Translated from *Rev Prescrire* May 2012; 32 (343): 378-381

INITIATIVES Management of serious adverse drug reactions: proposals from a victims' organisation

Abstract

● **Amalyste is a French patient-advocacy group for victims of two very serious adverse drug reactions: Lyell and Stevens-Johnson syndromes. The aims of this organisation are to represent the interests of patients who have experienced these syndromes; to better inform the public about these syndromes; to provide analyses of drug-related risks; and to demand collective compensation for victims of serious adverse drug reactions.**

● **The following text is our translation of an Amalyste position statement on drug-related risks. It provides valuable food for thought, both for healthcare professionals and for drug regulatory agencies, and has the potential to improve practice (a).**

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"The Mediator° (benfluorex) scandal called into question the entire drug risk management approach (see *Prescrire Int* n° 126 page 110). It was high time: serious drug-related accidents cause at least 13 000 deaths every year in France according to the latest official statistics, dated 2001...

Drugs are authorised and maintained on the market, on the basis of their so-called risk-benefit ratio, whether or not their risks are known at the time. This concept is an "open door" for approval and ongoing marketing of drugs, and is used repeatedly by the various stakeholders, including physicians, drug companies, governments, and regulatory agencies.

No "risk management system" worthy of the name

This theoretically attractive concept proved to be inadequate, scandalously ineffective in fact, in the case of the Mediator° scandal. In our opinion, the reason for this failure does not lie in the "risk-benefit" concept itself, but rather in its application, because the scientific, ethical and legal implications are not properly taken into account. As a result, there is currently no drug risk management plan worthy of the name in France.

Contrary to official claims, pharmacovigilance failings alone are not responsible, and the weaknesses of drug safety monitoring cannot be effectively addressed without a radical re-evaluation of this key concept of drug risk management.

Risk-benefit ratio: a concept that needs rethinking

Basically, the theoretical framework adopted by French authorities assumes that the severity of a drug-related risk can be offset by:

– High efficacy for patients at high risk initially. Clearly, if a drug is able to cure a deadly disease, a certain degree of risk is considered acceptable;

– The lack of an effective, safer alternative. If, in certain situations, a dangerous drug may be replaced by another drug that is equally effective and less dangerous, then the former should not be used in these situations;

– A low frequency of the risk, inversely proportional to its severity: a very serious risk is not considered acceptable unless it is extremely rare (in addition to the two previous conditions).

Theoretically, the aim of the analysis is to ensure that the new risk posed by a drug is lower than the present danger (the disease) or the potential risk (of contracting an infection from vaccination, for example).

The "risk-benefit ratio" is unquantifiable. What happens in practice? From a scientific point of view, this concept is not clearly defined or supported by measurable and therefore objective criteria.

The assessment is not based on standardised, quantitative criteria. While the word "ratio" implies a mathematically defined quantity, the assessment is essentially a judgement call, despite being based on numerical data in some cases. In practice, this "ratio" is derived from an attempt to synthesise a set of vague value judgements that depend on the opinions of various experts. Thus, it is more of a "balance" than a true "ratio" in the mathematical sense of the term. This "fuzziness" raises two major issues.

The seven principles upheld by Amalyste

● **The patient-advocacy group Amalyste upholds seven principles intended to improve the management of drug-related risks (1).**

"The principle of collective responsibility. This principle flows directly from the concept of the risk-benefit balance (collective acceptance of a risk). Victims must not be left to their fate. In addition, drug-related risk management is a collective issue that must not be left solely in the hands of experts and the pharmaceutical industry. A balanced representation of stakeholders (civil society, citizen groups, the government, the medical and nursing sectors, and drug companies), as well as their independence, must be guaranteed.

The principle of control, knowledge and understanding of risk. The concept of "acceptable risk" implies an obligation to provide the means necessary to document, understand (through research), monitor and control this risk.

The principle of "auditability". The assessment process must be quantitative and standardised in order to ensure its transparency and subsequent auditability.

The principle of "shared risk". Drug-related risks, and the way they are insured, must be seen as a collective responsibility, shared by society as a whole.

The principle of risk internalisation. The pharmaceutical industry is part of the private sector. The costs relating to the risks induced by this activity must be internalised and included in the cost of each drug. The pharmaceutical industry is a profitable activity that should be able to integrate, under proper conditions of risk control, the cost of this risk. Furthermore, integration of the cost of this risk in the price of each medication will improve the competitiveness of companies that develop, for a given disease, effective drugs that carry a lower risk of adverse effects.

The principle of full compensation for harm. Harmful effects incurred under collective responsibility must be fully compensated. This implies that the necessary means must be available: compensation provided by the entire community extends far beyond individual responsibility. For instance, in addition to providing individual victim compensation, the community should allocate resources to research and treatment programmes that aim to mitigate the consequences of adverse drug reactions.

The principle of equity regarding the burden of evidence. It may be difficult for victims to prove that an accident was due to a particular drug. They should be given the benefit of the doubt; the first condition for "acceptability" of a severe risk is its very rarity, making it even more difficult for victims to provide conclusive evidence (**a**)" (1).

a- For a transcription of Amalyste's arguments (in French) before the French National Authority for Health in favour of scleral lenses by the national health insurance system, see www.amalyste.fr

1- Amalyste "La gestion du risque médicamenteux grave". www.amalyste.fr accessed 8 February 2012: 7 pages.

Lyell and Stevens-Johnson syndromes

"These serious reactions (fatal in 30% of cases) cause sudden and sometimes extensive detachment of the skin and mucous membranes. Nine in ten cases are due to drug reactions. Some are due to *Mycoplasma* infection. About a dozen high-risk drugs have been identified (antibiotics, anti-inflammatory drugs, antiepileptics, *allopurinol*, *nevirapine*).

Victims must always be managed in a specialised unit. These drug reactions are extremely painful.

This is an orphan disease, with 150 cases occurring per year in France and about 1000 in the European Union.

It is also a chronic illness: 95% of survivors are left with debilitating and progressive sequelae that totally disrupt their lives.

Identification of the implicated drug is very difficult, as there may be a delay of up to several weeks between drug intake and onset of symptoms, co-administration of several drugs, and inability to carry out rechallenge with the suspected drugs.

Research is inadequate and the mechanisms of these reactions are still not understood" (1).

1- Amalyste "La gestion du risque médicamenteux grave". www.amalyste.fr accessed 8 February 2012: 7 pages.

First, the lack of a standard procedure prevents any comparison: it is currently impossible to compare assessments of different drugs on the basis of objective criteria. These assessments are neither comparable nor "auditable", and are incompatible with any quality-assurance process worthy of the name. Second, the lack of standardised criteria means that it is not possible to set thresholds at which risks are considered acceptable.

What is an "acceptable" risk? Although the French Public Health Code (Article L. 5121-9, R. 5121-45-1 Article, Section L. 5311-1, etc.) repeatedly refers to *"the ratio between the benefits and risks"* of a drug as the basis for the evaluation that precedes marketing authorisation or market withdrawal, this ratio is never defined in legal terms, and its evaluation, as well as the methods used, are left to the discretion of the French drug regulatory agency or its director. Any reassessment therefore depends solely on the authorities' goodwill, which is often influenced more by media pressure and lobbying by the pharmaceutical industry than by rational decision-making.

From an ethical standpoint, it is the notion of "sacrifice" that underlies this concept. Yet it has never been properly thought through in terms of responsibility.

Sacrifice of the few for the common good

Experts rarely explicitly point out that this "risk-benefit ratio" is assessed statistically, at the population scale, when estimating the collective acceptability of ▶▶

a- Amalyste defines itself as "the association of victims of Lyell and Stevens-Johnson syndromes. Its objective is to encourage the authorities, the pharmaceutical industry, the medical profession and the general public to assume their responsibilities with respect to the known and accepted risk of rare but serious drug-related accidents. (...) Amalyste is approved by the French General Health Directorate to represent users of the healthcare system. It participates in the French drug regulatory agency-patient groups working group. Amalyste is a member of the Medicines in Europe Forum.
Amalyste receives no funding from the government or the pharmaceutical industry" (ref 1).

The 10 key measures proposed by Amalyste (excerpts)

The following are extensive excerpts from the 10 proposals made by the Amalyste patient group (1).

"**1 - Risk awareness.** The frequency and management of serious adverse drug reactions and their impact on society must be considered a national priority (...); the following measures must be implemented:
- an information and awareness campaign for healthcare professionals to improve the diagnosis of adverse reactions to healthcare products and to make prescribing safer;
- a national public information campaign on drug-related risks;
- a national "serious adverse drug reaction action plan" to fund research into these illnesses and to provide management for victims in specialised centres;
- a delegation to inform the French parliament, with participation by the different stakeholders and experts, is needed to challenge the concept of the "risk-benefit ratio", from the scientific, ethical and legal points of view;
- the French Agency for Shared Healthcare Information Systems (*Agence des systèmes d'informations partagées de santé, ASIP*) should make concrete proposals to integrate data relevant to epidemiological monitoring of the harmful effects of drugs in health databases and individual medical records.

2 - Risk governance. Decisions on whether or not a risk is acceptable cannot be left solely to experts and drug companies, [but] (...) should include all stakeholders, including victims' organisations. Stakeholders' independence must be guaranteed through equitable funding (...).

3 - Stakeholders' roles – a fairer balance. The French drug regulatory agency must refocus on its overriding priority: vigi-lance and monitoring of the risks relating to healthcare products. This will entail reinforcing and safeguarding the activities of pharmacovigilance networks (see below), and creating a dedicated team to monitor epidemiological studies. (...)

4 - Risk assessment. Evaluation of a drug's risk-benefit balance must be based on a standardised methodology and an auditable, transparent process using measurable criteria. Criteria and indicators of risk acceptability must be based on "risk acceptance scenarios" that are also standardised. (...)

5 - Framework for risk acceptability. The decision to authorise a drug that may cause rare and serious accidents must be accompanied by the establishment of a pre-set threshold at which authorities are alerted (...); if this threshold is passed (occurrence of the risk), it will trigger an immediate reassessment of the drug's risk-benefit balance. (...)

6 - Pharmacovigilance. Reporting of harmful effects to pharmacovigilance networks, and maintaining their visibility, must be reinforced, simplified and safeguarded:
- reporting of serious adverse events must become mandatory, under the threat of sanctions (...);
- anonymised raw data in pharmacovigilance databases should be made publicly available, online;
- reporting of harmful effects to pharmacovigilance networks must be systematically followed by epidemiological studies of all implicated medications.

7 - Recognition of responsibility. The probable drug-related nature of a serious accident must be validated by a committee of experts, independent of the public authorities and the pharmaceutical industry, who are known for their expertise in matters relating to serious adverse effects. (...) The victim should receive the benefit of the doubt. (...)

8 - Responsibilities. Marketing authorisation of a drug that might cause serious injury will be contingent on:
- notification of the level of risk by the manufacturer, clearly visible in the patient leaflet (...) ("black box");
- contribution by the manufacturer to a "compensation fund for serious drug-related risks", the level of which will be based mainly on the "risk acceptance scenario" (see note above) (...).

9 - Risk management. The compensation fund for serious drug-related risks will cover:
- fair compensation for victims (advance payments may be made when the injuries take several years to stabilise);
- registries for "the most frequent" serious adverse drug reactions;
- medical care for victims (hospitalisation, treatment, disability, etc.);
- funding of research on the mechanisms of serious adverse drug reactions, and on appropriate treatment of both the acute phase and sequelae;
- funding of epidemiological studies on risk monitoring for suspected drugs;
- assessment of the cost of the risk, based on the individual "risk acceptance scenario" (see note above).

10 - French national health insurance system. A specific branch of the French national health insurance system should be created. It should be funded by the "compensation fund for serious drug-related risks" and will cover 100% of the true costs of medical care, social support and home care necessitated by adverse drug reactions, as well as disability benefits, and any other spending necessary to maintain the victim's autonomy" (1).

1- Amalyste "La gestion du risque médicamenteux grave". www.amalyste.fr accessed 8 February 2012: 7 pages.

► a risk. This is not the same as the risk-benefit balance at the individual level. A positive "collective" risk-benefit balance implies that the majority of the community may benefit at the expense of a minority, who must bear a sometimes disproportionate burden of harm at the individual level.

How, then, can the use of this concept be interpreted, other than as a vindication by the State of the choice to sacrifice a minority in order to preserve the well-being of the majority? As the entire community, with the legislator's approval, may benefit by receiving a given medication, is it reasonable to leave a small number of victims to shoulder alone the burden of risk? How then to compensate for this implicit rupture of the social contract created by this disparity, at the individual level, between the benefits provided to some and the risks suffered by others?

The legal consequences of the ethical implications of this concept remain to be established.

Towards fair compensation

While liability for "breach of equality of public burdens" was recognized during the 20th century, victims of drug-related accidents are still not covered, at the dawn of the 21st century, by a dedicated management procedure.

Theoretically, this responsibility is incurred whenever a private individual suffers an "abnormal" (serious) and "special" harm, resulting from a situation or measure by which some members of the

community are "sacrificed" for the public good.

National compensation. In the case of serious adverse drug reactions, it is high time this responsibility translated into an obligation for compensation.

It should also be pointed out that victims of serious adverse drug reactions cannot obtain compensation through the courts if the adverse effect in question was mentioned in the patient leaflet, even if the risk is not fully understood (how many people are aware of the severity of Lyell or Stevens-Johnson syndromes?). In practice, for patients who experienced serious adverse drug reactions before 2001 in France, this means a lack of compensation.

Conclusion

Drug therapy currently resembles a gigantic game of Russian roulette. The "risk-benefit ratio" – the concept on which the current system is based – creates a situation in which society and drug companies reap most of the benefit while leaving a handful of victims to shoulder the risks.

How can this situation be remedied? Regulatory authorities must create a level playing field in which the community fully assumes its responsibility for the consequences of marketing a high-risk drug. This implies acknowledgement of the existence of the risk; an obligation to provide the means necessary to reduce drug-related illness (means compatible with the importance of the public health implications); an obligation to conduct research on adverse reactions to high-risk drugs; and proper management of the consequences when harmful effects occur, including financial compensation. These measures are the minimum that one is entitled to expect from a responsible state.

We, an association of victims of very serious drug-related accidents, are determined to participate in this debate. We recommend a fundamental re-working of the notion of the "risk-benefit ratio" and propose principles and actions necessary for radical reform of the management of drug-related harms."(1)

1- Amalyste "La gestion du risque médicamenteux grave". www.amalyste.fr accessed 8 February 2012: 7 pages.

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Medical devices: marketing authorisations are needed

The Mediator° disaster highlighted the weaknesses in health authorities' regulation of the pharmaceutical market. The Poly Implant Prothese (PIP) breast implant scandal shows that the situation is even worse for medical devices.

Inadequate regulation. Under European regulations, supervision of the medical devices market is largely outsourced to various "notified bodies" that are supposed to audit medical device manufacturers, rather than assigning responsibility to health authorities (1,2). There is no need to obtain Marketing Authorisation (MA) or to demonstrate a favourable harm-benefit balance in clinical use: the product has only to meet the technical specifications to obtain CE marking (1).

The European Commission too susceptible to industry influence. In 2008, following a public consultation it organised on the legislation of medical devices, the European Commission reported "*the rejection of a larger role for European Medicines Agency by the vast majority of respondents, (…)* [fearing] *the adoption of a pharmaceuticals-like regulation for medical devices, (…)* [leading] *to undue delays and higher costs for placing new devices on the market, which (…) would have an adverse effect on small- and medium-sized enterprises, which make up around 80% of the sector"* (3).

The Commission did not take into account the fact that most of the "respondents" to the consultation had conflicts of interest, i.e. medical device manufacturers and other interested parties, who were defending their commercial interests. Of the 200 respondents, 92 were from the medical device industry, 18 were notified bodies that grant the CE mark, and 7 were experts and consultants, while only 33 organisations represented healthcare professionals and 8 represented patients (**a**)(3).

Business versus patients' interests. The Commission concluded that if Marketing Authorisation were required for medical devices, it would not improve public health, but would be detrimental to competition and innovation in the industry, *"and thus ultimately be against patients' interests"* (3). The Commission has chosen sides: industry comes first, not patients.

In reaction to the PIP breast implant scandal, the European Commission tried to reassure the public by announcing *"tighter measures aimed at tracing medical devices"* (4). Traceability is certainly necessary in dealing with the harm caused by dangerous devices. But it is far more important to prevent harm, by assessing the harm-benefit balance of medical devices before considering their introduction to the market, beginning with those that pose the greatest risk.

a- *The Medicines in Europe Forum and other representatives of civil society responded to this consultation by calling for tighter regulation of medical devices, and above all for marketing authorisation to be obtained before market launch (ref 5).*

Selected references from Prescrire's literature search.

1- Prescrire Réaction "Distinguer les médicaments des autres produits d'apparence médicamenteuse" *Rev Prescrire* 2011; **31** (334): 572-576.
2- Prescrire Rédaction "Conflits d'intérêts: les dispositifs médicaux aussi" *Rev Prescrire* 2012; **32** (339): 69.
3- European Commission "Recast of the medical devices directives - Summary of responses to the public consultation" 5 December 2008. ec.europa.eu accessed 11 January 2012: 15 pages.
4- "EU evaluates danger, number of faulty breast implants. www.euractiv.fr accessed 11 January 2012: 2 pages.
5- EAHP, HAI Europe, ISDB, Medicines in Europe Forum "Recast of the European Medical Devices Directives: an opportunity to reinforce patient safety: 4 pages. english.prescrire.org/en/79/207/46302/364/355/SubReportDetails.aspx.