

GENERICS *bulletin*

THE BUSINESS NEWSLETTER FOR THE GENERIC MEDICINES INDUSTRY

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Europe reaches agreement on revisions to pharma law

Masures to promote innovation and affordability in Europe's pharmaceutical sector should now be focused in other areas, according to Greg Perry, director general of the European Generic medicines Association (EGA).

Speaking after the European Parliament adopted the so-called "compromise package" of new legislation thrashed out between Council, Parliament and Commission last month, Perry said adopting the revisions should "draw a final line under the need to extend market protection".

"All sides of industry should benefit from the new system," he commented. "Whilst there could be delays in patient access caused by increased periods of data exclusivity, the law will nonetheless create the foundation for a more efficient regulatory system for authorising medicines in the European Union."

Areas in which innovation and affordability measures should be focused, he continued, were in increasing generic market competition, reviewing pricing systems, and creating a European Centre of Pharmaceutical Research to rival the National Institutes of Health found in the US.

European countries currently with six years' data exclusivity will have to accept an extension of the period to 11 years through an 8+2+1 formula. However, the wording clearly states that existing products will not be able retrospectively to claim additional data exclusivity. The increased period will apply only to new products submitted after the law comes into force.

"This will delay the negative impact of the data-exclusivity extension for six-year countries," commented Perry, "particularly in the new member states, which rely heavily on the savings from generic equivalents."

The 8+2+1 formula will apply equally to the centralised and decentralised marketing authorisation procedures, following adoption of the compromise package. Generic firms

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Tempest to replace Brar at Ranbaxy

Ranbaxy's chief executive and managing director **Davinder Brar** has decided to step down, effective from 4 July 2004. The company's directors have appointed current Pharmaceuticals president and whole-time director **Dr Brian Tempest** as joint managing director and chief executive designate.

Brar, who recently celebrated his 50th birthday, feels that he has "fulfilled his role in the company and would like to devote his time and energy to other pursuits of his interest at this stage of his life and career". He sits on the board of several institutions, including the Reserve Bank of India and the India Trade Promotion Organisation (ITPO), as well as chairing the Confederation of Indian Industry's national committee on drugs and pharmaceuticals.

His resignation, which the board has accepted reluctantly, came as Ranbaxy announced that consolidated sales in 2003 would exceed US\$950 million. Group turnover, the company said, was well on its way to meeting the 2004 turnover target set 10 years ago of US\$1 billion, with Ranbaxy established as a major international player in both the branded and generic pharmaceutical markets.

Tempest, who will take over from Brar as chief executive on 5 July, joined Ranbaxy in

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European revisions offer new freedoms for generics

Europe's generics industry finally has a revised regulatory framework that stretches data exclusivity but promises many new freedoms. Greg Perry, director-general of the European Generic Medicines Association (EGA), highlights the opportunities and reviews the setbacks for editor Mike Rice.

Long sighs of relief were to be heard in Strasbourg, Brussels and all over Europe on 17 December. The European Parliament had adopted at second reading the compromise package of amendments – thrashed out by Council and Parliament representatives – to the proposed revisions of the European Union's pharmaceuticals legislation.

As the number of Parliamentary amendments grew in the days leading up to the plenary vote, and with the EU's elected chamber apparently moving further away from the common position adopted in the Council by member states, conciliation seemed inevitable. But with more delay in prospect, and with the distinct possibility that what had been achieved would be dismantled by an enlarged Council and a new Parliament, a global compromise was reached just hours before the vote – and several years after the process had begun – by Parliament's rapporteurs for the legislation, Françoise Grossetête and Rosemarie Müller, and their opposite numbers in the Council.

Speaking to Parliament before the plenary vote, Erkki Liikanen, commissioner responsible for enterprise and the information society, said the Commission could "accept entirely" the global compromise package proposed by the Council and accepted by the two rapporteurs.

What remains now is for both of the main parts of the new legislation to be formally adopted by the current Council president – Ireland now holds the Presidency – and the Parliamentary president. The new regulation revising the centralised marketing authorisation procedure and establishing a European Medicines Agency will have a direct impact on all member states, but the directive amending the Community code on human medicinal products – including the decentralised or mutual-recognition

marketing authorisation procedure – will have to be transposed into national legislation.

This could take some member states as long as 18 months to complete, pushing back first use of the new system to mid-2005 or even 2006. Meanwhile, however, the 10 new member states joining in May will also be bound by the new regulation and obliged to transpose the directive into their own laws.

Greg Perry, director-general of the European Generic Medicines Association (EGA), says his response to seeing the legislation finally adopted, like many others heavily involved with it for the past 30 months (see Figure 1), was a great sense of relief. He has some regrets and disappointments, but overall he believes all sides of industry should benefit from the new system.

Achieved the best we could

"Nothing is perfect, but we have probably got the best we could out of it," he says. "The biggest disappointment is probably on data exclusivity, but there was tremendous pressure for longer periods everywhere. And overall, we have come a long way in the past two and a half years," he adds, noting a long list of achievements, including a Bolar provision, the European reference product and a regulatory route for biosimilar products, among others (see Figure 2).

"We have got a legal framework for harmonising SmPCs – summaries of product characteristics – that does not exist now, and we also have a clear statement that the SmPC does not have to include patented indications," outlines Perry. "And the decentralised procedure will allow simultaneous applications to the reference member state and concerned member states in an almost carbon copy of the proposal the EGA originally put forward."

"We now have a definition of a generic which, although we preferred the version in the common position, we can live with," Perry continues, adding that the definition allows differences in salts, provided they have been proven not to affect safety and/or efficacy (see box on page 21).

"And we have a regulatory framework for biosimilar products. This is a tremendous advance in the sense that two and a half years ago it was said there could not even be biosimilar products," he maintains, noting that Europe has taken a lead over the US in this respect.

Perry is wary, however, of the issues that might be raised at a national level in implementing the directive. Foremost amongst these is the Bolar provision. This states in Article 10 of the directive that "conducting the necessary tests and trials with a view to application of paragraphs 1, 2, 3 and 4 to a generic medicinal product and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary

Date	Stage
July 2001	European Commission launches revision proposals
26 November 2001	Commission adopts proposals
23 October 2002	First reading in European Parliament
10 December 2002	Commission adopts amended regulation proposals
3 April 2003	Commission adopts amended directive proposals
29 September 2003	Council reaches common position
27 November 2003	Parliamentary committee agrees Second Reading amendments
11 December 2003	Deadline for all second reading amendments Compromise package of amendments agreed between Council and Parliament
17 December 2003	Parliament supports compromise package at second reading in plenary vote
2004-2005	Regulation published; directives transposed into national law

Figure 1: Revising Europe's pharmaceutical legislation. Key stages in introducing a new regulation covering the centralised procedure and medicines agency, and a directive amending the Community Code for human medicines, including the decentralised procedure. The full legislative package also includes a directive on veterinary products and a directive on traditional herbal medicines

protection certificates for those medicinal products”.

This is the wording established by the Council in the common position, and not that of Parliament, which clearly included a reference to exports. The Council was adamant, however. Explaining its attitude to Parliament’s first reading amendment, the Council stated that it accepted the Bolar clause “in principle, except the part referring to products for exports”.

Submission of applications and granting of an authorisation, it said, were of an “administrative nature” and thus would not infringe patent protection. In fact, the Council and Commission had already underlined their view in a joint statement which clearly spelled this out.

“It is neither necessary nor appropriate to include those activities in a provision on exemptions from patent protection,” the Council continued. “As concerns the submission of samples, this will be covered by the addition agreed by the Council: ‘and the consequential practical requirements’.”

Perry points out that what will have to be changed in national law to accommodate the Bolar clause could vary from country to country. In some it might be simple addition to patent law; while in others it could involve complex changes to different strands of existing legislation. “Where changes are to be made, how they are made and what they comprise will vary from member state to member state,” he observes.

“The main problem is that it is quite a general statement and does not go into specifics. That means the detail will be defined by the courts, by guidelines or other means. And because it is not specific, differences may be created when it is implemented at member state level.”

Perry acknowledges that the general nature of the wording could be considered advantageous. “Some lawyers think that of course the provision can be used for export and it doesn’t specifically have to say so. But others maintain it should,” Perry explains. “That is why of all the directive’s provisions, the Bolar clause is particularly important to monitor during implementation.”

“It is vital that national legislators remember what the aim is. And that is to give European generics and biogenerics companies the same rights as those enjoyed by their counterparts in the US,” maintains Perry.

Addressing the Parliament in Strasbourg before the plenary vote, commissioner Liikanen reminded members of the three main objectives of the original package of revisions drawn up by the Commission in response to the 2001 legislative review.

These objectives, he said, were:

- To guarantee European citizens a high level of health protection
- To increase the availability of innovative medicinal products; while at the same time encouraging competition with generic products
- To prepare for enlargement.

“I am glad,” he said, “that the final compromise proposed by the two rapporteurs and by the Council would indeed meet these objectives.”

Referring to data protection and generic competition, Liikanen continued: “The Commission wanted to strike the right balance between

Issue	Details
Data exclusivity: 8+2+1 for centralised and decentralised procedures. 8 years’ data exclusivity + 2 years’ market exclusivity + 1 year for new indication/s	No restriction on manufacturing during the 2 years’ market protection period Prospective implementation: Does NOT apply to applications for reference products made before regulation comes into force and before date of transposition of directive
Data exclusivity: Well-established substances	1 year non-cumulative for a new indication as a result of significant pre-clinical or clinical studies
Data exclusivity: Switch to OTC	1 year for a change of classification on the basis of significant pre-clinical tests and clinical trials
Data exclusivity: NOT for line extensions	Single marketing authorisation: Any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions, will belong to same global authorisation
Bolar provision	NOT patent infringing to carry out tests, trials and authorisation of generic medicines
Doha Agreement	Provisions NOT included for exporting generic versions of patented products for compulsory licence in third countries
Generics definition	See box on page 21
Biosimilar products	See box on page 21
European Reference Product	Reference product need only have been authorised in a member state at some time
SmPC harmonisation	Legal basis provided for harmonising originator’s summary of product characteristics References to indications or dosage forms still covered by patent law may be omitted by generics firms
Route of authorisation	Choice of centralised or decentralised route for generic versions of centrally-approved reference products
Decentralised procedure	Simultaneous applications and discussions with reference member state and concerned member states (as proposed by the EGA)
Sunset clause	Authorisation is invalid if product missing from market for three consecutive years
One five-year renewal	Marketing authorisations valid for unlimited period once renewed, unless pharmacovigilance indicates one additional five-year renewal
Different linguistic versions of the international non-proprietary name (INN)	All versions of the INN are considered the same

Figure 2: Main provisions affecting the generics industry in Europe’s new pharmaceutical legislation

innovation and generic competition by adjusting the criteria for achieving it.”

“The measures in favour of generic competition we proposed were agreed upon – and even improved – thanks to the Parliament’s amendments during the first reading,” Liikanen maintained. “Regarding innovative industry, the Commission proposed harmonising the data protection period at 10 years across the board as an essential element for smoother operation of the single market. This period also represented one of the major tools available in the context of pharmaceutical legislation for rewarding innovation,” he added.

Noting the Commission’s proposal of a one-year extension for an innovative indication granted after the initial marketing authorisation, Liikanen said the compromise known as 8+2+1 “meets our objectives and expectations”.

The formula now applies equally to the centralised and the mutual recognition procedures. The wording in the regulation covering the centralised procedure says: “[Authorised products] shall benefit from an eight-year period of protection and a 10-year period of marketing protection, in which connection the latter period shall be extended to a maximum of 11 years if, during the first eight years of those 10 years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring significant clinical benefit in comparison with existing therapies.”

Perry says the EGA would have preferred an eight-year provision with no “plus two, plus one”, but realised it had to compromise and that the formula agreed was much better than the original 10+1 proposed by the Commission. New products will now get up to 11 years of exclusivity, but importantly generic companies will be able to begin registration after eight years. Furthermore, there will be nothing to stop generics companies manufacturing during the two-year market protection period, and innovative companies will only be allowed one extra year for new indications, and not a whole series of extra years.

Important difference to US approach

He warned, however, that the extra year of exclusivity will apply to the product as a whole, and not just to its use for the new indication. “That is an important difference between the European approach and what happens in the States, where originator firms get data exclusivity only on the indication.”

Significantly, originator firms will not be able to claim data exclusivity for line extensions, and there will be only one overarching marketing authorisation for the reference product. This will stop originator firms trying to combat generic competition by introducing new line extensions and claiming exclusivity.

Article 6 in the directive states: “Any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions, shall also be granted an authorisation.... or be included in the initial authorisation. All these marketing authorisations shall be considered as

belonging to the same global marketing authorisation.”

Standardising on a 10-year minimum for market exclusivity will mean that about half the existing member states, and all 10 of the accession states, will have to increase their protection period from six to 10 years.

“I am fully aware that the impact of this harmonisation in the new member states was much discussed during the debate,” Liikanen acknowledged. He added, however, that he welcomed the compromise provision on the “non-retroactivity of this harmonisation”. “This provision will limit the effect of the new protection period to medicinal products authorised after implementation of the directive,” he stated.

Will consider transitional periods

“I would like to state that the Commission will give full consideration to any request for a transitional period presented by the new member states on adoption of the legislative package.”

Perry admits the EGA wanted a clear transitional period for the new member states on data exclusivity. “Obviously, we would have preferred to have it in the legislation,” he said. Nevertheless, he welcomed commissioner Liikanen’s statement.

“It is not totally over,” Perry commented. “At some point in the future, let us say in 12 months’ time, a new member state can go to the Commission. If it provides evidence that the extended data-protection period will cause severe problems for public health, the Commission will look into a transitional period.”

“It is also very significant,” Perry adds, “that the law clearly states the increased data-exclusivity period will only apply prospectively to reference products. This will delay the negative impact of the data-exclusivity extension for six-year countries, particularly the new member states, which rely heavily on savings from generic equivalents. Commissioner Liikanen should be congratulated for his efforts to accommodate new member states.”

New member states will also benefit from the new European reference product clause, which allows generic applications to refer to products licensed at any time in any member state. At the moment, applicants must refer to current authorisations in the country of application. An additional advantage of the new clause in existing member states is that it will stop originator firms preventing generic competition.

“The European reference product is not only important for central and eastern European countries to maintain the medicine selections they already have,” comments Perry, “it also helps everybody in the event that a product is withdrawn by the originator for commercial reasons.”

The wording of Article 10 in the directive states: “If the reference medicinal product was not authorised in the member state in which the application for the generic medicinal product is submitted....the applicant shall indicate in the application the name of the member state in which the reference medicinal product is or has been authorised.”

This means case law established by the European Court of Justice (ECJ) last October

If a new member state provides evidence that the extended data-protection period will cause severe problems for public health, the European Commission will look into a transitional period

(*Generics bulletin*, 7 November 2003, page 12) will be superseded by the provision establishing the European reference product. A single marketing authorisation and a European reference product will put an end to the originator obtaining exclusivity for a line extension and then withdrawing the original product to prevent generic competition.

Perry notes the single year of data exclusivity gained by the OTC industry for significant switches, but underlines the fact that Parliament wanted three years, and the exclusivity only refers to OTC use.

He also acknowledges the non-cumulative year of data exclusivity for a new indication of a well-established substance. "Non-cumulative means the year doesn't accumulate on the existing data exclusivity," he comments, "and it refers only to the new indication, not the whole product."

"What's been argued is that this is a form of exclusivity that can be used by any company," explains Perry. "It applies to any well-established product, including generics, and not just the first authorised product."

An omission from the new pharmaceutical law, according to Perry, is a direct reference to the Doha Agreement, covering the granting of compulsory licences for the export of patented medicines to countries with insufficient manufacturing capacity.

Commissioner Liikanen explained to Parliament that the omission had more to do with ways and means than a lack of political commitment. The Commission was committed, he said, to implementing Doha, and that "the right conditions are in place for its operation and efficient application". But amendments 6 and 19 had a "problem of form", he said, because a clause regulating exports could not be part of a directive dealing with placing medicines on the EU market.

"The Commission fully agrees with the principle of the implementation of the WTO General Council Decision of 30 August 2003, both at Community and at member state level, in the context of patent legislation," he said.

"The Commission undertakes to address the implementation of this Decision in the EU as a matter of the highest priority in early 2004, with a view to bringing forward an appropriate legislative proposal," promised Liikanen.

Problems with the sunset clause

Perry also highlights an implementation problem with the so-called three-year sunset clause. This states that a product's marketing authorisation ceases to be valid if the product is absent from the market for three consecutive years. The EGA's problem is that a generic company may obtain a marketing authorisation for a product, which is then excluded from the market for reasons beyond its control, such as legal action. The company may win the case, but meanwhile lose its authorisation.

He believes the issue needs to be solved during implementation or by a guideline, possibly contained in the Notice to Applicants.

But looking beyond implementing the new legislation, Perry insists measures to promote innovation and affordability should now be focused elsewhere. "The regulatory framework is in place;

Definition of a generic medicine

Generic medicinal product shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorised active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.

Requirements for bio-similar products

Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided.

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now it's a question of putting the market framework in place," he says.

"Giving patients greater access to low-cost generics will mean introducing more proactive generics policies at national level. These policies will include more generics prescribing and dispensing, better generics information, and computer systems which promote generics use to doctors and pharmacists," he maintains.

Perry says it is now time to draw the line completely under the whole issue of increasing data exclusivity and patents. "Policymakers should focus on other issues for innovation," he says. "We are becoming less innovative than the US because innovation itself is not being developed in Europe. The Americans provide publicly-funded research through their national research centres and we would like to see more of that in the EU."

The third issue on his agenda is pricing, which is a problem that will not go away. "Is there an argument," he asks, "for allowing more price freedom at the beginning of a truly innovative product's lifecycle, which is then compensated by heavy generics encouragement at the end of patent life?"

"These are the issues we think should now be the focus of pharmaceutical discussions at a European level," maintains Perry, adding that the high-level G10 forum may be the appropriate mechanism for trying to get a European agreement in areas like pricing, which are principally of national competence.

Meanwhile, however, Europe's generics companies now have the prospect of freedoms that could only have been imagined when the Commission started its 2001 review of Europe's pharmaceutical legislation. "A number of doors have been opened," Perry observes. "We will now have to see what awaits us as we pass through them." G