



**AIM**

ASSOCIATION INTERNATIONALE DE LA MUTUALITE



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## **AIM and ESIP joint opinion on the European Commission's legislative proposals on pharmacovigilance**

***To protect patient's health and really strengthen pharmacovigilance systems, social health insurers call for changes built on independent expertise and more stringent marketing authorisation requirements***

AIM and ESIP, the umbrella organisations of social health insurers in Europe, call for more stringent marketing authorisation requirements to protect patients from exposure to adverse effects of new medicines which could have been avoided. A European pharmacovigilance system build on clear competences, independent expertise and full access to information would contribute to greater efficiency and improved patient safety.

### **Summary**

- AIM and ESIP share the European Commission's opinion that pharmacovigilance is a key public health function.
- AIM and ESIP support the Commission's proposed objectives to strengthen the EU pharmacovigilance system<sup>1</sup>. However, AIM's and ESIP's views on how these objectives should be best achieved diverge from those of the Commission in a number of key areas. We believe that as they stand a number of the Commission's proposals could in fact weaken the current pharmacovigilance system and increase the risks to patients and the general public.
- To strengthen the EU pharmacovigilance system AIM and ESIP call for:
  1. More stringent marketing authorisation requirements;
  2. Clear definitions and competences to guarantee independent pharmacovigilance expertise and assessment free from conflict of interest, based on
    - publicly financed pharmacovigilance activities;
    - an empowered, autonomous pharmacovigilance committee;
    - monitoring of adverse effects by independent bodies appointed by public authorities;
  3. Complete transparency and access to information.
- To ensure that public health considerations and objectives are central to the legislation AIM and ESIP urge that the responsibility for pharmacovigilance and pharmaceutical legislation within the new Commission is transferred from a Directorate General whose focus is industry to one whose core focus is public health.

<sup>1</sup> As codified in Regulation (EC) No. 726/2004 and Directive 2001/83/EC

## **Introduction**

AIM and ESIP share the European Commission's opinion that pharmacovigilance is a key public health function. According to the Commission, adverse drug reactions present an important public health burden in the Community. It is estimated that 5% of all hospital admissions are due to an adverse drug reaction, 5% of all hospital patients suffer an adverse drug reaction and adverse drug reactions are the fifth most common cause of hospital death. Considering these facts, AIM and ESIP agree with the Commission analyse that the current EU pharmacovigilance system contains major weaknesses that need to be urgently addressed.

AIM and ESIP share the Commissions proposed objectives to strengthen the EU pharmacovigilance system through:

- the establishment of clear roles and responsibilities at European and Member State level;
- strengthened requirements for the monitoring and assessment of the safety of medicines
- effective reaction measures and
- increased transparency and communication

However, AIM's and ESIP's views on how this should be done diverge from those put forward by the Commission in its proposals in a number of key areas. Indeed, we fear that the Commission proposals could in effect weaken the current pharmacovigilance system and increase the risks to patients and the general public.

## **AIM and ESIP concerns and proposals**

### **1. Need for more stringent marketing authorisation requirements**

The **Commission proposals lay the ground for increased, premature granting of marketing authorisations** with overemphasis on post-authorisation pharmacovigilance activities and risk management systems. AIM and ESIP are of the opinion that the more widespread use of "risk management systems" will falsely reassure the authorities and the public and lead to increased premature granting of marketing authorisation of inadequately tested new medicinal products.

#### **Premature marketing authorisation due to more widespread use of "risk management systems"**

The European Commission's proposals provide for more widespread use of "risk management systems", particularly if there are concerns about risks "*affecting the risk-benefit balance of an authorised medicinal product*". The risk management system should be "*proportionate to the (...) risks*"<sup>2</sup>. According to the proposals, if concerns exist about the safety of a drug being authorised for "exceptional circumstances", it is also proposed that a marketing authorisation can be granted provided that post-authorisation studies are to be conducted (this condition has to be stated in the risk management plan)<sup>3</sup>.

#### **Conditional authorisations would become the general rule**

In contrast to the current provisions for centralised marketing authorization procedures, the Commission proposals mean that it will no longer be necessary to prove an unmet public health need when requesting "conditional" marketing authorisation. It would be enough for Member States to grant the marketing authorisation accompanied by conditions, such as the conduction of post-authorisation studies<sup>4</sup>, even though experience in the USA and Europe has shown<sup>5</sup> that pharmaceutical companies often do not fulfil their commitments as regards such studies.

<sup>2</sup> Proposed amendment to article 1(2) point (e) and proposed article 104(3) point (c) and 104a of the Directive, and proposed article 21 of the Regulation.

<sup>3</sup> Proposed article 22a of the Directive and article 10a of the Regulation.

<sup>4</sup> Proposed Directive article 21 a.

<sup>5</sup> (a) US Government Accountability Office "Drug safety – Improvement needed in FDA's postmarket decision-making" and oversight process" Report GAO-06-402, 2006. www.gao.gov: 63 pages. (b) Lexchin J "Notice of compliance with conditions: a policy limbo" *Healthcare policy* 2007; 2 (4) : 114-122 (+ Annexes: 5 pages).

## Recommendations

- A first step to minimising the risk to the general public of a new medicine should be to increase the stringency of marketing authorisation requirements. Well documented dossiers for the marketing authorisation represent the first opportunity for regulatory authorities to identify and notify of possible adverse effects that may pose a risk to patients. Further, the **requirement to demonstrate “added therapeutic value”** wherever possible would avoid unnecessary public exposure to the adverse effects of medicinal products which show no added therapeutic benefit compared to existing treatments. Therefore, **AIM and ESIP strongly call for the submission of comparative clinical trial data for marketing authorisation approval** in order to reduce the risks for patients and public health budgets.
- Conditional marketing authorisations need to be fully justified.

## 2. Need for clear definitions and competences to guarantee independent pharmacovigilance expertise and assessment free from conflict of interests

### Need for public financing of pharmacovigilance activities

A major step forward in the 2001 Review (article 67 of the Regulation) was the provision of **public funding for pharmacovigilance activities**. Conflict of interests can only be avoided through independent financing of pharmacovigilance activities. The **Commission proposals re-open the door for industry funding of public pharmacovigilance activities**<sup>6</sup> which is not acceptable.

### Need for an empowered autonomous pharmacovigilance committee

AIM and ESIP fully support the establishment of a **pharmacovigilance committee** within EMEA. However, instead of what is proposed, we request that this committee **should have full responsibility for decisions on and for coordinating pharmacovigilance** activities and should not be limited to an advisory role as proposed by the Commission<sup>7</sup>.

### Monitoring of adverse effects should remain a task for public authorities

Pharmaceutical companies have a clear role and duty in the collection of data on the adverse effects of their products, especially during clinical trials or post-authorisation safety studies. As regards the monitoring of the adverse effects of their drugs post market authorisation, the Commission proposals provide a number of opportunities for pharmaceutical companies to bypass the public pharmacovigilance systems in the Member States:

- Healthcare professionals may be authorised to send their reports only to drug companies<sup>8</sup>,
- Pharmaceutical companies receive healthcare professionals' and patients' reports<sup>9</sup>,
- Companies will be responsible for sending these reports to the Eudravigilance database.

Further, as regards recording and analysing the adverse effects data the proposals foresee a shift of responsibility from public authorities to pharmaceutical companies.

Given the devastating effect that safety concerns about marketed products can have on pharmaceutical companies' profitability, entrusting the companies themselves with the task of gathering and analysing data, issuing warnings and informing on their products adverse effects is to put them in an untenable situation faced with major conflict of interest.

<sup>6</sup> Proposed article 105 of the directive and proposed amendment to article 67 of the Regulation.

<sup>7</sup> Proposed article 27 of the directive and article 56(1)(aa) of the regulation

<sup>8</sup> Proposed article 102(1) of the Directive.

<sup>9</sup> Proposed article 107(1) and (2) of the Directive.

### Periodic safety update reports (PSURs)

PSURs constitute a key element of pharmacovigilance systems. According to the Commission proposals, the PSURs should be compiled by drug companies and the role of public authorities is limited to their assessment<sup>10</sup>. This subcontracting of data interpretation to pharmaceutical companies is an important failing in the current pharmacovigilance system. Further extension of these subcontracting arrangements would in fact mean that the public authorities would lose their authority, expertise and credibility and undermine their autonomy. This would in the end put patients at greater risk.

Furthermore the Commission proposals foresee that PSURs will no longer be required for longstanding products considered to have been in “well-established medicinal use” for at least 10 years. However, many examples (including the very recent case in June 2009 of dextropropoxyphene-containing medicines<sup>11</sup>) have shown that adverse effects are not rare, even 30 years after a product has been on the market.

### **Recommendations**

- The proposed Pharmacovigilance Risk Assessment Advisory Committee (PRAAC) must be defined as a European instrument for cooperation between national pharmacovigilance systems, intellectually and hierarchically independent from drug licensing committees. It should be renamed the “*European Pharmacovigilance Committee*”.
- This *European Pharmacovigilance Committee* must be entirely financed by public funds. Its human resources must be increased, to, at least, one representative per Member State, and its members should have no conflict of interest with pharmaceutical companies. Delegates from consumer organisations, families and carers and social health insurance organisations should also be involved in the committee activities. Meeting transcripts must be made public, including voting details.
- The *European Pharmacovigilance Committee* must have powers similar to those of the Committee for Medicinal Products for Human Use (CHMP). After analysis and discussions of Member States’ assessments performed under its supervision, the Committee must be able to propose decisions directly to the European Commission, namely pertaining to withdrawals or changes to marketing authorisations, without being subject to any censorship by the CHMP or the Coordination group for mutual recognition and decentralised procedures (CMDh). Further, the Committee should have the prerogative to ask for post-authorisation safety studies and risk management plans and to recommend sanctions.
- The *European Pharmacovigilance Committee* must be sufficiently autonomous to carry out any research it deems necessary (proactive pharmacovigilance) and not only in response to “alerts” by health authorities or pharmaceutical companies.
- Reports from patients, healthcare professionals or drug companies must be collected and centralised by the independent pharmacovigilance systems in each Member State. This also requires that pharmaceutical companies systematically and exclusively send the reports they collect to these independent pharmacovigilance systems. The independent pharmacovigilance systems will then be responsible for sending the data (to which valuable information based on their particular expertise could be added) to the Eudravigilance database to ensure the high quality of its content.
- The analysis of reported adverse effects and the re-evaluation of the risk-benefit balance of medicines must be entrusted to working parties composed of experts,

<sup>10</sup> Proposed articles 107b, d and e.

<sup>11</sup> <http://www.emea.europa.eu/pdfs/human/press/pr/40106209en.pdf>

who are independent of both the drug companies and the licensing committees, in complete transparency. These working parties, appointed by the public authorities, should have access to all available data: reports received by the Pharmacovigilance authorities from patients and healthcare professionals, well-documented case reports sent by pharmaceutical companies (raw data), published data recorded by the EMEA in Eudravigilance, etc. Even for so called “well-established” medicines, periodic safety update reports (PSURs) must be submitted regularly, at least every 5 years.

- Sanctions imposable by Member States in case of non compliance of the legal requirements governing medicinal products<sup>12</sup> should list financial penalties and the direct revocation of marketing authorisation.

### 3. Complete transparency and access to information

AIM and ESIP call for complete transparency concerning information on pharmacovigilance (to include not only product-related data but also information regarding the decision-taking process and its results)<sup>13</sup>. Mechanisms to ensure easy and immediate access to safety information for health professionals, patients and all interested stakeholders should be put in place.

#### Improved reporting system through direct patient reporting

AIM and ESIP welcome the Commission proposal to allow direct patient reporting to the competent national authorities. The participation of all health professionals (doctors, nurses, pharmacists), together with patients and carers, will result in a better reporting system. In addition, a reflection should be launched on how incentives/bonuses could be provided to encourage health professionals to fulfil this obligation of continuous reporting, with a special emphasis on the use of drugs in children. Patient and consumer organisations should also be allowed to play an active role in patient reporting (collective reporting).

#### **Recommendations**

- All information regarding pharmacovigilance should be available on national as well as EU medicines safety web-portals: agreed risk management plans and the post authorisation safety study protocols but also details of the decision-making process (demands, responses, reasons), the periodic safety update reports (PSURs), inspection reports and sanctions taken, as well as full details of meetings, agendas, minutes decisions, votes, and minority opinions<sup>14</sup> also in cases of suspension, revocation or non-renewal of marketing authorisation on the basis of safety issues. Appropriate measures should be put in place to enable easy access to safety information for all stakeholders (including health professionals, patients, consumers and carers).
- The assessment reports of the PSURs prepared by national health authorities and delivered to the *European Pharmacovigilance Committee* must be made public, including data on consumption, which is essential for evaluation of the level of exposure of the population.
- The content of the Eudravigilance database at the European level, as well as the content of the national databases must be publicly accessible in a user-friendly format<sup>15</sup>.
- Strict requirements need to be upheld that non interventional studies should be non

<sup>12</sup> Proposed amendment to article 111, paragraph 8 of the Directive.

<sup>13</sup> The proposed article 106 of the Directive regarding the creation of web portals by member states and “appropriate level of access” to the Eudravigilance database is not sufficient.

<sup>14</sup> As laid down in Art 126 of Dir 2004/27/CE.

<sup>15</sup> The USA Food and drug Administration already provides this type of information through quarterly data extracts from its adverse event reporting system database.

promotional (bearing in mind the current proposal on information to patients concerning information on non-interventional studies).

- During the first two years following market launch of newly authorised products, products should be marked with an EU symbol (e.g. a triangle) next to the brand name on each box and on immediate packaging drawing immediate awareness of health professionals and patients to the newness of the product as well as the need for close surveillance of the effects of these products (adverse reactions, side effects, etc.). Belgium started such an initiative in the commented drug repertory at the beginning of January 2008<sup>16</sup>.
- To help identify drugs which are under intensive monitoring, a pictogram in form of a black triangle should be put next to the brand name on each box and on immediate packaging.
- As regards direct patient reporting during the first two years of market availability of a new drug, a pre-printed patient reporting form should be included in the product package. This would serve to empower patients to play an active role as regards their health.

#### **4. Public health objectives must be at the centre of pharmaceutical legislation**

To ensure that public health considerations and objectives are central to the legislation AIM and ESIP urge that the responsibility for pharmacovigilance and all EU pharmaceutical legislation within the new European Commission is transferred from a Directorate General whose focus is industry to one whose core focus is public health.

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##### **About the Association Internationale de la Mutualité (AIM)**

The 'Association Internationale de la Mutualité' (International Association of Mutual benefit societies) brings together 42 national federations of autonomous health insurance and social protection bodies in 27 countries. All these organizations are operating according to the principles of solidarity and not-for-profit orientation. In Europe, they provide coverage against sickness and other social welfare risks to more than 140 million people, either by participating directly in the management of compulsory health insurance, by providing voluntary health insurance or by delivering directly health care and social services through own facilities.

AIM's goal is to defend and promote, at international and European level, the social values and basic principles shared by its members: access to health care as a fundamental right, solidarity and non-exclusion as essential means to ensure this access to quality health care for all, irrespective of health status or financial capacity to pay; and non profit orientation as guiding principles for health insurance based upon the needs of citizens.

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##### **About the European Social Insurance Platform (ESIP)**

The *European Social Insurance Platform* (ESIP) represents the social insurers in sixteen EU Members States and Switzerland, active in the field of health insurance, pensions, family benefits, occupational safety and accident insurance and unemployment insurance. The aims of ESIP and its members are to preserve high-profile social security for Europe; to reinforce solidarity-based social insurance systems and to maintain European social protection quality. ESIP builds strategic alliances for developing common positions to influence the European decision-making process and is a consultation forum for the European institutions and other multinational bodies active in the field of social security.

*NOTE: ESIP members support this position insofar as the subject matter lies within their field of competence.*

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<sup>16</sup> <http://www.cbip.be/nieuws/index.cfm?welk=251>