarantees with regard to the respect of individual freedoms (*Art. R. 1114-4*).

The members of the associations referred above should not have any direct interest in the pharmaceutical industry or any other producer. It undertakes to produce a “public declaration of

interest” concerning the association, the main legal representatives (members of the Bureau – president, vice-presidents, secretary- general and treasurer) as well as for its representatives at AFSSAPS. The association also undertakes to produce the list of members of the Management Board (name, forename, address, profession).

#### 5. Retransmission of information

The appointed representatives undertake to release authorised (non confidential) information to their members as well as to other non-represented associations intervening in their sector of activity. A list of these associations or networks may be drawn up jointly with AFSSAPS on acceptance.

The association or representative structure must indicate in its application package the modes it intends to set up for releasing information and providing dynamic feedback on information received from non-represented associations.

#### 6. Compiling a submission

Each association or representative structure wishing to participate in AFSSAPS’ work must compile a dossier setting out the relevance of its participation and its expectations as well as its ability to relay information to partner associative networks in the same sector of activity.

#### 7. Duration of the mandate

The representatives will be appointed for a mandate of a determined duration depending on the workshops.

#### 8. Obligations

The duration of the above mandate will not be a firm undertaking by AFSSAPS. The association or representative structure undertakes to participate in the work for which it has been designated and to be represented efficiently for that work.

#### 9. End of mandate or termination

The representatives’ mission may come to an end on completion of the work according to the initial undertaking of participation.

AFSSAPS reserves the right to terminate the mandate in the case of vacation or non-participation of the representatives. The participation in AFSSAPS’ work may be suspended when the association or representative structure ceases to fulfil the above-mentioned conditions or if it fails to respect them.

AFSSAPS may terminate this participation by registered letter sent to the legal representative of the association or structure, which will be required to vindicate itself if need be.

## **ANNEX 6: PROPOSAL OF FRAMEWORK AGREEMENT**

Between:

The association ... on the one hand,

And:

The French Agency for the Safety of Health Products, a public establishment of an administrative character, situated at 143-147 boulevard Anatole France - 93285 SAINT-DENIS Cedex, represented by its Head, Mr JEAN MARIMBERT,

Hereafter called "French Agency for the sanitary safety of health products"

on the other hand,

hereafter collectively called "the parties".

Preamble:

The missions of the association ... and those of the 'French Agency for the sanitary safety of health products', a public establishment of an administrative character, placed under the protection of the minister for health, are defined in articles L. 5311-1 and L. 5311-2 of the public health code.

Aware of the usefulness of setting up exchanges of information and skills, the association.... and the French Agency for the sanitary safety of health products have agreed to develop collaborations on themes relating to health products.

In order to develop these collaborations, it appears necessary for the parties to conclude a framework agreement setting out the general terms and conditions of same.

It is agreed that each specific collaboration shall take place on the basis of a precise specifications sheet formalised by a special agreement for application of the framework agreement.

## THE FOLLOWING IS AGREED:

### Article 1: Purpose of the framework agreement

The French Agency for the sanitary safety of health products and the association ... may collaborate on the project .... On health products provided that a common interest relating to the missions of both signatories shall have been identified by the services concerned and validated by the Head of Agency of ..... For each action envisaged, a specifications sheet shall be defined jointly, which shall mention as a minimum the following information:

- name and purpose of the collaboration
- health product(s) concerned
- conditions for conducting trials (if necessary)
- duration of the study
- use and publication of the results
- modalities of financing the study

### Article 2: Modification of the framework agreement

Any modification of the framework agreement must be agreed by common accord by the parties and set out in a rider to the agreement.

### Article 3: Duration and termination of the framework agreement

The framework agreement shall take effect as from its signature for a period of one year. It is renewable by tacit renewal, up to a limit of a total duration of three years. It may be terminated at any time, without notice, by either of the parties notifying the other party by registered letter with acknowledgement of receipt. The termination of the framework agreement shall also imply the termination of special implementation agreements.

Done at Saint-Denis on  
In two original copies

The Head of the French Agency for  
the sanitary safety of health products

## **ANNEX 7: THE AFSSAPS COMMITTEES IN WHICH THE ASSOCIATIONS ARE REPRESENTED**

### **National pharmacovigilance committee**

It evaluates risks and proposes measures concerning the information transmitted to it: results of surveys relating to all the information available on adverse effects from regional pharmacovigilance centres, pharmaceutical laboratories, European and international data.

### **National cosmetics committee**

It issues opinions on the drawing up of lists of regulated substances relating to the composition of a cosmetic product. It may also formulate opinions on the safety of cosmetic products, their composition, the toxicity of ingredients that form or may form part of the composition of cosmetic products. It may also formulate an opinion on requests to waive the reference to an ingredient on the packaging of cosmetic products, on information relating to adverse effects associated with the use of cosmetic products of which AFSSAPS is aware.

### **Committee in charge of medicinal products advertising control and recommendations on proper use**

Its mission is to issue opinions:

- on projects for the prohibition and amendments of advertising for health professionals which may have failed to comply with the regulatory provisions and on certificates and possible suspensions and withdrawals
- on authorisations for advertisements targeting the public which relate to medicinal products and other health products.

It also gives a consultative opinion on proposed sanctions in function of each infringement. The advertising commission may also issue recommendations on the proper use of medicinal products and other health products.

### **Committee in charge of advertising control in favor of other products presenting health allegations**

Its mission is to monitor advertising concerning objects, equipment and methods presented as being beneficial for the health, that is, presented as favouring the diagnosis, prevention or treatment of diseases, surgical conditions or physiological disturbances; diagnosis or modification of the physical or physiological states; restoration, correction or modification of organic functions.