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Federal Trade Commission
Office of the Secretary
Room H-135 (Annex F)
600 Pennsylvania Ave., NW
Washington, D.C. 20580
United States of America

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Dear Madam / Sir

Emerging Health Care Competition and Consumer Issues
Competition Issues Involving Follow-on Biologic Drugs
Comment, Project No. P083901

We thank the Federal Trade Commission for the opportunity to comment on Project P083901 – Emerging Health Care Competition and Consumer Issues. The implementation of an appropriately regulated, abbreviated pathway to approve safe and effective biologicals in a timely manner is an incredibly important issue.

Background

We seek here to provide a balanced perspective to the ongoing debate. Our firm advises clients based around the world about using intellectual property strategically and globally. A significant proportion of our clients are either 'Innovator' or 'Generic' pharmaceutical / biotechnology companies. (In truth, the distinction between these two is fading as more traditional innovators launch authorized generics, particularly via 'generic' subsidiaries, and more traditional generics undertake or in-license new drug developments from smaller entities.) For obvious reasons these clients have a large interest in follow on biologics, and particularly in the United States.

Summary of comments

While the final details of an appropriate regime must be carefully worked out, we set out below the broad principals which in our view should apply:

1. The existing chemical drug data exclusivity regime is appropriate for biological products (questions A7 & A8).
2. There should be a system to have patent issues determined before regulatory approval (questions B1, B3, B4 & B5, A6).
3. The early resolution system should be based on the form of the present day Orange Book patent system and include one or more 'generic' exclusivities (questions A10 & B6).
4. The system as it applies to biologicals should be updated to deal with specific issues, including:
    a. All relevant patents owned by the innovator should be listed (including for example, process patents).
    b. All relevant patents in-licensed by the innovator should be listed.
    c. All relevant pending applications should be listed.
    d. There should be no automatic stay of regulatory approval just because an innovator commences legal proceedings.
    e. The follow-on biologic producer may commence non-infringement or invalidity legal proceedings at any time after a patent issues.

We have referenced comments from panelists at the November 21 2008 roundtable throughout this letter to provide further color and analysis. We cite these comments by reference to the page number of the transcript from the panel sessions.

1. There is no need to change the existing data exclusivity regime (questions A7 and A8).

We don't think anyone would seriously contend that there should be no data (or market) exclusivity period for biological drug products. Mr Norman (Eli Lilly) rightly pointed out that innovators should be compensated for being the first to introduce a new biological drug to the US

market– transcript p 155. Indeed this is the very reason why data exclusivities currently exist – for chemical as well as biological drugs and for the same reasons.

The policy behind data exclusivities is to compensate innovators for taking the trouble to develop new drugs and obtain FDA approval for the sale of that drug in the US. This policy must be carefully balanced against the policy of providing incentives for other companies to develop lower cost follow-on biologics.

There is no evidence to suggest that innovators of biologic drugs require any more compensation in respect of biological drugs as compared to chemical drugs. The development cost to produce a new biological drug is comparable to that of producing a new chemical drug (~$1.2 – 1.3 billion) – see also transcript, Dr Buckley (BIO), p 70; Dr Grabowski (Duke University) p 112 and Dr Brill (American Enterprise Institute), p 115.

Although the development costs for innovators making biologics are comparable to their costs to make a chemical drug, it is much more expensive to develop a follow-on biologic product than a generic chemical drug. This operates as a significant disincentive for generic companies to develop follow-on biologics.

In our opinion, the present data exclusivity regime is suitable for biologicals and should be preserved. In particular, the same data exclusivities should apply for new indications, pediatric indications, and so on irrespective of whether the drug is a pharmaceutical product or biopharmaceutical product. In our view, the current five year data exclusivity for new chemical entities should apply to new biological entities.

Some have argued that data exclusivity does not need to fully recompense developers of new drugs because it will lessen competitive tension and therefore lessen the pressure to innovate and develop new drugs. However, we think it only fair that at least the current (chemical drug) data exclusivity periods apply in order to provide appropriate opportunities for innovators to recoup costs of the collation of clinical data necessary to obtain FDA approval. In this regard, we note the comments of Dr Allan (Insmed) that a five year data exclusivity would be sufficient to recoup all such costs for a biopharmaceutical product as the cumulative revenue of every major biologic exceeds $5 billion after the first five years of sales – transcript, p 111-112.

There is only a 7.4 month difference in the average time that it takes to obtain FDA approval (97.7 months for biologics as compared to 90.3 months for chemical drugs) (see Dr Kotlikoff's paper). This period is already compensated by patent term extensions.

A longer data exclusivity right would clearly delay the onset of generic competition and thereby decrease the pressure on innovators to develop improvements and new drugs.

As noted by others, Kotlokoff estimated that extended data exclusivity terms would deprive America of cost savings of $25-108 billion over the next decade.

2. There should be a system to have patent issues determined before regulatory approval (questions B1, B3, B4 & B5, A6).

A system to enable patent issues to be determined before launch is in the interests of all parties. It provides greater certainty and lower risk for innovators and generics, and greater continuity in supply of follow on biologic products to the public. Many of the participants at the roundtable on 21 November 2008 agreed with this basic premise – see for example transcript: 226 (Mr Sauer, BIO); p 238 (Ms Siwik, Rakoczy, Molino Mazzochi Siwik); 246 (Mr Kushan, Sidley Austin); 250 (Mr Manspeizer, Wyeth).

Implementation of such a system would need to be carefully crafted as explained (with some examples) in section 4 of this letter.

Innovators interests

Innovator companies suffer large business risk each time they undertake a biological development - see also transcript: p 228 (Dr Sauer, BIO), p 207 (Mr Norman, Eli Lilly), p 235 (Mr Kushan, Sidley Austin), p 178 (Mr Dow, Johnon & Johnson).

One such risk concerns the scenario in which a generic company may launch before the innovator has obtained final determination of patent related issues. Under the current system, if the generic were to launch a follow-on biologic and later be found to have infringed a patent, then (at that stage) there is great uncertainty about whether the generic would be required to leave the market, or be able to continue under a court enforced license arrangement. A sentiment also expressed by Mr Dow (Johnson & Johnson), p 178. Mr Dow also made the point that the price drop that occurs on first follow on (or generic) launch will distort the market and may never be recoverable - transcript p 234.

This obviously increases the uncertainty for innovators at a crucial time for the profitability of the drug – towards the end of the monopoly period. Consequently, a system which provides innovators and generics the opportunity to have patent issues determined prior to generic launch will reduce the business risk to innovators – see for example Dr Sauer (BIO), transcript p 228; Mr Kushan (Sidley Austin), p 236.

The history of biological developments to date has proven that innovators are willing to develop biologicals that are similar in some respects to those already placed on the market by other innovators. In each instance there has been heavy litigation surrounding the launch of the second generation product. Clearly both sets of innovators in this instance would benefit from the certainty of early resolution of patent issues.

Dr Seide (Schwegman) pointed to the eight growth hormone products currently on the market as evidence that there is no need for early determination of patent issues because competition has not to date been impeded (transcript p 172). However these were full developments without an abbreviated pathway only available to the largest companies to pursue and are not cost effective for the community. This is not what we are concerned with here. Here we are looking at ways to provide incentives for generic companies to produce follow-on biologics.

Generics interests

Clearly there are significant risks to the generic company in launching prior to determination of any patent issues. Freedom to operate on launch is a very significant issue for generic companies and they expend large resources on it. The damages payable on infringement (for lost sales of the higher priced innovator version) would be much greater than any profit made by the generic from the product sales – see also Ms Siwik (Rakoczy, Molino Mazzochi Siwik), transcript p 238. There is of course, always the risk of treble damages as well.

Mr Goldman (Novartis) stated that launching at risk is the current norm in the biotech industry (for innovators and generics) - transcript page 229. This is correct, precisely because no pre-approval patent resolution system has been developed yet. However, it is a less than ideal situation and severely inhibits the number of generic companies willing to develop follow on biologics. Launch at risk raises the distinct possibility that a court might order an interim injunction pending resolution of the proceedings, which would amount to a de facto extension of the data exclusivity period.

Generic companies would ideally have all patent issues determined prior to the date on which they will receive regulatory approval so that they are in the best position possible to launch on approval (see also Ms Siwik, Rakoczy, Molino Mazzochi Siwik, transcript p 225; Mr Manspeizer (Wyeth) p 250). This is particularly important for smaller generic companies because each biologic development is a large proportion of their entire expenditure and presents a greater risk (see also Mr Leicher, transcript p 232). Mr Goldman (Novartis) suggested the converse – that it would be better for smaller generics to wait and not bring expensive litigation forward (transcript, p 240), but as explained above, this only compounds the risk.

Some have argued that there is no Orange-Book like system for early resolution in other jurisdictions, such as in Europe and therefore it is unnecessary in the United States (see for example Mr Goldman, transcript p 229). This misses the point that the American community stands to gain a great deal by providing incentives for earlier generic launch. Furthermore, the legal systems in Europe allow for early resolution in any event by providing jurisdiction to seek declarations of non-infringement or revocation of the relevant patents.

Finally, as pointed out by Mr Leicher (Momenta), the Hatch Waxman legislation gave the quid pro quo of patent term extensions in return for a streamlined process and procedure for challenging patents. As things stand, biological innovators get the benefit of the term extensions without the other part of the deal – the generic patent process (transcript, p 163).

Are biological patent portfolios simpler and easier to avoid?

Some commentators have argued that patent portfolios covering biological drugs are narrower and easier to circumvent so that there is no need to provide for early resolution of patent issues as launch at risk is not a major problem.

Firstly, in our experience, the patent portfolios covering biological products are in fact more complicated. This sentiment was also expressed by Dr Kushan (Sidley Austin), transcript p 139.

Secondly, in many ways, the claims covering biological inventions are quite broad indeed. So for example a claim which covers a small functional sequence of amino acids will cover any molecule having that sequence for that function (see also Mr Leicher (Momenta) transcript p 161 and Mr Goldman (Novartis), transcript p 165). Some have argued that chemical composition of matter patents are much broader because they can include Markush claims with tens of thousands of combinations. However, a similar, or perhaps even unlimited number of biological compounds would be covered by a functional amino acid sequence. In addition, the broad Markush claims in a chemical patent are not relevant to a generic company who cannot avoid even the narrowest claim as they need to have an identical molecule in order to get regulatory approval. The same applies in biologicals – the functional area which is claimed will not be avoidable if an abbreviated regulatory pathway is sought. Instead, the broader subject matter claimed around the precise product is only relevant to other innovators looking to produce second or third generation products based on the same pharmacophore. These are the rare companies with the capabilities to undergo a full development and regulatory approval program for something which is outside the claims of the core patents.

Thirdly, the narrowness of biological patent claims is not an issue that impacts on generic manufacturers seeking to produce follow-on biologicals. This is because when they exist, such claims may be avoidable, but the non-infringing product will be so different from the original product that it will not be capable of attracting an abbreviated ('generic') regulatory approval pathway. Instead, it will require a separate full or nearly full development and regulatory pathway. This approach clearly applies to the other innovators willing to undertake this sort of development, but not the smaller generic companies who would be incentivized by an abbreviated pathway – which is the subject of this project.

3. The early resolution system should be based on the form of the present day Orange Book patent system and include one or more 'generic' exclusivities (questions A10 & B6).

The Hatch-Waxman scheme has proven enormously successful in balancing the interests of consumers, innovators and generic drug companies and has delivered annual cost savings of $8-10 billion to patients while encouraging innovation (Kotlikoff). Clearly this should be the starting point from which any regulatory regime for biologicals is developed. Mr Shultz (Zuckerman Spaeder) agreed, stating that we should be aiming for a system based on the same theory as the Hatch-Waxman system – innovators get patent term extensions of up to five years and generics get a streamlined system to get their products to market on the day that a blocking patent or data exclusivity period expires.

The economic, innovation and other arguments supporting this view have been made by others and we won't restate them here.

'Generic' exclusivities

A crucial part of such a system is an appropriate incentive for generic companies to seek to have their products on the market as soon as possible. In our view, the current 180 day generic exclusivity is the appropriate incentive.

We note that this was not the view of some panelists at the roundtable discussions on 21 November. Dr Barkoff (McDonnell Boehnen Hulbert & Bergoff) argued that a generic exclusivity is not necessary because it does not exist in other jurisdictions and generics still develop drugs for the US market, even knowing that they will be the 2nd or 3rd filer (transcript, p 205). Mr Zielinski (Pfizer) had the same view based on suggestions that there will be less competition in follow on

biologics than in generic chemical drugs and the follow-on price will be closer to the innovator price than with chemical drugs - transcript, p 196.

It may well be true that the provision of a generic exclusivity does not provide incentive to produce a product – however, the expected profit will take care of that. It must be the case that a generic exclusivity does provide incentives to develop such products as early as possible. Given the great economic benefits to America in earlier access to follow on biologics, it seems clear cut that early launch should be incentivized.

Mr Allan (Insmed) argued that a generic exclusivity provision would cause unnecessary delays for the other generics developing follow-on biologicals – transcript, p 207. However, the race to be first that such a provision creates and the cost savings due to earlier generic launch would far outweigh the benefits to the broader generic community of having no generic exclusivity. Furthermore, it must be possible to design a generic exclusivity that provides incentive for earlier follow on biologic development without inhibiting subsequent applicants – see also similar comments by Mr Goshko (Teva) - transcript p 197.

Mr Norman (Eli Lilly) argued against a 'generic' exclusivity saying that there should not be a bounty on the intellectual property rights of innovators - transcript, page 199. There is no policy reason not to provide such a bounty (on invalid/circumvented patents) if it results in more competition and costs savings to government and consumers.

We recognize that in the context of follow on biologics, there may be a need to slightly adjust this regime depending on the outcomes sought. Thus, by way of example, a better exclusivity period may be awarded to the first entity to obtain approval for a follow on biologic drug that is interchangeable. Similarly, a concern Mr Norman voiced was that the first filer gets all the rewards and if they are ill prepared and fail, then no rewards go to the second filer. This could be readily addressed by adjusting the award of the 'generic' exclusivity – for example to the first to file and win – rather than just the first to file.

4. The system as it applies to biologicals should be updated to deal with specific issues, including:

4a. All relevant patents owned by the innovator should be listed (including for example, process patents).

It has clearly been established and repeated many times during the course of this project that other kinds of patents (beyond those required to be listed in the current Orange Book for chemical drugs) are very important in the biological context. This particularly applies to process patents.

Consequently, all patents which relate to the reference biological drug need to be listed in order to have all patent issues resolved at the earliest possible time. The same point was also made by several panelists, see for example Mr Kushan (Sidley Austin) p 246; Dr Seide (Schwegman, Lundberg & Woessner), p 265.

4b. All relevant patents in-licensed by the innovator should be listed.

It has also been clearly established and often repeated that cross-licensing of technologies (particularly platform technologies) is a critical part of the biologic patent landscape. Accordingly, patent issues can only be determined at an early stage if all relevant in-licensed patents are also listed (see also Dr Sauer (BIO), transcript, p 261; Mr Dow (Johnson & Johnson), p 186). Several of the panelists made the same broad point, see for example: Dr Seide (Schwegman, Lundberg & Woessner), p 238; Dr Sauer (BIO), p 261; Mr Kushan (Sidley Austin), p 236.

As Ms Siwik pointed out, the innovator companies are the only ones who know which patents they have in-licensed – transcript p 263.

4c. All relevant pending applications should be listed.

There is a great level of uncertainty for generics when it comes to unpublished, pending patent applications filed before 1995 ('submarine patents') in biologicals. A regime that is truly aimed at determining all patent issues prior to launch of the follow on biologic will also have a mechanism to deal with these patents. A number of the panelists called for an open, transparent and accountable regime to be put in place (see for example Mr Maspeizer, p 229). It would make sense that a listing of relevant pending applications should also be required.

The issue of certification and litigation in relation to pending applications is not straight forward because the breadth of the final claims is not certain and patents cannot be enforced until they issue. In our view, the act of listing them can at the very least trigger a predetermined, formal exchange of information and intentions about ways to resolve any potential dispute.

4d. There should be no automatic stay of regulatory approval just because an innovator commences legal proceedings.

The current 30 month stay of generic FDA approval which operates in Hatch-Waxman proceedings is unnecessary in our view. The stay provides an incentive for the innovator company to commence legal proceedings so that the patent dispute can be resolved. It was designed so that the dispute would be resolved prior to FDA approval.

The effect of the 30 month stay is that it provides an incentive for litigation, but delays generic entry and so has had the opposite effect on early generic launch than was intended (see also Ms Siwik (Rakoczy Molino Mazzochi Siwik, p 273). Furthermore, since Hatch-Waxman litigation usually takes closer to 48 months and generic companies will almost never risk launch at risk prior to determination of the proceedings, the effective monopoly period for the innovator is further prolonged.

4e. The follow-on biologic producer may commence non-infringement or invalidity legal proceedings at any time after a patent issues.

As discussed in section 1 of this letter, many commentators agree that patent issues should be determined as early as possible in the process and preferably before FDA approval. To do this means commencing them as early as possible because the proceedings take a long time (see for example Ms Siwik (Rakczy, Molino Mazzochi Siwik) p 249; Mr Manspeize (Wyeth) p 250.

In our view, there is a better way to enable the litigation to be commenced without the incentive of the 30 month stay. It is simply to enable the generic to commence proceedings seeking a non-infringement declaration or revocation of the patent(s) at any time (ie prior to, during or after regulatory approval) – see also Mr Schultz (Zuckerman Spaeder), p 279. This is the system in almost all other jurisdictions.

Under this model, the generic maintains the incentive to file and have proceedings determined early by being awarded a generic exclusivity. The innovator also maintains the incentive to seek business certainty through early determination.

To put this model into effect, it would be necessary to create specific jurisdiction for the generic company to commence proceedings for a declaratory judgment or revocation of the patent – see also Mr Kushan (Sidley Austin), p 293. A deemed infringement (as exists under the current system) should also be created in order to allow the innovator company to counter-sue for infringement and thereby seek remedies such as an injunction.

In contrast to this suggested approach, Mr Goldman (Novartis) suggested that the generic must provide the innovator with 45 to 90 days notice after FDA approval in which to decide whether to sue – transcript, p 241. The problem with this approach is that it substantially delays generic launch as most generics won't wish to take the risk and will therefore wait until resolution of the legal proceedings (up to four years later than they might otherwise have launched).

Thank you once again for the opportunity to comment on these important issues.

Very truly yours

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