Reorienting European policy on medicines for human use

Medicines are not "just another industrial product." On the contrary, they must be a integral part of an efficient and transparent health policy that takes into account the rights and responsibilities of all the involved parties, namely patients, health care professionals, public authorities, and manufacturers, within the context of together financial limitations on public health spending.

On 23 October 2002, after the first reading of the draft Directive and Regulation on medicines for human use, the European Parliament voted to uphold patients' interests, strongly amending the drafts that had been almost exclusively industry-oriented. The Council of health ministers met on 3 June 2003 and also endorsed a series of amendments aimed at guaranteeing patients' interests (see at the end of this document). However, other important amendments, most of which were actively opposed by the European Commission (Enterprise Directorate-General), were not endorsed by the Council of ministers; others were left to one side, either for lack of time, or because they were considered "unimportant details" (see below).

Points that remain to be defended at the second reading

The second reading is the last opportunity to explain why some points are crucial, not only for patients and health care professionals, but also for EU member states' medicines policies and for the long-term health of the European pharmaceutical industry. This second reading must not be allowed to degenerate into a bartering session on measures aimed at preserving the short-term interests of the pharmaceutical industry. The EU Parliament and Council must endorse a sound legislative and regulatory framework, promoting the long-term interests of all the different parties, and allowing all EU citizens to rationally use the true therapeutic advances, in a well-informed and responsible manner.

To help EU members of Parliament and ministers understand the stakes involved, the Medicines in Europe Forum lists below the points that remain to be re-examined, and proposes one or several amendments for each, along with their justification.

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1. Functioning and transparency of medicines agencies

● **Representation of civil society (patients, consumers, health care professionals, organisations paying for medicines) on the Management Board of the European Medicines Evaluation Agency** (amendment 116, article 58-1 of the Regulation, voted by Parliament, endorsed by the Council during its preparatory work, then finally withdrawn).

New proposed amendment – article 58-1 of the Regulation (replaces): "The Management Board includes fifteen members designated by the Council, and endorsed by the European Parliament within a period of three months, and selected from a list established by the Commission that includes a larger number of candidates than the number of members to be appointed, and a representative of the Commission. Two of the selected members must be from industrial organisations (including a representative of generic drug manufacturers), one from a patient organisation, one from a health professionals' organisation, and one from a health insurance organisation. Members of the Management Board are designated in such as way as to guarantee a high level and broad range of expertise and, as far as possible, the widest possible geographic distribution within the Union."

Justification*: the European Parliament and Council of health ministers have endorsed the principle that the regulation on public access to EU documents be applied to the European Medicines Evaluation Agency. This will ensure that this key institution offers transparency to European citizens – a key guarantee of its proper functioning. The presence of citizens' representatives on the Agency's Management Board will offer a further guarantee of safe functioning, especially with regard to application of transparency rules.*

● **More public funding for the European Medicines Evaluation Agency (notably for the medicines database, and for regulatory tasks, and especially marketing authorisations)** (amendments 152 and 91 respectively, recital 17a and article 51-1-2-j of the Regulation, voted by Parliament but not endorsed by the Council).

New proposed amendment – recital 17a of the Regulation (new): "The Agency's budget must be composed of contributions from the community budget for implementing community policies, and of fees paid by the private sector. The Agency's key regulatory tasks, which contribute to health safety and consumer protection in the field of medicines, must be entirely covered by the community budget."

New proposed amendment – article 51-1-2-j of the Regulation (to be added): "(…) and ensure the maintenance of this database, independently of pharmaceutical companies, through funding from the community budget."

Justification*: the funding of medicines agencies, an issue currently being debated worldwide, is particularly important for the European Agency, which represents a large number of nation states. For example, a medicines database financed by the pharmaceutical industry (through fees paid by companies) would not allow medicines to be compared properly: what company would be willing for the public to see that its product is less well assessed and therefore lacks certain indications granted to its competitors, or that it has more numerous or more serious adverse effects?*

● **Public funding of national medicines agencies' pharmacovigilance activities, in the same way as for the European Agency** (amendment 117 – article 102a of the Directive voted by the Parliament, not endorsed by the Council).

New proposed amendment – article 102a of the Directive (new): "In order to guarantee that the relevant authorities remain totally independent, with a view to ensuring health safety and consumer protection, their activities relating to pharmacovigilance and market surveillance must receive public funding commensurate with their tasks."

Justification*: pharmacovigilance is an extremely sensitive area, as illustrated by the recent affairs surrounding cerivastatin, appetite suppressants, hepatitis B vaccination, COX 2-antiinflammatory drugs, etc. Identification of a new adverse effect can have major negative financial implications for the company concerned, and companies may therefore be tempted not to be entirely forthcoming in this area. Only public funding can give national agencies, as the European Agency, the necessary independence to calmly analyse pharmacovigilance data and to take any necessary measures. This is why the principle of public funding was adopted for the pharmacovigilance activities of the European Medicines Evaluation Agency, and why it is also required for national agencies.*

● **Participation of experts in the EMEA scientific committee evaluating marketing authorisations, and not only representatives of national agencies** (article 54-1-2 of the Regulation, but no specific amendment voted at the first reading).

New proposed amendment – article 54-1-2 of the Regulation (new): (…) "Each member must always be accompanied by an independent scientific expert, also appointed by the chief executive officer, each member state thus being represented by a scientific-administrative tandem. (…)"

Justification*: it is difficult for member state representatives to overlook national interests, whether administrative or industrial; and experience shows that it is nearly impossible for these representatives to oppose their national agency or a large pharmaceutical industry present in their country. These last years, failures in the assessment of new medicines, and in the analysis of suspected adverse effects of old medicines, have been brought to light by experts in the scientific committee evaluating marketing authorisations; these failures were due not only to weaknesses of expertise, but also to a lack of independence from individual member states or drug companies.*

● **Obligatory seizure of the EMEA scientific committee when member states come to diverging decisions on a given drug** (amendment 64 – article 30 of the Directive – voted by the Parliament, but not endorsed by the Council).

New proposed amendment – article 30 of the Directive (replaces): "When several marketing applications are put down for the same drug, in keeping with articles 8, 10 and 11, and member states take diverging positions on marketing authorisation, suspension or withdrawal, the differences that appear in the relevant summaries of product characteristics in the European database defined in article 51-1 of the Regulation (*add final number after adoption*) must be brought to the attention of the EMEA human medicines committee. The committee must give its opinion on these divergences, and this opinion must be made public immediately. If major divergences arise between member states' decisions, the procedure described in article 32 will apply."

***Justification**: with the existence of the single market, citizens are puzzled to see that some medicines do not have the same indications, the same dose regimens, the same regulatory status, the same information leaflet, etc., in the different member states. Market harmonisation must not only take place at the administrative level; it implies a thorough scientific analysis of data available in the different member states. If it is to be correctly understood, it must also take into account therapeutic habits in each member state. Many examples, in the fields of contraception, diabetology, cardiology, neuropsychiatry, etc., show the benefit of the opinions reached by the Committee and by the Agency's scientific working groups.*

2. Evaluation of medicinal products

● **Companies must be obliged to conduct at least one clinical trial comparing their new drug to the reference treatment; at the very least, medicines agencies must be obliged to state in their assessment reports whether or not the marketing application included comparative data on the possible added therapeutic value of the drug concerned** (amendments 136 and 29 – article 8-3-i of the Directive – voted by Parliament, but not endorsed by the Council) *(also see chapter 4: Patient Information).*

New proposed amendment — article 8-3-i of the Directive (to be added): "(…) at least one of these clinical trials must compare the new drug with the treatment considered the best option at the time the trial was designed."

***Justification**: many medicines are currently marketed without having been compared with the proper reference treatment. They are only compared with placebo, or with treatments other than the reference treatment, or with reference treatments administered at sub optimal doses, or, on the contrary, at excessive doses that are less well tolerated; or they are compared in populations that are not representative of the patient groups actually targeted by the new drug (patients of different age groups, patients at different disease stages, etc.). As a result, it is impossible to know whether the new drug is more effective and/or safer than the treatment considered optimal for the category of patients concerned. It is therefore impossible to know whether patients are likely to benefit from using the new drug, and whether this new drug warrants a high price or special data protection because of its added therapeutic value.*

● **A 90-day period must be explicitly guaranteed for scientific analysis of marketing applications by experts in medicines agencies** (amendment 175 – article 6-3-1 of the Regulation, and amendment 49 – article 17-1-1 of the Directive – voted by Parliament but not endorsed by the Council).

New proposed amendment – articles 6-3-1 and 13-6-2 of the Regulation and article 17-1-1 of the Directive (to be added): *(identical amendment in the two texts)* "(…) including 90 days for the analysis of the scientific data and for writing the assessment report, unless the rapporteur comes forward to say he/she has completed the report before the end of this period."

***Justification**: this point is not a simple "detail" as stated by the European Commission. The EMEA flow chart describing the different steps followed by a marketing application shows that, within the periods allocated for this process, experts designated as rapporteurs currently have about two months to analyse the scientific content (i.e. pharmaceutical data, animal pharmacology and toxicology data, clinical data, and statistical analyses). This is very short, given that these experts do not work full time, and have to conduct further search strategy for published and unpublished data on their own in order to gather data that the company has not provided (and that the Agency does not provide either). Indeed they receive only the application drawn up by the firm, which is necessarily selective and presents the drug in a favourable light. The corresponding periods allocated by national agencies are also very short, and this can be detrimental for the quality of the assessment. Recent examples, such as the superficial analysis of data on agalsidase by EMEA, clearly illustrate the fact that robust scientific analysis takes time.*

● **Obligation to conduct long-term clinical trials of medicines intended for long-term use (in chronic diseases, for prophylaxis, etc.)** (amendment 176 – article 8-3-i-4 of the Directive – voted by Parliament but not endorsed by the Council).

New proposed amendment – article 8-3-i-4 of the Directive (new): "(…) results of long-term trials appropriate for medicines intended for long-term use by patients."

***Justification**: a drug intended for the treatment of a chronic health disorder or for long-term prophylaxis (cardiovascular prevention, diabetes, asthma, inflammatory disorders, neurodegenerative diseases, contraception, schizophrenia, etc.) must be tested over a sufficiently long period to verify that efficacy persists, and that no unexpected adverse effects occur. Such trials remain rare, despite the increasing tendency to administer medicines for increasingly long periods in many areas, such as cardiovascular prevention, osteoporotic fracture prevention, or depression. In addition, current assessments often fail to show when and how a particular treatment can be stopped: for example, children treated with methylphenidate for attention deficit-hyperactivity disorder are reaching adulthood without clear data on the conditions in which their treatment can safely be withdrawn.*

● **Clinical trials conducted outside the European Union must observe good clinical practices and ethical requirements** (amendment 24 – article 6-1-1 of the Regulation, and amendment 32 – article 8-3-i-3 of the Directive, adopted by Parliament but not endorsed by the Council, whereas the corresponding recitals were adopted).

New proposed amendment – article 6-1-1 of the Regulation and article 8-3-i-3 of the Directive (to be added): *(amendment identical in the two texts)* "(…) The applicant must provide evidence that clinical trials of the drug in question were conducted in accordance with the criteria described in Directive 2001/20/EC. This general- ▶▶

► ly excludes clinical trials done in developing countries when the local population is not the first beneficiary of the drug in question."

Justification: *many trials are now done in developing countries, both for financial reasons, and because previously untreated patients are more abundant (e.g. AIDS), such patients being more likely to have a clear-cut reaction to the new medicine. Some of these trials have given rise to abuses, leading the World Medical Association to reinforce the Helsinki Declaration, which forms the basis for national legislation on clinical trials. It is no longer considered ethical to conduct clinical trials in populations who will not be able to benefit from the treatment in question.*

3. Pharmacovigilance

● **Obligatory use of the centralised marketing authorisation procedure for new substances, and for medicines belonging to classes that have previously given rise to pharmacovigilance measures** (Annex I of the Regulation; no amendment was voted on this point, but the initial proposal of the Commission and the report prepared by the rapporteur (Mme Grossetête) both favour the use of the centralised procedure for all new substances).

New proposed amendment – Annex I point 4 of the Regulation (new): "All drugs intended for human use that contain a new substance, or a substance belonging to a pharmacological class having given rise to pharmacovigilance measures or to a re-assessment of the risk-benefit ratio, by EMEA, by a EU member state, or by a non EU country."

Justification*: for example, the muscular adverse effects of statins, the cardiac adverse effects of COX2 inhibitors and antihistamines, the various adverse effects of neuroleptics and antidepressants, led to several pharmacovigilance measures, implying that new products belonging to these drug classes should be obliged to follow the centralised procedure. For all these "sensitive" drug categories, and for all new substances that are, by definition, not fully characterised, patients would be offered more serious guarantees by combining the expertise of all EU member states through the centralised procedure, which is also presently more transparent than procedures conducted in individual member states.*

● **Obligation for medicines agencies, both European and national, to take into account pharmacovigilance data obtained in non EU countries and by the World Health Organisation** (amendment 172 – recital 15 of the Directive, voted by Parliament and endorsed by the Council of ministers; a corresponding amendment remains to be inserted).

New proposed amendment – article 25b of the Regulation (new): "When analysing pharmacovigilance data, the Agency must take into account the data contained in the pharmacovigilance databases of the World Health Organisation and of non EU countries."

New proposed amendment – article 102 paragraph 4 of the Directive (new): "This system also takes into account the information present in the pharmacovigilance database of the World Health Organisation and those of non EU countries."

Justification*: many medicinal products are now sold throughout the world, and it would be scientifically unacceptable not to share knowledge among all countries, especially in the field of pharmacovigilance. The European Agency's database on adverse drug reactions, although not yet accessible to the public, is already thought to be large. However, by taking into account data gathered by other countries or by other organisations with pharmacovigilance activities – especially the WHO collaborating centre on adverse drug reactions – drug-related risks can be assessed more rapidly, and therefore managed and prevented more efficiently.*

● **Patients should be encouraged to make spontaneous notifications of adverse effects, by labelling new medicinal products as such** (amendments 42 – article 13-3 bis of the Regulation, and 81 – article 59-1-d- bis of the Directive, voted by Parliament but not endorsed by the Council).

New proposed amendment – articles 13-3a of the Regulation and 59-1-d-a of the Directive (new): "(…) for all new drugs, during the first five years on the market, the patient leaflet should bear the words 'newly authorised drug; please contribute to better knowledge of this drug by reporting any adverse effects.'"

Justification*: the recent BBC Panorama programme, which included interviews with patients who had suffered adverse effects while taking serotonin reuptake inhibitor antidepressants, and a comparison of these statements with notifications of the same effects by physicians, clearly shows the importance of listening to individual patients. Indeed, this investigation led the British medicines agency to re-evaluate paroxetine. Spontaneous notification of an adverse effect by patients does not suffice to prove that the incriminated drug is actually responsible – no more than notification by health care professionals. Indeed, all these information sources, combined with prospective pharmacovigilance surveys, are the best way to fully characterise and rationally use medicinal products. The World Health Organisation has frequently underlined the additive nature of the different pharmacovigilance approaches.*

● **Possibility for patients to notify the authorities directly when they have no other option** (amendment 54 – article 20-3 of the Regulation and article 101 of the Directive).

New proposed amendment – article 20-3 of the Regulation (to be added)*:* "(…) patients are encouraged to report possible adverse drug reactions, either to a physician, a pharmacist or a nurse, or, if need be, directly to the authorities in charge of pharmacovigilance, using a form made available in pharmacies."

New proposed amendment – article 101 of the Directive (to be added): "member states must take all necessary meas-

ures to encourage patients to report possible adverse drug reactions, either to a physician, a pharmacist, or a nurse, or, if need be, directly to the authorities in charge of pharmacovigilance, using a form made available in pharmacies."

***Justification**: experience has shown, in all countries with pharmacovigilance networks, that only some health care professionals regularly participate in the reporting of adverse effects. If a patient's physician and pharmacist fail to report an adverse effect, or if a patient's relationship with his/her doctor is unsatisfactory, or if opinions diverge as to the interpretation of an adverse event, the individual patient must still have the means to report the event.*

● **Obligation to integrate all pharmacovigilance data into the European Agency's public database** (amendment 157 – article 51-2 of the Regulation voted by Parliament but not endorsed by the Council).

New proposed amendment – article 51-2 of the Regulation (to be added): "(…) The database described in paragraph 1 point j is designed to provide access, for each medicinal product marketed in the European Union, to the summary of product characteristics, the patient leaflet, the information provided on the packaging, and pharmacovigilance information mentioned in paragraph 1 point d."

***Justification**: medicines have both beneficial and adverse effects. To optimise their use, patients must be able to access all relevant information, on both benefits and risks, and thereby to be in a position to know a given drug's risk-benefit balance. Secrecy surrounding information on adverse effects, or difficult access, undermines patients' confidence, not only in the medicines they are prescribed, but also in medicines agencies and the pharmaceutical industry. In addition, unless both the benefits and the adverse effects of a given medicine are taken into account, the latter cannot be properly evaluated and prevented. This can lead to crises, panic, and unwarranted abrupt treatment interruption when a medicines agency suddenly decides to announce an adverse effect, to restrict use, or to withdraw a drug.*

4. Information for patients and health care professionals

● **Permitting comparison of medicines marketed in the EU through consultation of the European Agency's database** (amendment 91 – article 51-1-2-j of the Regulation voted by Parliament and partly endorsed by the Council).

New proposed amendment – article 51-1-2-j of the Regulation (completes the second sentence): "(…) and the database must permit comparisons between available information on different medicines."

***Justification:** patients need comparative information on medicines, and on all treatments in general, whether drug-based or not, in order to make enlightened decisions. Only independent authorities can provide such information. The European Agency must be one such source, and must therefore offer comparative information.*

● **Official information on new medicines (and new indications) must include comparisons with existing treatments used in the same therapeutic indication** (amendments 4 and 100 – recital 28a and article 53a of the Regulation – partially inadequate, but voted by Parliament and not endorsed by the Council; no corresponding amendment in the Directive; harmonisation required).

New proposed amendment – recital 28a of the Regulation (replaces): replace the last two sentences by: "(…) consequently, companies will be encouraged to provide comparative clinical data, notably by mentioning the existence of such data in Agency evaluation reports on new medicines submitted for authorisation."

New proposed amendment – article 12-3-2 of the Regulation (complete): "(…) The summary must also mention the existence or non existence of comparative clinical data on the new drug and existing treatments used in the same therapeutic indication, at the time when marketing authorisation is granted; when relevant, the summary should briefly summarise these data."

New proposed amendment – article 21-4-1 of the Directive (complete): " The assessment report must also mention the existence or non existence of comparative clinical data on the new drug and existing treatments used in the same therapeutic indication, at the time when marketing authorisation is granted; when relevant, the assessment report should briefly summarise these data."

***Justification**: what use is non comparative information on the effects of a drug when we do not know if the drug in question is going to be more effective than existing alternatives (and on which criteria defining cure, improvement or preventive efficacy?) or if it is going to carry a higher or lower risk of adverse effects (or different effects in terms of frequency or severity) than existing medicines used in the same setting(s), or if it is going to offer advantages in terms of convenience of treatment? Patients, health care professionals, and all those likely to use, buy, or refund a drug, need to have this comparative information if they are to make valid choices.*

● **Complete information for caregivers: description of clinical trials protocols in the summary of product characteristics** (amendment 189 – article 11-5-10a of the Directive, voted by Parliament but not endorsed by the Council).

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► ***New proposed amendment – article 11-4-10 of the Directive (new):*** " a summary of the protocols and results of clinical trials conducted to evaluate the drug before its market release."

Justification*: before prescribing or recommending a drug to a patient, health professionals should know how the drug was evaluated, in which patient categories, in which age groups, in what circumstances, and for how long. Experience shows that drug evaluation dossiers are of highly uneven quality, that many trials are not reported in the medical literature, and that health professionals have to look for more information. Companies must not be allowed to veil in secrecy in Europe the methods used to evaluate their medicines, when this kind of information is already available in other countries, such as the United States for example.*

● **Complete information on the packaging and the patient leaflet: clearly legible INN, blank space for the dose regimen, Braille, etc.** (amendments 74 and 78 – article 54 of the Directive, voted by Parliament but not endorsed by the Council).

New proposed amendment – article 54e of the Directive (to be added): "(…) A blank space must be provided on which the pharmacist can write the dose regimen prescribed to the patient."

New proposed amendment – article 56 of the Directive (replaces): " The information mentioned in articles 54, 55 and 62 must be clearly legible and comprehensible. The information mentioned in article 54a must also figure in Braille on the packaging and patient leaflet. The text of the patient leaflet must be available, free of charge and on request, in other formats, including large print, Braille, magnetic recordings, electronic format, and translations in other languages."

Justification*: one major advance in the 20th century was the disappearance of "secret remedies", and the obligation placed on manufacturers to correctly label their medicines. Although globalisation is complicating the task of manufacturers (labelling and patient leaflets in many languages, various regulations, etc.), the labelling must remain informative, even for visually and otherwise disabled patients. Strict labelling requirements are placed on non-drug products, and the public would find it hard to understand if the information on medicinal products was not of the highest standard.*

● **The INN(s) must be mentioned on all advertisements (aimed at patients or at health care professionals), even if the drug contains several substances, and even if it is a "recall" advertisement** (amendments 106, 108 and 191 – articles 89 and 91 of the Directive voted by Parliament but not endorsed by the Council).

New proposed amendment – article 89-1-b-1 of the Directive (modifies): delete the end of the sentence and stop at "non proprietary name."

New proposed amendment – article 89-2 of the Directive (replaces): replace the words "or the trade name" by "and the trade name."

New proposed amendment – article 91-2 of the Directive (replaces): replace the words "or the trade name" by "and the trade name."

Justification*: advertisements are not intended to provide neutral information, but they must at least mention the composition of the medicinal product, especially if it contains several substances. Advertisements for "secret remedies", hiding behind a simple trade name, would lead to confusion, errors, and irrational medical prescribing and pharmaceutical advice. The concept of the "secret remedy" is unacceptable in the 21st century.*

5. Compassionate use

● **Incentives for national agencies and health authorities to guarantee access to compassionate use for patients with no therapeutic alternative** (article 73 of the Regulation. The adopted amendments allow compassionate use, but do not guarantee effective access, and this point is not dealt with in the Directive. The texts must therefore be harmonised and completed).

New proposed amendment – article 73-1b of the Regulation (new): "The decision to authorise a programme of compassionate use can be taken at the request of a member state, or a patient group, or a group of health professionals concerned by the health disorder."

New proposed amendment – article 73-3a of the Regulation (complete): "(…) and they are charged, in accordance with article 5a of the Directive (2001/0253 (COD) - *replace by final number*), to set up a system guaranteeing that patients with no therapeutic alternative who might benefit from the drug may receive it within the framework of a compassionate use programme."

New proposed amendment – article 5 bis of the Directive (new): "If an exception to article 6 arises, following the procedure described in article 73 of the Regulation (2001/0252 (COD) *replace by final number*), member states are charged with setting up a system guaranteeing that patients with no therapeutic alternative who might benefit from the drug may receive it within the framework of a compassionate use programme."

Justification*: the creation and funding of a compassionate use programme should not be dependent solely on the goodwill of the company developing the drug. Allowing under certain conditions compassionate use of medicines that have not completed the evaluation phase, by patients who have no other alternative, is a good thing. But patients must be in a position to request such treatment, and member states must be committed to guaranteeing access, without depending exclusively on pharmaceutical companies.*

6. Prolongation of marketing exclusivity

● **No prolongation of data protection above limits tolerable by all member states** (amendments 34 and 202 – article 10 of the Directive and amendment 46 – article 13-8 of the Regulation).

Clarification: *medicines are protected by patents of various types. In addition, marketing authorisation holders in Europe now benefit from a protection of results of clinical trials (or "data protection"). This places further constraints on companies that market generic medicines (copies of the originator, or "princeps", drug).*

Generic medicines can be marketed after obtaining "light" marketing authorisation, granted on the basis of an application that does not comprise data from tests on animals and humans: the relevant tests done on the originator drug are considered sufficient, and their results can be included in the marketing application of the generic.

"Data protection" consists of forbidding the use of the clinical evaluation dossier on the originator drug for a certain number of years. Up to now, in the European Union, this period was set at 6 years in half of the member states and 10 years for the other half. It was also set at 10 years for biotech products (which have to follow the centralised marketing authorisation procedure).

In 2001, in the new draft Directive and Regulation, the European Commission proposed to increase this "data protection" to 10 years for all medicines, and to add 1 year whenever a princeps drug is granted a new therapeutic indication "judged (…) to offer a major clinical benefit relative to existing therapies". In 2003, after amendment by the EU Parliament and examination by the Council, the draft Directive now stipulates that applications for "light" marketing authorisation will only be able to be made 8 years after authorisation of the princeps drug, and that the generic will only be able to be marketed two years later, i.e. a "data protection" of 10 years (8 + 2) for all medicines authorised through a national procedure (or by mutual recognition). And the draft Regulation stipulates that, for drugs authorised through the centralised procedure, the period of administrative protection will be 10 years + 1 year for a new therapeutic indication "offering a clinical benefit relative to existing therapies."

Thus, at this stage of the review, "data protection" for all medicines is markedly prolonged, with no clear justification (except for the extra year for new indications approved through the centralised procedure).

No new amendment.

Justification*: Prolongation of "data protection" delays the arrival of generic drugs onto the market. .*

Non justified bridling of the generic drug market would cause further financial problems and could not be bearable for welfare systems, especially in the less affluent member states. An excessive prolongation of "data protection" would rapidly challenge the notion of equal access to medicinal products for all patients. One has to keep in mind that the European "data protection" adopted after the first reading is the longest in the world.

● **No systematic clinical trial to evaluate copies of medicines whose bioequivalence is difficult to demonstrate by classical methods, or medicines manufactured by biotechnology: such trials would not be relevant** (articles 10-3 and 10-3a of the Directive, already currently inadequate, and which risk being further weakened by complementary amendments).

New proposed amendment – article 10-3 *(non demonstrable bioequivalence)* ***and 3a*** *("biogenerics")* ***of the Directive (deletes):*** these two articles should be deleted, as they demand clinical trials which would be both a false solution and ethically questionable.

Justification*: There are already a number of pharmaceutical formulations that are not suitable for traditional bioequivalence studies aimed at showing that "generics" are interchangeable, according to the criteria currently proposed for the regulation. Forms for cutaneous application and suspensions for inhalation both pose this type of problem, and other methods are thus required to show their therapeutic equivalence.*

For many years, certain manufacturing methods have posed a problem of reproducibility, even from one batch to the next (for example, extraction from natural products, or fermentation).

But experience shows that it is not by repeating pre-marketing clinical trials (necessarily involving limited populations and follow-up) that the total equivalence of these medicines, or possible differences, can be demonstrated. The results are always the same: these medicines have similar risk-benefit balances and can be used for the same purposes. Possible differences linked to the manufacturing process can only emerge after lengthy use in a large number of patients. For example, questions are arising as to a possible causal link between the manufacturing processes of the different epoetins and adverse effects such as erythroblastopenia, but a further small clinical trial would offer no relevant information.

In the current state of our knowledge, obliging manufacturers of generic drugs whose bioequivalence cannot be demonstrated by classical methods, or generics manufactured by biotechnology, to conduct new, falsely reassuring trials, would simply offer the manufacturers of princeps medicines excessive protection. Such trials would imply the inclusion (which would be ethically questionable) of patients who would derive no therapeutic benefit, and the investment of major financial and human resources, in order to obtain results that would not be relevant.

It would be more useful to devote these means to developing new study methods (other than current bioequivalence studies) aimed at demonstrating therapeutic equivalence, and to their international recognition. It would also be more beneficial to create more efficient post-marketing surveillance of adverse effects (of princeps drugs and their generics), in order to better characterise these effects, to identify any differences linked to the manufacturing process, and to offer patients better protection. Active pharmacovigilance (prospective, and not "wait-and-see") would help to determine whether particular categories of generic medicines necessitate specific clinical assessment, simply because of their manufacturing process; this information is currently lacking. At all events, it would be premature to legislate without first obtaining sound scientific data.

Points already agreed on

A series of points defended by the Medicines in Europe Forum, including some major points, have been voted by Parliament and endorsed by the Council of health ministers. These points can be considered secured.

1. Functioning and transparency of medicines agencies

– application to EMEA of European Regulation 1049/2001 on access to documents (article 63a of the Regulation);

– obligatory declaration of conflicts of interest, and their public access, for all members of EMEA working groups and committees (article 56-2 of the Regulation);

– the yearly report of the European Court of auditors on the European Agency will be obligatory and rendered public (article 60-a of the Regulation);

– penalties inflicted on companies by the European Agency are to be rendered public, with the company's name and the underlying reasons (article 74-3 of the Regulation);

-public access to the medicines database held by the European Agency; with extension in future to all medicines sold in Europe (article 51-2 of the Regulation);

-withdrawals of marketing authorisation applications to be made public, with the underlying reasons (article 10a of the Regulation);

– marketing authorisation rejections are to be made public, together with the underlying reasons (article 11-2a of the Regulation);

– scientific conflicts between the European Agency and other national or European scientific institutions: documents to be made public (articles 53-3 and 53-4 of the Regulation);

– health professionals are to be informed rapidly of drug withdrawals or suspensions, together with the reasons (article 18-4a of the Regulation).

2. Evaluation of medicinal products

– obligatory re-evaluation of the risk-benefit balance after 5 years on the market, and a further re-evaluation at 10 years if pharmacovigilance problems arise in the interval (articles 13-1 and 13-1-a of the Regulation and articles 24-1 and 24-1-a of Directive 2001/83/EC);

– obligatory use of the centralised marketing authorisation procedure, not only for biotech products, but also for medicines intended to treat AIDS, cancer, neurodegenerative diseases and diabetes (article 3-1 and annex I of the Regulation);

– measures facilitating access to the centralised procedure for small and medium-sized companies (especially lower fees) (article 61-2 of the Regulation);

– clinical trials conducted outside the EU will have to observe good clinical practices and ethical standards (recital 12a of the Regulation and recital 10 bis of the Directive. But the amendments adopted by Parliament, which modify the articles of the two texts, were not endorsed by the Council: amendment 24 of article 6-1-1 of the Regulation, and amendment 32 of article 8-3-i-3 of the Directive);

– unannounced inspection of manufacturers (article 111 of the Directive).

3. Pharmacovigilance

– a second re-evaluation of the risk-benefit balance will be obligatory, after 10 years on the market, for medicines that pose pharmacovigilance problems in the interval (articles 13-1 and 13-1-a of the Regulation, and articles 24-1 and 24-1-a of the Directive);

– the European Agency's pharmacovigilance activities will be more precisely defined (article 51-1-c of the Regulation);

– public funding of the European Agency's pharmacovigilance activities (article 60-3-a of the Regulation);

– companies will be obliged to provide data on quantities sold and quantities prescribed if a pharmacovigilance problem arises (article 12-4 of the Regulation and article 23-a of the Directive);

– application of the Regulation on access to documents (article 63-a of the Regulation).

4. Information for patients

– prior to market release, patient information leaflets and information figuring on the packaging will have to be tested on panels of potential users (articles 59 and 61 of the Directive);

– banning of direct-to-consumer advertising of prescription-only medicines, even when disguised as "information on health problems" (article 88 of the Directive).

5. Compassionate use

– for patients with no therapeutic alternative, compassionate use will be possible before marketing authorisation is granted, in all member states, and supplies will be guaranteed until effective market release (article 73-7 of the Regulation).

6. Supply without interruption

– companies will be obliged to provide uninterrupted supplies of their products (article 81 of the Directive);

– marketing suspensions and withdrawals will have to be announced at least two months in advance (article 12-4 of the Regulation and article 23-a of the Directive).

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