

Translated from *Rev Prescrire* July-August 2004; 24 (252): 481.



Medicines in Europe: the most important changes in the new legislation

As we digest the results of the European elections and the last-minute agreement on the European Constitution, the drafting process of the new legislative framework on medicines for human use reminds us once again that European citizens' voices can and must be heard.

For more than two years the pharmaceutical majors and their lobbyists took it for granted that they could obtain made-to-measure legislation supporting their own narrow financial

But we must not drop our guard: patients, health professionals, consumers, health insurers and concerned politicians still have to ensure that the "competent authorities" fulfil their new obligations and make the pharmaceutical industry respect the legal framework that European society has chosen for it.

"Europe" is not some distant land, but is at the heart of many of the most important decisions that shape our society. And Europe is neither

É D I T É O R I A L

Action bears fruit

interests, with scant regard for public health or for the economic survival of national health care systems.

What they failed to realise was that European citizens from all quarters, including this *Journal*, its subscribers, the "Association Mieux Prescrire" and the diverse member organisations of the Medicines in Europe Forum would come together to scrutinise the draft texts, explain the stakes, sound the alarm, make counter-proposals, meet with European deputies, and lobby ministers.

What we achieved together was a major change of perspective: in the end, European legislators endorsed the view that medicines are not just another consumer good. The drafts underwent major improvements, not least ensuring greater transparency on the part of medicines agencies.

inaccessible nor incomprehensible: we just have to roll up our sleeves and make sure that special interest groups are not given a free hand. Finally, Europe is not "too technical": each new dossier implies important choices for society.

Europe was founded on the notions of free trade and free circulation, and was bolstered by the successful introduction of a single currency. In future, "Europe" will be increasingly synonymous with welfare and public services, chief among which is health care. Many battles remain, given the inevitable clashes between major financial interests and basic human health needs?

We offer our congratulations to all those who contributed to correcting the course of European legislation on medicinal products. And we stand shoulder to shoulder with all those defending accessible, high-quality health care.

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Translated from Rev Prescrire July-August 2004; 24 (252): 542-548.

Medicines in Europe: citizens' successes

- **The new European legislative framework for human medicines was published on 30 April 2004, after a procedure lasting more than two years.**

- **The stakes were high, as the new texts determine the level of guarantees offered to EU citizens on marketing authorisation, risk management and information on medicines.**

- **Patients, consumers, health professionals and health insurance organisations joined forces, notably within the Medicines in Europe Forum, to make their views heard and to act as a counterweight to the powerful pharmaceutical lobby.**

- **The citizens' lobby made several noteworthy gains, especially regarding medicines agencies' transparency. But pharmaceutical majors, with support from the European Commission's Enterprise Directorate-General, succeeded in ensuring that the notion of "added therapeutic value" will not be taken into account when considering whether or not to authorise new drugs, and that the "clinical data protection period" will be even longer than before.**

- **EU citizens must remain mobilised to ensure that the texts are effectively enacted in national legislation and are strictly applied in patients' best interests. We must also be on the lookout for the tricks that the drug companies will inevitably employ to preserve their financial interests.**

Medicines in Europe :

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European harmonisation on medicinal products started in the 1960s, with the founding Directive 65/65/EC. It continued over subsequent years, notably with the creation of the European Medicines Evaluation Agency in 1995 (1).

After multiple additions and amendments, two major texts, valid until 2003, set out the legislative framework for medicinal products: namely Directive 2001/83/EC, instituting the community code on medicines for human use (grouping together the provisions of previous Directives); and Regulation 2309/93, establishing community procedures and creating the European Medicines Evaluation Agency (2,3).

The European Commission, which initiates legislative changes, presented two drafts: one to replace the 2001 Directive, and one to replace the 1993 Regulation. The Enterprise Directorate-General of the European Commission is responsible for matters relating to medicinal products. Its overriding aims were to make the European pharmaceutical industry more competitive, and to ensure that the single European market continued to function after EU expansion on 1 May 2004. The draft texts placed too much stress on relaxing marketing authorisation procedures and permitting advertising, while largely overlooking public health concerns (1,4).

The European Commission had to revise its work. The two new texts were adopted through the co-decision procedure, involving the European Parliament and the Council of Ministers (a). This procedure took more than two years, from late 2001 to early 2004 (1,4-9).

At the first reading by the European Parliament, in 2002, deputies adopted many amendments intended to place the accent on public health, despite strong pressure from the industry lobby (6). Some European health ministers subsequently rejected a number of amendments they thought might undermine the funding of national medicines agencies or the financial interests of their countries' drug companies. Others rallied to defend patients' interest, but the determined European Commission continued to support the industrial sector (see select-

ed extracts on Prescrire website, www.prescrire.org). A joint position was finally adopted by the Council of Ministers on 3 June 2003 (8).

In late 2003, deputies and ministers again came under pressure, notably from the Enterprise Directorate-General and industry representatives, to complete their work before the new member states joined the Union. The last compromises, adopted on 17 December 2003, were reached after hasty negotiations.

As a result, the final Directive and Regulation, published in the *Official Journal* of the European Union on 30 April 2004 (10,11), differ substantially from the initial drafts. We list the most important changes affecting patients and health care professionals, comparing the new text with the previous wording, and pointing out the most negative proposals that were ultimately rejected (b).

Transparency of medicines agencies: unprecedented obligations

The main change concerns transparency obligations by medicines agencies, which was barely an issue in the previous texts.

National agencies: public access to the agendas and reports of meetings, and to assessment reports. The Directive now requires that "*member states shall ensure that the competent authority (i.e. the national medicines agency) makes publicly accessible its rules of procedure and those of its committees, agendas for its meetings and records of its meetings, accompanied by decisions taken, details of votes and explanations of votes, including minority opinions*" (D article 126b). It further stipulates that the competent authorities will make marketing authorisation "*publicly accessible*", "*without delay*", together with the assessment report and the underlying reason for their opinion provided separately for each indication (D articles 21-3 and 21-4).

The European agency: public access to all documents underlying decisions. In the 2004 Regulation, almost all the articles concerning deci-

sions made by the European Medicines Evaluation Agency and the documents underlying these decisions mention an obligation to make these documents available to the public (see below for details of each of the agency's core tasks). In addition, article 73 of the 2004 Regulation stipulates that European Regulation 1049/2001 on public access to documents held by European institutions now applies to the medicines agency. The agency is therefore required to create a "register (...) to make available all documents that are publicly accessible (...)", as is already the case for other institutions. These registers were created to make documents easily accessible, even when they are numerous and diverse. In addition, article 80 of the 2004 Regulation states that the agency's internal rules and procedures must be made available to the public, both at the agency's headquarters and via the Internet.

Penalties to be made public. According to article 84 of the 2004 Regulation, the European Commission "shall publish the names of the marketing authorisation holders (this applies only to the centralised procedure) (...), and the amounts of and reasons for the financial penalties imposed" when companies fail to follow the Regulation.



The Medicines in Europe Forum, among others, had demanded such measures. If citizens remain vigilant to ensure that these measures are fully and durably implemented, medicines agencies' notorious secrecy will be a thing of the past.

Medicines agencies' independence: minor progress

Currently, medicines agencies' main sources of funding are the fees paid directly to them by pharmaceutical firms, notably for evaluating marketing applications (12). As the experts who work for these agencies are also often involved in assessing drugs on companies' behalf, drug companies wield considerable influence over medicines agencies' decisions (13). The previous Directive did not even mention conflicts of interest, while an article of the previous Regulation only mentioned this problem in passing.

Public declaration of financial interests. The 2004 Directive requires member states to "ensure that members of

staff (...) responsible for granting marketing authorisation, rapporteurs and experts (...), have no financial or other interests in the pharmaceutical industry which could affect their impartiality. These persons shall make an annual declaration of their financial interests" (D article 126b).

The 2004 Regulation states that the financial interests of members of the management board, committee members, rapporteurs and European Medicines Evaluation Agency experts must be declared on a yearly basis. The same article requires that declarations be made at each meeting of "specific interests which could be considered prejudicial to their independence with respect to the items on the agenda. These declarations shall be made available to the public" (R article 63-2).

More public funding for pharmacovigilance. In addition, the Directive stipulates that "management of funds intended for activities connected with pharmacovigilance, the operation of communication networks and market surveillance shall be under the permanent control of the competent authorities in order to guarantee their independence" (D article 102a); this does not, unfortunately, mean that the funds will necessarily come from public sources.

The 2004 Regulation clarifies the funding of the pharmacovigilance activities of the European agency: these activities "shall receive adequate public funding commensurate with the tasks conferred" (i.e. from the community budget) (R article 67).

The publicly accessible European medicines database (c), the creation of which is provided for in the 2004 Regulation, must also be established, updated and managed by the agency, "independently of pharmaceutical companies" (R article 57-1-1).



These obligations may appear to represent the strict minimum. But at a time when drug companies are funding more and more public-sector activities, these obligations are a major victory for those seeking to ensure that medicines agencies are and remain independent.



Drug evaluation: lip-service to the notion of "added therapeutic value"

Previously, the only criteria that needed to be met before a drug could be marketed were pharmaceutical quality, efficacy and safety of use. Nothing has changed in this respect: no comparative clinical evaluation is required to determine whether a new drug offers a real therapeutic advance (added therapeutic value) relative to reference drug or non drug treatments.

The need for comparisons is finally quoted. The 2004 Regulation states that, on request of the Commission, the European Medicines Evaluation Agency will be required to "collect any available information on methods that Member States' competent authorities use to determine ►►

a- European ministers of industry could have been charged with the file (medicinal products being the responsibility of the Enterprise Directorate-General), but it was health ministers who actually participated in the co-decision process.

b- We specify each reference to articles of the new texts by either the letter D (for 2001 Directive, modified in 2004), or the letter R (for articles of the 2004 Regulation).

c- This will be a new database, with only basic contents: it will contain only the texts of patient leaflets, but will have the advantage of including, eventually, all drugs marketed in Europe, whether authorised through national procedures or the European centralised procedure.

Keep watch on this timetable

Directive 2004/27/EC, published on 30 April 2004 (1), makes a number of changes to the previous Directive (2001/83/EC). It will not be applicable in individual Member States until it has been transposed into national legislation, which must be done by 30 October 2005 at the latest (article 3). Regulation (EC) 726/2004, replacing Regulation 2309/93, applies immediately, without transposition, to all Member States. Nevertheless, some of its measures can be applied only when the 2004 Directive comes into effect (3).

Here are the application dates of the texts and their parts, and the corresponding measures:

- **20 May 2004:** immediate application of the part of the 2004 Regulation relating to the functioning of the European medicines agency;
- **20 November 2004:** the medicines agency's management board must rule on the application of European Regulation 1049/2001 (on public access to documents) to the agency;
- **30 October 2005:** actual transposition of the 2004 Directive into national legislation by all Member States. This covers all items dealing with the authorisation and monitoring of medicines at the national level;
- **20 November 2005:** application of the rest of the 2004 Regulation; in particular, the centralised marketing procedure will become obligatory for four new therapeutic classes;
- **20 May 2008:** the centralised marketing procedure will become obligatory for two further therapeutic classes;
- **No later than 2014:** the European Commission must publish a general report on experience accumulated with the application of the new procedures.

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1- "Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use" *Official Journal of the European Community* 30 April 2004: L 136/34-L 136/57.

2- "Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency" *Official Journal of the European Community* 30 April 2004: L 136/1-L 136/33.

3- The European agency for the evaluation of medicinal products "Press release - New pharmaceutical legislation enters into force on 20 May 2004" London 3 May 2004: 2 pages.

► *the added therapeutic value that any new medicinal products provide*" (R article 60). The end-use of this information is not stated, but the existence of this measure acknowledges that Member States are obliged to compensate for the insufficiencies of marketing authorisation, by sorting out the new drugs.

The concept of added therapeutic value also appears in an article of the 2004 Directive concerning data protection (D article 10-1), and in the corresponding article of the Regulation: the extra year of data protection will be granted for "one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies" (R article 14-11).



Thus, the comparison of new drugs with available reference treatments, long demanded by patient groups and health care professionals but rejected by pharmaceutical firms, finally appears in the European regulation on medicinal products. This comparison is not obligatory prior to marketing application, but at least a small step has been made in the right direction.

Ethical clinical trials, wherever they are done. The conduct of clinical trials is not dealt with in the 2004 Directive or Regulation. Other specific texts focus on clinical trials, notably Directive 2001/20/EC on good clinical trials practice. Nevertheless, an important document has now been added to the list that applicants must provide (for both national procedures and the European centralised procedure), namely "a statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC" (D article 8-i-b, R article 6-1).

Thus, the principles of Directive 2001/20/EC (which has still not been transposed into French law) must be followed, with respect to the protection of participants, ethics committee and adverse event reports, even when a drug intended for the European market is tested outside the EU.

Marketing authorisation: the worst-case scenario avoided

Up to now, the centralised European marketing authorisation procedure was

obligatory only for biotech drugs. National procedures were commonly used, followed increasingly by mutual recognition among Member States — a loosely regulated and highly secretive procedure (4). Agencies had 210 days to examine marketing applications, and marketing authorisation had to be renewed every five years for a drug to remain on the market. All these points have been extensively modified.

European centralised procedure: obligatory for other types of substances. The field of application of the centralised procedure has been extended. This application procedure is based on an assessment of marketing applications by the European Committee for Medicinal Products for Human Use (CHMP, previously CPMP), rather than by a national agency. From 20 November 2005, in addition to biotech drugs, it will also be obligatory for all new drug substances intended for use in AIDS, cancer, neurodegenerative disorders and diabetes, and also to orphan drugs (d). And as of 20 May 2008, it will also become obligatory for drugs intended to treat autoimmune diseases and other immunological disorders, and for antiviral drugs (R article 3-1 and annex).



Despite pressure in favour of the mutual recognition procedure, which companies consider more "flexible" and agencies consider more lucrative (at least the agencies of the "reference Member States"), the centralised procedure is gradually gaining ground. This had been another demand of the Medicines in Europe Forum.

National procedures: a little less secretive. Companies can still choose the national marketing authorisation procedure or the mutual recognition procedure for all other medicines. But the coordinating group responsible for examining questions relating to the mutual recognition procedure now has a legal framework: the 2004 Directive defines the group and its composition, and stipulates that its rules of procedures must be made public (D article 27). In the 2004 Regulation, the opinion of the CHMP will be requested "whenever there is disagreement in the evaluation of medicinal products through the mutual recognition procedure". This practice already existed, in principle, but the 2004 Regulation states "the opinion of the Committee shall be made publicly accessible" (R article 5-3).



Provided medicines agencies are forced to implement the new transparency demands (see above), this would permit more insight into exchanges between national agencies during mutual recognition of a national marketing authorisation.

Maintenance of the 210-day period for examining marketing applications. The 210-day period currently permitted for examining marketing applications will be kept for both the centralised procedure and national procedures (D article 17; R article 6-3). This is another victory for EU citizens, because companies were seeking a shorter period, and the European Commission had proposed just 150 days for national procedures.

For the centralised procedure, the 2004 Regulation provides for a shorter period of 150 days, but only if the drug is *"of major interest from the point of view of public health and in particular from the point of view of therapeutic innovation"* and if *"the request is duly substantiated"* (R article 14-9).

No less than 80 days for rapporteurs to analyse the scientific data. The 2004 Regulation guarantees, in the centralised procedure, that CHMP rapporteurs will have the time necessary to do their work thoroughly: *"the duration of the analysis of the scientific data in the file (...) (within the overall 150- or 210-day period) must be at least 80 days, except in cases where the rapporteur and co-rapporteur declare that they have completed their work before that time"* (R article 6-3).

In case of arbitration during the mutual recognition procedure, the CHMP will have up to 80 days to give its opinion (D article 32-1).



Despite drug companies' lobbying to have their products authorised more rapidly, only the time allowed for certain administrative tasks has been shortened. In principle, the scientific assessment should not be botched because of unreasonably tight deadlines.

Information to be provided on withdrawals of marketing applications and refusals of European centralised marketing authorisation. Until now, withdrawals of marketing application often went unnoticed. Now, for drugs following the centralised procedure, firms must inform the European agency of their reasons for

withdrawing their application, and the agency must make this information available to the public (R article 11).

Similarly, if centralised European marketing authorisation is refused, the agency must make the underlying reasons available to the public (R article 12-3).

Public release of conditions placed on marketing authorisation. Now, when marketing authorisation is granted with conditions (such as further clinical trials, or specific pharmacovigilance studies), the relevant agency (national or European, depending on the procedure) must make them public, together with the deadlines. Continued marketing authorisation will be subject to a yearly assessment of whether these conditions have been met (D article 22; R article 14-7).

Publication of centralised marketing authorisations in the *Official Journal* of the European Union must now, according to the 2004 Regulation, mention the international non proprietary name (INN) of the active substance (R article 13-2). This was not previously mandatory.

No "permanent" marketing authorisation: obligatory reassessment after 5 years. One constraint that companies would have liked to see removed was the five-year renewal of marketing authorisation. This was often a simple administrative formality, but could also offer an opportunity to re-assess the evidence. The Commission had recommended that marketing authorisation be granted for an unlimited period. However, the 2004 Directive and Regulation stipulate that *"marketing authorisation shall be valid for five years"*, and *"may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the competent authority"* (D article 24-2; R articles 14-1 and 14-2). The new texts also provide for a second reassessment: *"once renewed, the marketing authorisation shall be valid for a unlimited period, unless the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal (...)"* (D article 24-3; R article 14-3).



This 5-year reassessment of the risk-benefit balance has a strategic importance. Vigilance will be required to ensure that medicines agencies do not make it a simple administrative formality, but, on the contrary, take consideration of all available data.

Drug access prior to marketing authorisation: "compassionate use" now officially recognised. An article of the 2004 Regulation introduces a new concept: that of "compassionate use". It authorises access to drugs that are under review by the centralised authorisation procedure or undergoing clinical evaluation for *"patients with a chronically or seriously debilitating disease, or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product"* (R article 83-2).

The CHMP opinion on these exceptional cases must be made public (R article 83-6). Continuous access to medicinal products must be ensured between the moment when marketing authorisation is granted and the drug is effectively marketed, in order to avoid treatment interruption (R article 83-8).



This is a first, in Europe, for patients who have no effective therapeutic alternatives, and is similar to the French system of "temporary licence" (14). But the relevant text does not cover drugs following national marketing authorisation procedures, and does not satisfy all patient associations' demands. For example, it does not stipulate who can initiate the request for compassionate use programmes, or who will pay for them.

Better labelling and patient information leaflets

Drug labelling was already regulated, but mainly with the aim of protecting companies and medicines agencies when adverse effects occurred. European deputies proposed a number of amendments intended to make drug labelling more informative for patients. Some of these amendments were adopted, despite pressure by some quarters.

Greater use of the INN, and inscriptions in Braille. The outer pack and primary packaging (bottle, blister, etc.) must now mention the international non proprietary name (INN) *"where the product contains up to three active substances"* (D article 54-a), instead of only one previously. Fixed-dose combinations should be easier to identify, even if ►►

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d- In Europe, a medicine can have orphan drug status if it is indicated for a disorder that affects less than 5 per 10 000 EU inhabitants. See reference 22 for the Regulation specifically dealing with these drugs.

► the texts do not stipulate a minimum print size for the INN. The outer packaging will have to mention the INN, the dose strength, the pharmaceutical form and the trade name in Braille format (D article 56a).

Information leaflets to be tested by patient panels before marketing authorisation. The patient information leaflet “shall reflect the result of consultations (by the company) with target patient groups to ensure that it is legible, clear and easy to use” (D article 59-2), and “the results of assessments carried out in cooperation with target patient groups shall also be provided to the competent authority” when requesting a marketing authorisation (D article 61-1).



If patients and consumers are vigilant to ensure that the Directive is effectively applied, the information on the drugs they use will be simpler and clearer.

No direct-to-consumer advertising of prescription drugs

Although authorised in other countries, “direct to consumer advertising” (DTCA) is still forbidden in the European Union, despite pressure from drug companies and the European Commission, which had recommended authorising advertising for the public, disguised as information (5).

Strong opposition from deputies and most health ministers ensured that DTCA of prescription drugs remains forbidden in the EU. As before, this “prohibition shall not apply to vaccination campaigns carried out by industry and approved by the competent authorities of the Member States” (D article 88).

Beware “information” on some conditions. The Commission has been asked to prepare “a report on current practice with regard to information provision — particularly on the Internet — and its risks and benefits to patients” (D article 88a).

According to the same article of the 2004 Directive, the Commission will be able to make proposals defining a drug information policy.



It is noteworthy that the EU commissioner responsible for Health and Consumer Protection recently announced the development of a public-private partnership

for patient information on drugs at the general meeting of the European Federation of Pharmaceutical Industries (EFPIA)(15).

Pharmaceutical majors are already gradually expanding their public “information” campaigns on certain conditions. The most recent, on erectile dysfunction, cholesterol, depression, osteoporosis, obesity and mycosis, are highly instructive: companies are simply seeking to persuade as many people as possible that they have these disorders, and that they should ask their doctor for a prescription drug.

In practice, the regulation is increasingly bypassed.

Pharmacovigilance: still too secretive, and no extra power for patients

The 2004 Directive and Regulation do not fundamentally modify the current pharmacovigilance system, but more precisely define collaboration among Member States. Some advances have nonetheless been achieved.

Funding: a small dose of independence. The funds necessary for pharmacovigilance activities must be managed at the national level by the relevant authorities; at the European level, funding must come from the EU coffers (see above).

Few extra constraints on drug companies. Regarding the collection of data on adverse effects, few extra demands on drug companies have been made, even though the new texts are slightly more precise than before. Companies are still required to provide periodic reports on adverse effects — every six months during the first two years, every year for the next two years, then every three years (previously every five years). These reports (Periodic Safety Update Reports (PSUR)) must now “include a scientific evaluation (done by the company) of the risk-benefit balance of the medicinal product” (D article 104-6; R article 24-3).

Data collection: still no patient involvement. The recommendation that patients be encouraged to report suspected adverse effects directly was rejected, mainly because health ministers feared their agencies would be swamped by the extra workload. Yet the usefulness of such patient reports is now widely recognised (16).

Proposed amendments that called for boxes of new drugs to carry a statement meaning “newly authorised drug, please report any adverse effects” were fought by the Commission and were finally rejected.

Data analysis: sales figures too. Drug companies must now provide medicines agencies, on request, with “all data relating to the volume of sales (...) and volumes of prescription”, along with other information required to assess safety profiles (D article 23a; R article 23c).

Market withdrawal of products with negative risk-benefit balances.

The list of reasons for which a Member State may withdraw a drug from the market has been extended. The 2001 Directive mentioned the following reasons: wrong drug composition, harmfulness in normal conditions of use, and lack of therapeutic activity. To these has now been added “the risk-benefit balance is not favourable under the authorised conditions of use” (D article 117-1-c). This is better than the wording “an unacceptable level of risk” which was very nearly adopted.

Data distribution: minimal requirements. The new texts imply that the European drug surveillance network will continue to collect data, but that patients and health care professionals will have virtually no access to them.

The 2004 Regulation simply states that the European agency will make public CPMH’s opinions on necessary measures in case of pharmacovigilance problems (R article 22). The EU Commission’s proposals did not include even this small measure. Moreover, data on “serious adverse reactions and other pharmacovigilance data (...) shall be made publicly accessible, if relevant, after evaluation” (R article 26).



This latter wording is sufficiently vague to prevent public access to pharmacovigilance data. It is therefore unlikely that the field of pharmacovigilance will become transparent any time soon. But at least the authorities responsible for pharmacovigilance will no longer be able to use the lack of a regulatory framework as an excuse for inaction.



Industrial protectionism: a victory for drug companies

Drug companies employed all the means at their disposal to prolong the period during which their drugs are protected from generics (17). Prior to the 2004 Directive and Regulation, protection of clinical trial data lasted 6 years in about half the 15 Member States, and 10 years in the others (including France) (e,f)(18).

Delayed generic development. After two years of intense debate and infighting between the powerful pharmaceutical majors and the less powerful generics manufacturers, clinical trial data protection in Europe was harmonised towards a longer period. The period is now 8 years, but generics will not be able to be marketed for 10 years, whether the originator drug was authorised through the national or the centralised procedure (g) (D article 10-1; R article 14-11).

A bonus for new indications. A further year of data protection can be granted if a new indication is authorised during the first eight years, and if this indication offers "a significant clinical benefit in comparison with existing therapies" (D article 10-1; R article 14-11). It will be interesting to see how this applies in practice.

A further year of data protection can also be given to companies that are granted a new indication for an old, "well-established substance" (D article 10-5). This extra year may encourage companies to conduct further research on substances they had previously considered unprofitable. Article 10-5 of the Directive states that this work must include "significant pre-clinical or clinical studies".

A gift to self-medication industry. A far more debatable new measure is that an extra year of data protection can be granted to a firm for a prescription drug that is switched to over-the-counter (OTC) sale; this protection covers data from trials done specifically to support the switch (D article 74a). It generally concerns substances that have been in use for a long time, for which new trials are not necessary (19).

Protectionism aggravated by the invention of "biogenerics". The definitions of "generics" and "biogenerics" (the latter term was invented for the occasion) have been rendered sufficiently

vague and complex to make it more difficult for generics manufacturers to obtain marketing authorisation (D article 10-2, 3 and 4). In particular, it will be more difficult to avoid conducting new pre-clinical and clinical trials when the manufacturing process (especially when based on biotechnology) is only slightly different from that used for the originator product (20).



The money spent by pharmaceutical majors to influence deputies and ministers, and to spread malicious rumours on the potential risks of generic drugs, was well invested. Welfare organisations and mutual health insurers will soon feel the economic pinch.

Last but not least

It is impossible to describe in detail all the provisions of the 2004 Directive and Regulation (h), but here are some other noteworthy changes:

- When a drug is not actually marketed, its marketing authorisation becomes void after three years (D article 24-4; R article 14-4);
- Holders of marketing authorisation are required to ensure continuous availability of their products (no supply interruption) (D article 81), and must notify agencies of temporary or permanent market interruption at least two months in advance, except in exceptional circumstance (D article 23a; R article 13-4);
- Member States must create systems for collecting unused or expired drugs (D article 127b), but the relevant article does not state how these drugs are to be disposed of;
- Marketing application files must include information on the environmental impact of the products (D article 8-3), especially drugs containing genetically modified organisms (R article 6-2);
- The management board of the European Medicines Evaluation Agency will now include two representatives of patient organisations and one representative of physician organisations; neither group was represented in the past (R article 65) (i).

Transposition of the Directive into national legislation, and application of the Regulation



The pharmaceutical companies have won a major victory for protectionism, but advocates of patients' interests won many other battles.

The worst-case scenario has been avoided, as there will be no indefinite marketing authorisation; no reduction in the period allotted to assess marketing applications; no direct-to-consumer advertising of prescription drugs.

Major victories include unprecedented obligations placed on the European and national medicines agencies to be more transparent; the concept of added therapeutic value is now mentioned in several articles; information leaflets must be tested by relevant patient groups, and the results must be included in marketing applications; patient representatives will be present on the management board of the European Medicines Evaluation Agency.

The new European legislative framework for medicinal products is at the same time basically sound but fragile in parts. Sound, because it is based on the principles of the EU Treaty and Charter of fundamental rights, such as the public right to access official documents (21). Fragile, because it may not be ►►

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e- "Data protection" consists of prohibiting competitors from using clinical trial data on an originator drug for a number of years. This means that generics manufacturers cannot use such data in their applications (ref 18).

f- In France, data protection used to last 10 years, and not 15 years as stated by the Minister of Health in a television interview in May 2004. Patents last 20 years.

g- This means that a generics manufacturer can use the results of clinical trials conducted with an originator drug, at the end of the 8-year data protection period. It can thus obtain marketing authorisation, and prepare to market its generic, but actual market release can only take place another two years later. Originator drugs are now therefore protected for 10 (8 + 2) years.

The new Directive also allows the clinical trials necessary for marketing authorisation to be conducted before the patent or complementary protection certificate expires (equivalent to the "Bolar exception" in the United States) (D article 10-6). Such trials can now be conducted in the European Union, instead of outside as previously (ref 23).

h- A chapter of the 2004 Directive, not discussed here, is devoted to homeopathic drugs. Plant-based drugs are the subject of another Directive, also published on 30 April 2004, to which we will return later.

i- There are no representatives of pharmaceutical companies or health insurers on the board, despite recommendations to the contrary in several drafts of the Regulation.

► fully applied in practice: transposition of European directives into national legislation is often slow (particularly in France), and the law and regulation are often simply ignored.

It is up to patients, health care professionals, consumers, health insurers and responsible politicians to ensure that the "competent authorities" fulfil their new obligations, and that the pharmaceutical companies observe the legal framework.

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Annexe

Revealing extracts on our website www.prescrire.org

The EU co-decision process that resulted in the new Directive and Regulation on medicines lasted more than 2 years. Representatives of the European Commission, of ministers and other interested parties expressed their views at length: some of their statements are worth reading.