The new Medicinal Products and Health Products Safety Reform Act in France: Reform or storm?

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Abstract
Following the Mediator drug scandal (see Box) and the consequent damage done to the regulatory processes in France, the Law n° 2011-2012 of 29 December 2011 – to strengthen the safety of medicinal product and health products, sponsored by the French Ministry of Labour, Employment and Health – has been enacted by the National Assembly in order to restore public confidence and enhance the safety of medicinal and health products. All stakeholders and healthcare professionals will be affected by the law, as it will impact virtually all stages in the life of a medicinal product, and particularly the marketing authorisation (MA), reimbursement, advertising, promotion, distribution, prescription, dispensing, safety monitoring and off-label use. It also gives the director-general of the new French agency, the National Agency for Medicine Safety (ANSM), the power to impose financial, administrative and criminal penalties intended as deterrents. This new law introduces a revolution in the public health landscape and the behaviour and mentality of all involved, with a currently unpredictable end result.

The new safety reform act

Mediator® was discontinued in France in 2009 after more than 30 years of marketing in France, following an estimated 500 to 2,000 deaths from valvular heart disease, thought largely to be due to off-label prescribing as an anorectic. The subsequent scandal and the reports that followed in 2011 pointed to weaknesses in the French health system, which caused the resignation of the director-general and the director of pharmacovigilance of Afssaps, the previous drug regulatory authority. The Minister of Labor, Employment, and Health proposed a new law to strengthen the control of medicinal products and health products in order to restore public confidence. The so-called Bertrand law, named after the Minister, was adopted on 29 December 2011. Key issues and components of this reform are presented below.

There are seven objectives of the reform:

- To ensure greater transparency of expert advisors' interests
- To optimise the governance of agencies involved in the regulation of medicinal products
- To redefine the conditions for granting an MA
- To better inform prescribers
- To strengthen surveillance
- To improve quality information to the public
- To strengthen the regulatory framework for medical devices (MD).

To achieve these objectives, the reform is based on three pillars: transparency of professional interests and prevention of such conflicts; the benefit of any doubt must always be in favour of the patient; the strengthening of information to patients and healthcare professionals.

Transparency of the industrial interests of experts

The French government considered the existing rules covering potential conflicts of interest to be inadequate. Accordingly, provisions have been established to ensure that links between scientific expert advisers and industry are transparent and any benefits are declared – criminal penalties can also be imposed for non-compliance. Today, any expert serving on a committee must make a declaration of public interest ("Déclaration Publique d'Intérêt", DIP), indicating any direct or indirect ties the individual may have had during the previous five years with companies, institutions or organisations involved in the same sectors. The proceedings of such committees will be recorded and may be made public. A charter of health expertise, approved by decree, will oversee the implementation of all the expertise and define the notion of links of interest.

Inspired by the US Sunshine Act, the lawmakers require any company producing or marketing products or providing healthcare services associated with these products to make public the existence of agreements or benefits (in cash or in kind) granted to any healthcare professional and, especially, associations, students, media companies, advisory associations and consultancies in the field. A decree will be issued before 1 August 2012 with retroactive effect from 1 January 2011.

Any company that knowingly fails to make such statements will be punished by a fine of €45,000; additional penalties are provided for individuals or legal entities. The law also significantly changes and extends the rules governing gifts, especially by including students and associations of healthcare professionals.

Regulation of healthcare products

The French regulatory agency ANSM has replaced Afssaps. The new agency now has the authority to administer fines which may be subject to additional daily fines as provided by law and by decree. Violations subject to penalties include, in particular:

- The lack of implementation of the pharmacovigilance system
- The lack of reporting of adverse events
- The absence of periodic safety update reporting
- Failure to disclose the results of clinical studies within required deadlines after the MA has been granted
- Failure to disclose the cessation of marketing of a product
- Advertising of a medicinal product subject to a Temporary Use Authorisation (TUA)
- The dissemination of advertising for a medical device in violation of applicable rules.

The amounts of the fines and penalties are proportionate to the seriousness of the deficiencies identified. The maximum fine is 10% of sales up to a limit of €1 million, with the addition of a further maximum penalty of up to €2,500 per day. Penal sanctions against persons or entities, where applicable, are extra. These provisions are effective as of 21 July 2012.

Requirements for medicinal products

- Marketing authorisation

  Post-marketing studies. The director-general of the ANSM may request the marketing authorisation holder (MAH), at the time of grant of the MA or at any time thereafter, to conduct post-marketing safety and effectiveness studies.

  Suspension or withdrawal of an MA. The measures relating to pharmacovigilance in Directive 2010/84/EU of 15 December 2010 have been transposed into French law. An MA can be suspended, revoked or modified for the following reasons:
  - The product is harmful
  - The drug does not produce therapeutic results
  - The relationship between benefits and risks is not favorable
  - The product does not have the quality or quantity of ingredients as registered
  - The MAH fails to meet its obligations related to post-MA studies and pharmacovigilance.

  However, the measures in the new law have been extended to allow the suspension or withdrawal of an MA even if adverse event(s) result from failure by the patient to follow the recommendations for use.
- Reimbursement

  Any reimbursement is now dependent on completion of clinical trials versus other therapeutic strategies, where they exist, for the same pathology. This provision will apply to applications filed on or after 1 January 2012.
- Off-label prescriptions

  The conditions where a product may be prescribed for off-label use are now explicitly specified in the new law. The prescription of a pharmaceutical, outside the scope of its MA, is permitted in the absence of an appropriate alternative medication already approved or benefitting from a temporary use authorisation (TUA), where (a) this prescription complies with a temporary use recommendation ("Recommandation Temporaire d'Utilisation", RTU) issued by the ANSM for a maximum of three years, or (b) the prescriber considers it essential, based on the available science, to use the specialty to improve or stabilise the patient's clinical condition. The prescriber informs the patient that the prescription of the medicinal product does not comply with its MA, that there is a lack of appropriate alternative medication, and of the risks, constraints and benefits which may be provided by the drug. The prescription must include the statement: "Prescription not authorised."
- Prescription by International Nonproprietary Name (INN)

  Prescriptions for a medicinal product should now mention its active substance(s), referred to by their INN as recommended by the World Health Organisation (WHO) or, failing that, their name in the European or French Pharmacopoeia. In the absence of such names, their common name(s) or trade name can be used. An MAH or marketing company is given one year from the grant of the MA to make publicly available on its website the name of the active substance(s) of the medicine according to its INN or failing that, the name(s) in the European or French Pharmacopoeia.
- Dispensing

Background to the Mediator case

Mediator® (benfluorex), an amphetamine derivative, is structurally related to, and gives rise to the same active metabolite, norfenfluramine, as both fenfluramine and dexfenfluramine, drugs implicated in the US Fen-Phen scandal of 1997. All three drugs were developed by Servier, a French privately-owned pharmaceutical company and the second largest French pharmaceutical company worldwide. Mediator, an anorectic and hypolipidemic agent, was launched in 1976 and marketed in France as an adjuvant treatment for hypertriglyceridemia in diabetic patients, but was also widely used off-label as an appetite suppressant. The drug was approved in the EU via mutual recognition or national registration procedures, and in Africa and Asia, but never sought authorisation in the US. Following cases of cardiovascular complications, Spanish and Italian regulators raised concerns in 2003 and Servier withdrew the product in these markets by not renewing its marketing authorisations. Following a head-to-head trial versus pioglitasone at the request of regulators, safety data showed that benfluorex treatment was associated with valvular anomalies, and these results together with data from other studies led the French regulatory, Afssaps, to suspend the drug in November 2009, and the EMA to fully withdraw it in July 2010. A report on the affair, published in early 2011 by the French government's General Inspectorate of Social Affairs (IGAS), accused Servier of misleading the authorities about the true nature of Mediator. The report highlighted "aggressive marketing" tactics by Servier, overly complex bureaucracy within Afssaps, fear of litigation, and unhealthy ties between industry and the regulators. The French Health Minister, Xavier Bertrand, while stating that Servier was the prime culprit, conceded that there were also "serious malfunctions" in the drug regulatory system.

The new law gives the director-general of the ANSM the power to prohibit, in the interests of public health, the prescribing and dispensing of a pharmaceutical specialty and may withdraw it from the market under conditions determined by decree and especially for any of the following reasons:
- The product is harmful
- The drug does not produce therapeutic results
- The ratio between the benefits and risks is not favorable
- The drug does not have the qualitative and quantitative composition stated
- Appropriate controls on the medication or the ingredients and intermediates of the manufacturing process have not been conducted, or other requirements or obligations relating to the granting of the MA have not been respected.

The decision is to be made public without delay, at the expense of the MAH.

- Temporary use authorisation

  The new law now states that a TUA for an individual patient shall not be granted for the indication sought, unless (a) a cohort TUA application or an MA is pending, or (b) clinical trials of the drug in the indication in question are being carried out on French territory or a clinical trial application has been filed, or (c) the owner of the marketing rights promises to file, within a time specified by the agency, an MA or cohort TUA application. However there are exceptions.

- Pharmacovigilance
  As noted above, the French lawmakers have implemented in the new law the transposition of Directive 2010/84/EU regarding pharmacovigilance. Physicians, dentists, midwives and pharmacists are required to report any adverse event suspected to be due to a drug or product, while other healthcare professionals, patients and recognised associations' patients have the opportunity, but not the obligation, to report such adverse events. Measures are also established to protect individuals who report such events from harassment or litigation.
  With the aim of more effectively identifying medicinal product risks, the new law proposes the creation of a group ("Groupement d'Interêt Public", GIP) to be responsible for, and facilitate, the retrieval of healthcare data from the national health system and health insurance schemes (while respecting both patient/physician confidentiality and personal data protection), and with the authority to conduct pharmacovigilance and epidemiology studies.
- Information and advertising relating to medicinal products
  Advertising. In France, control of professional advertisements for medicines was traditionally made *a posteriori* by Afssaps (within eight days of the advertisement's appearance). Now, control is made *a priori* by the agency and the dissemination of advertising is subject to agency approval. The director will determine the ANSM time-windows during which industry must make its filings.
  Visits by medical sales representatives. The new law provides an experimental basis, for a period not exceeding two years, during which visits made by medical sales representatives to healthcare establishments must take place in front of two or more healthcare professionals. Drugs reserved for hospital use, as well as those subject to hospital prescription – initial or not – and medical devices, escape this obligation. Before 1 January 2013, the French government will present to Parliament a report taking stock of this experiment based on an evaluation conducted by the HAS ("Haute Autorité de Santé" – an agency which is similar in respect of some of its activities to the UK's National Institute for Health and Clinical Excellence (NICE).
  Moreover, the Economic Committee for Health Products, Comité Economique des Produits de Santé (CEPS), may set annual targets for medical visits for some pharmaco-therapeutic classes or for certain products. In addition, CEPS may impose financial penalties against any company that does not respect the Committee's decisions. The amount of the penalty may not exceed 10% of annual turnover in France. The mode of application of these provisions is defined by decree.
  Products' proper use commitment. Every company that markets a medicinal product has an obligation to contribute to its proper use, in particular ensuring that the specialty is used in compliance with its MA. The ANSM may impose administrative or financial penalties on any company that violates this obligation, where no agreement between the CEPS and the company has been concluded for the management of off-label prescriptions.
  Intellectual property. The holder of an intellectual property right protecting the appearance and texture of oral dosage forms of a specialty reference can now prohibit oral dosage forms of an equivalent generic from having an identical or similar appearance and texture.

Requirements for medical devices

- Advertising
  Advertising of medical devices was previously governed by common law, and advertising to the public for a reimbursed medical device was permitted provided there was no claim related to reimbursement. The new Law now requires compliance with the applicable essential requirements listed in appendix I of the Medical Device Directive. Advertising to the public is forbidden for reimbursed medical devices except for medical devices which present a low risk to human health (such products are defined and listed by government order, based on advice from the HAS).
  Advertising of reimbursed medical devices to healthcare professionals is authorized and not controlled *a priori*, except "for medical devices presenting a major risk" (again such products are defined and listed by government order) which are required to be controlled *a priori*. In cases of contravention of the law, the ANSM can apply administrative and criminal penalties.
- Compliance of medical devices with reimbursable list specifications
  Reimbursed medical devices are listed on an inventory of reimbursable products and services ("Liste des Produits et Prestations Remboursables", LPPR) either under the brand name (after submitting an application to both the "Commission d'Evaluation des Dispositifs Médicaux et des Technologies de Santé" (CNEDiMTS) of HAS and CEPS) or under a "generic description" (homogeneous group of medical devices with the same intended use *and* common described technical specifications). Any product listed under a generic description is covered by health insurance. The new law therefore provides for a control of conformity of products listed on the LPPR within a "generic description". Financial penalties are issued by CEPS for non-compliance with the technical specifications up to a maximum of 10% of turnover excluding tax.
- Assessment of medical devices within homogeneous patient groups (GHS)
  Prior to the new law, medical devices not listed on the LPPR were sold to, and used in, healthcare establishments without assessment by the CNEDiMTS (HAS). They were purchased on the basis of their CE mark alone. The costs of such devices (referred to as "intra-GHS") were included in the "daily cost" of treatment determined by the type of pathology, and were reimbursed to the healthcare establishment by social insurance.
  The absence of proper assessment was considered to be both a potential medical risk for patients and an economical risk for healthcare establishments, and so, under the new law, all such devices must be assessed by the HAS both for efficacy and cost-effectiveness, and will be placed on an "approved" list. Healthcare establishments purchasing off-list could be subject to a financial penalty from the Regional Health Agency.

Conclusion

In France, every crisis generates reform. These new provisions strengthen the constraints imposed on industry and give the competent authority new controls with, in particular, the possibility of strong sanctions that are intended as a deterrent. However, some legal experts have wondered about the constitutionality of the measures taken, and the compliance with European law of some of the measures (trademarks and patents law, compliance with the community code, etc). If the battle for public opinion seems to have been won by the instigators of the reform, the legal battle is likely just beginning. The reform could turn into a storm!