Is Europe ahead of the USA in biosimilars?

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Abstract This article is about a race between the USA and Europe in biosimilars. The race can be defined in several ways: the first launch of a biosimilar; the first cross-border use of a biosimilar in the USA or Europe which was approved in a neighbouring country; the greatest value or profits of biosimilars in 2004; the first legal provision for an abbreviated regulatory pathway applied in a consistent and continued manner; and the race for interchangeability or substitution of biosimilars for reimbursement, a race that is just beginning. The USA has won three of the five races, first-launch, first cross-border use and greatest value of biosimilars according to 2004 sales, but Europe is ahead in the most important race: the application of a consistent and continued regulatory pathway. This paper provides the race results and looks at the race for biosimilar regulatory pathways. Once the regulatory pathway is applied by governments in a consistent and continued manner and many biosimilars are launched, the race begins for interchangeability that affects physician prescribing and generic substitution. Biosimilar interchangeability and subsequent biopharmaceutical affordability, is the ultimate prize for the real winners of the race: the patients.

Keywords: *biosimilars, biogenerics, follow-on proteins, EPO, beta interferon, INN*

INTRODUCTION

The race between Europe and the USA for widespread generic biopharmaceutical use can be defined in several ways: the first launch, the first cross-border use, the greatest value or profits derived from generic biopharmaceuticals, the first legal provision for an abbreviated regulatory pathway, or interchangeability and substitution. This paper presents the results of the five different races in biosimilars. The use of the term 'biosimilars' will be interchangeable with all of the terms used in the generic industry and by the regulatory authorities to describe generic biopharmaceuticals.[1] Definitions are important since quantification of the current and potential market for biosimilars depends on how they are defined.

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PRELIMINARY RACE RESULTS

On 17th May, 1996, the Food and Drug Administration (FDA) approved Avonex®, launched by Biogen, as a biosimilar to Schering/Berlex's Betaseron®, both beta interferons, but distinguished by 1b (Betaseron) and 1a (Avonex) in the INN designation. The approval of Avonex was based on an 'abbreviated' biological licence application[2] (BLA), without pre-approval clinical trials, relying just on surrogate studies performed in Europe, and a comprehensive comparability study in the examination of the molecular characterisation of the two drugs which differ only by glycosylation, one amino acid and two positions of amino acid sequences. Avonex was approved in Europe one year later in 1997.

Human menopausal gonadotropin, or menatropins (Pergonal®), introduced in 1970, is extracted from the urine of menopausal women. An application was submitted by Ferring for a generic to Pergonal (branded as Repronex®, manufactured by Lederle Parenterals), and won the first approval of an abbreviated new drug application (ANDA)[3] biosimilar in the USA on 30th January, 1997 (although it was never distributed, it was later approved as an NDA co-administered with human chorionic gonadotropin (hCG) on 27th August, 1999[4]). At the time, the FDA considered the Ferring menatropins ANDA acceptable for approval without clinical trials and without comparability studies, because it was a complex mixture with a long history of use in its indications and routes. The FDA approved Repronex without full molecular characterisation: 'FDA and the courts held that absolute chemical identity is not required for generic approval, and indeed, that such a requirement would appear to be contrary to Congressional intent.'[5] Repronex was, and still is, the only protein approved through the ANDA abbreviated procedure authorised under 505(j) of the FFD&C Act.

Indeed, in the recent FDA/DIA Workshop held in Arlington, Virginia, in February 2005,[6] Steve Kozlowski (now Director, Office of Biotechnology Products, CDER) stated that generics of such complex mixtures — including pancreatic enzymes (1996: 505(b)(1)), non-glycosylated proteins (hGH: all 505(b)(1) to date) and glycosylated proteins (FSH all (505(b)(1) to date and menotropins 505(b)(2)[7] in 1999 and 2004) — can all be considered as follow-on proteins, even though they were submitted through 505 (b)(1) and 505(b)(2) with full, abbreviated or no clinical trials.

So the USA had won the race against Europe for first approval of a biosimilar through an abbreviated BLA route in 1996 and the ANDA abbreviated route in 1997, but now has fallen behind Europe by not *continuing its regulatory practice* of approving other follow-on proteins under abbreviated ANDA or NDA 505(b)(2) regulatory pathways, because there is no legal basis for the agency to continue such practice. Several pending generic applications of follow-on proteins await FDA approval under 505(b)(2) and probably will not be approved in 2006.

This 'continuation of inconsistent regulatory practice', the broad discretion of FDA in its approval process and its granting of marketing authorisations *by exception* are at the centre of controversy in the USA, representing a significant hurdle for the USA to overcome in the race, now that Europe has its own legal basis in place for continual approvals of biosimilars in a consistent manner.

ABBREVIATED BLAS OR THE PAPER BLA FOR BIOSIMILARS IN THE USA

David M. Dudzinski, a student at the Harvard Law School won first place and US$1,500 for his paper in which he coined the term ABLA for an abbreviated BLA.[8] At the time of writing, the Food and Drug Law Institute (FDLI) had not published his paper, but consider the following remarks made by Helen Winkle[9] at the June IGPA meeting[10] in Malta when asked if there was a possibility for an ABLA in the USA:

> . . . as all biologics are by definition also drugs, it is possible that BLAs could be considered interchangeable, even though there is currently no provision for abbreviated BLAs. There could be possible interchangeability between the statutes.

Instead of waiting for an abbreviated regulatory pathway for consistent continual

approval of biosimilars in the USA, some generic and specialty pharma companies have turned to submissions of the full BLA (under the Public Health Service (PHS) Act) seeking approval for biosimilar products that currently will not be interchangeable. The BLA is silent on the specific numbers of patients required for full clinical studies, and biosimilars filed (and planned for filing) under BLAs are not using as many patients as originators,[11] and do not require comparative studies. The FDA has a lot of discretion in granting approvals under BLAs. Teva submitted an NDA 505 (b)(1) to FDA's Center for Drug Evaluation and Research (CDER) for recombinant human growth hormone and was approved in 2005. Teva launched Tev-Tropin®, rDNA somatropin, on 11th February, 2005, three days before the FDA/DIA Scientific Workshop on Follow-on Protein Products. It was not mentioned in any of the presentations and neither did any of the attendees discuss the NDA 505(b)(1) biosimilars approach in the networking sessions, demonstrating a lack of knowledge in the USA about this approach for biosimilars.

Teva's strategy is to use its specialty sales force subsidiary, Gate Pharmaceuticals, to market the product and offer comprehensive services to healthcare professionals. Teva created 'Growth Solutions' to provide: a comprehensive patient benefits investigation to help secure insurance coverage; case referrals to an in-network pharmacy for prompt prescription fulfilment; and alternate forms of assistance to qualifying patients who lack sufficient insurance coverage and cannot afford therapy.[12] This is the same support system as the one used by Teva to sell Copaxone®. Human growth hormone products are sold through specialty distributors in the USA, since paediatric training must be implemented for self-administration. This kind of marketing support is necessary for this specific biosimilar and Teva hopes to achieve its market share goals in marketing a non-interchangeable biosimilar in this manner.

As of this writing, no one knows if Helen Winkle's remarks will have an effect on the creation of the interchangeability of statutes and, hence, interchangeability of Tev-Tropin and other BLAs of follow-on proteins. Rather, FDA's Office of the Chief Counsel, and newly-appointed Chief Counsel Sheldon Bradshaw, has more power to influence the interchangeability of statutes. If it did occur, BLAs would not be enough; instead, supplements would be required to show equivalence through comparative studies. Moreover, such studies would be made post-approval as BLAs do not require them.

CROSS-BORDER UTILISATION OF BIOSIMILARS: USA WINS RACE WITH BETA INTERFERON 1B

In a world of on-line pharmaceutical purchasing, the USA was the first to buy a biosimilar across its border. In July 2003, Probiomed launched Uribeta beta Interferon 1b in Mexico, a biosimilar to Schering's Betaseron. In less than 14 days, purchases were made by patients in California across the Mexican border.

In Europe, PLIVA was the first non-EU-25 country to register a biosimilar to Eprex® erythropoietin-alpha (EPO alpha), approved on 21st June, 2005, under the brand EPOETAL, which was launched in the first quarter of 2006 with a discount of 20 per cent to the brand. PLIVA filed the dossier nationally in Croatia and it is likely that cross-border sales will occur in Slovenia and Hungary, both EU-25 countries that border Croatia, since (according to IMS) the EPO-alpha market in Croatia was only US$6m in 2004. In addition, these cross-border sales are likely because it is doubtful that Croatia will join

Table 1: Sales of three biosimilars: USA *v* Europe

Biosimilar	Sales in 2004 ($m)	
	USA	Europe
Beta interferon	1,219	1,026
Recombinant somatropin	948	462
Recombinant insulin	2,022	330
Total	**4,189**	**1,818**

Source: Company financial reports, 2005

Table 2: Sales of beta interferon biosimilars: USA *v* Europe and worldwide

Drug	Sales in 2004 ($m)		
	USA	Europe	Worldwide
Avonex	923	494	1,420
Rebif	296	532	1,090
Total	**1,219**	**1,026**	**2,510**

Source: Company financial reports, 2005

the EU-25 soon, as its application status was placed on indefinite hold in March 2005, owing to the UN War Crimes Prosecutor, Ms Carla Del Ponte's, assertion that that Zagreb had not fully cooperated with the International War Crimes Tribunal for the former Yugoslavia with regards to the apprehension of the fugitive alleged war criminal, and former General, Ante Gotovina.

THE RACE FOR GREATEST VALUE OR PROFITS FOR BIOSIMILARS

Considering three biosimilars in this race: beta interferon, recombinant human growth hormone (somatropin) and recombinant insulin, the USA has won the race for greatest value measured by sales in 2004 by a factor of more than two. The start of the race began after the first approval of a new biological entity. The race results are shown in Table 1.

Beta interferon biosimilars

Avonex and Serono's Rebif® are the two biosimilars approved and launched in the USA and EU to compete with Schering's Betaseron (Betaferon in Europe). Sales of the two biosimilars are presented in Table 2.

Somatropin (recombinant human growth hormone) biosimilars

Genentech's Protropin®, a recombinant human growth hormone, was approved by the FDA on 17th October, 1985 (later discontinued) but not in Europe. Rather, Kabi's Genotropin® was first approved in Europe in 1985 and then in the USA in 1995. Based on these first approvals, Saizen®, Nutropin® (successor to Protropin), Humatrope®, Norditropin® and Zomacton® are somatropin biosimilars. Again, the USA leads Europe in sales of these biosimilars based on their reported sales in 2004 ($948m to $462m). TevTropin was approved in the USA in 2005, but had been selling in Europe as Zomacton since 1996.

Recombinant insulin biosimilars

Europe won the value race for recombinant insulin in 2004 by 10.6 per cent. Total 2004 sales for the NovoNordisk recombinant insulin biosimilar brands in Europe were $1,362m *v* $775m for the USA; Aventis's biosimilar Lantus® had sales of $660m in the USA *v* $330m in Europe.

THE RACE FOR LEGAL PROVISION TO PROVIDE A CONSISTENT BIOSIMILARS REGULATORY PATHWAY

Europe is winning this race, but the race is not yet over. By the time this paper is published, there will be many articles published about the success of the current legal provision for a regulatory pathway for biosimilars in Europe, with the approval of Omnitrope®. What remains to be seen is whether the EC accepts the European Agency for the Evaluation of Medicinal

Products (EMEA) recommended approvals of more complex biosimilars under the centralised procedure in a consistent and continual manner, as concisely presented in June 2005 by Dr Peter Richardson, Scientific Administrator, Quality of Medicines Sector, EMEA.[13]

At the time of writing, only three marketing authorisation applications (MAAs) for biosimilars under the new EMEA guidelines and legislation have been submitted (one in October 2004) and three have been accepted by EMEA as valid submissions, two by the same company.[14] At least 14 MAAs for EPO biosimilars will be submitted to EMEA during 2006–2007.[15] Two of the three biosimilars already submitted have been recommended by EMEA for approval.

Dissidents within the European generics industry complain that the European regulatory pathway for biosimilars is 'case by case'. EMEA's publication of four product class-specific guidelines[16] on clinical and non-clinical issues for insulin, somatropin, EPO and granulocyte colony stimulating factor (G-CSF) specifically state how many patients are required for establishing safety, however,[17] and the numbers are certainly much less than could be expected for a new chemical or biological entity. Nevertheless, Mayne Pharma has withdrawn its biosimilar application for EPO, because the final guidelines on EPO requiring 300 patients for establishing immunogenicity safety is too costly, thus the expected return from an EPO biosimilar is not attractive and does not justify the cost of the immunogenicity study of such magnitude. It remains to be seen if the 14 MAAs to be submitted for EPO biosimilars will have a similar fate.

Update on US legal provision for abbreviated regulatory pathway for biosimilars

At the time of writing, FDA's white paper, which will contain the definitive history of new biological entity and biosimilar approvals over the last 50 years is still awaited. It was due in August 2005 but is unlikely to be published in 2006 without the intervention of Congress. The white paper is the first step in FDA's procedure to provide guidelines for follow-on protein products. There are several legislative initiatives that are on-going which may lead to biosimilar[18] congressional action. The Senate Appropriations Committee has requested a feasibility report on follow-on proteins. The House Energy & Commerce Committee's Health Subcommittee's chairman, Nathan Deal, has suggested that follow-on biologicals will be the subject of a future hearing on Hatch-Waxman reforms, but there is still no pending legislative action as of now. On February 10, 2006, Congressman Henry Waxman and Senator Orrin Hatch wrote a letter to Andrew von Escherbach, Acting Commissioner of FDA, urging the release of the white paper and other guidance documents, so that the approval of insulin and hGH biosimilars pending at the Agency (since 2002) can be accelerated. At the GPhA meeting the following week the author, after showing several delegates of the generic industry this letter, mostly heard the comment that, 'FDA will continue to do as it pleases, until a permanent Commissioner is appointed, unlikely in 2006'. Then in April 2006, a federal judge ordered FDA to decide on approval of Omnitrope, but gave the FDA no time table.

An NDA 505(b)(2) biosimilar wins the race *v* ANDA synthetic: nasal recombinant calcitonin

On 12th August, 2005, FDA approved Fortical®, Unigene's nasal recombinant calcitonin, a biosimilar to Novartis's nasal synthetic salmon calcitonin. The IND was filed by Unigene in January 2000 and

the NDA[19] was filed in March 2003. It was accepted by FDA for review in May 2003. The normal review cycle for an NDA 505(b)(2) was on time, and Unigene received an approvable letter from the FDA on 5th January, 2004. A Citizen's Petition was filed on 9th January, 2004, however,[20] delaying final approval for more than 18 months. Nevertheless, the 505(b)(2) pathway won the race *v* an ANDA on the same product filed in October 2002 by Novex (Apotex).

THE RACE FOR INTERCHANGEABILITY AND SUBSTITUTION OF BIOSIMILARS

This race has already begun. In Europe, there are different requirements for substitution in different member states:

- Some require doctors to prescribe by international non-proprietary name (INN).
- Some require generic substitution.
- Some encourage doctors to prescribe generics.
- Some permit branded generic medicines interchangeability (eg Germany and Hungary).

A biosimilar can be substituted for a brand by generic prescribing by the doctor, and most likely the prescription is filled at the hospital pharmacy.

Are doctors required to prescribe by INN?

Greg Perry, Director General of the European Generics Association (EGA), presented a series of slides in November 2004[21] that summarised the Association's members' answers to the EGA survey on generics prescribing practices. In answer to this question, the members answered that in 36 per cent of the member states, doctors were required to prescribe by INN in the UK, Spain, France, Italy, Ireland, the Netherlands, Portugal, Sweden, Estonia and Malta. One slide in Perry's presentation raised the question of whether biosimilars will receive an INN and thus be able to be prescribed by doctors in these 10 member states. The World Health Organization (WHO) assigns INNs to pharmaceuticals, including recombinant drugs. Suzette Kox, Senior Director Scientific Affairs of the EGA, contacted the WHO and presented the results in May 2005.[22] In short, every biosimilar will receive an INN, except recombinant vaccines and cell therapies.[23] The biosimilar INN will have a Greek letter spelled out as the second part of a two-word name if the biosimilar is glycosylated and a Roman letter for cytokines and interferons. Therefore, one can expect that in the near future, European sales forces will explain to doctors how to prescribe their company's biosimilars by writing the INN on the prescription.

Looking more carefully at the 2004 survey, the requirement for mandatory physician prescribing by INN is not widespread in practice. According to the notes of this survey (available on the EGA website)[24] it would appear that the implementation of this national policy is done in Spain (always for reimbursed drugs); in France (for 25 per cent of prescriptions); Italy (but pharmacists can dispense any product including the brand); Ireland (but rarely, only 2 per cent written as INN); in the UK by hospital physicians (although all doctors are trained to write by INN[25]); in Estonia (but not widely implemented); and by doctors in Maltese state institutions.

Member states requiring generic substitution

The answers to the 2004 survey question, 'Is generic substitution allowed?' show that

Table 3: USA *v* Europe race in biosimilars

Type of race in biosimilars	USA	Europe	The winner
First launch	Avonex (17th May, 1996)	Avonex (May 1997)	USA
First cross-border use	Uribeta (June 2003)	Epoetal (1Q06)	USA
Most value in 2004	US$4,189m	US$1,818m	USA
First legal provision for consistent regulation	Not yet	Implemented for Omnitrope	Europe is winning
Interchangeability	No	Yes, in most member states	Europe is winning

some member states have implemented legislation that link substitution to reimbursement. In the UK, generic substitution is forbidden by law, but it is the general practice in hospitals because generic prescribing is widespread. In Sweden, generic substitution is compulsory, unless the patient is willing to pay the difference in price. In Italy, substitution is a legal obligation, but pharmacists rarely override the doctor's prescription.

Generic substitution in the USA

Given Europe's fragmented substitution/reimbursement schemes at the national level, the USA will have the lead in the race for interchangeability and substitution of biosimilars, once a consistent FDA regulatory policy is established and implemented continuously for biosimilars. The 'AB rating' is the basis for generic substitution at the pharmacy, which can be awarded to a generic drug on the basis of its meeting the bioequivalency requirements of existing regulations. Moreover, it is generally known that the USA pharmacist makes a higher profit dispensing generics than dispensing brands. The point is that an existing and consistent commercial mechanism is in place for generic substitution in the USA that is not in place in all European member states. If, however, a regulatory policy is not established to allow biosimilars to take advantage of existing generic substitution mechanisms, then Europe will surely win this race, too.

A biosimilar may be more affordable than an AB-rated substituted generic

The recently-approved Fortical recombinant calcitonin may eventually be priced considerably lower than the current pending ANDA AB-rated generics from Apotex and Par Pharmaceuticals (licensed from Nastech). This is because the recombinant API produced by Unigene costs a fraction of the synthetic salmon calcitonin API, owing to Unigene's proprietary direct expression recombinant technology.[26] The nasal salmon calcitonin market in the USA is largely a managed care market and Unigene has stated that its partner Upsher-Smith Labs has the objective of capturing the maximum market share,[27] implying aggressive pricing versus generics.

CONCLUSION

Table 3 shows the final race results. The USA has won three of the races in biosimilars over Europe, but is losing the most important one: enactment of a legal provision for the application of a consistent abbreviated regulatory pathway for approval of biosimilars. The most recent approval of an NDA 505(b)(2) for recombinant calcitonin had a faster approval time than competing ANDAs for the same molecule, but it was not awarded an AB-rating permitting substitution at the

pharmacy level. Other NDAs for biosimilars are still pending at the FDA, these include Novartis' Omnitrope recombinant growth hormone, which is a puzzle to those in industry pondering the BLA *v* NDA regulatory approval route for their biosimilars. Interchangeability issues aside, the point is for an approval of a new biosimilar product, the FDA still grants final approval through a policy of exception.

References and notes

1. See the excellent paper by Suzette Kox which explains the list of terms for biosimilars: Kox, S. (2005) 'The saga of the legal framework for biogenerics in Europe', *Journal of Generic Medicines,* Vol. 2, p. 105.
2. BLAs are authorised under the Public Health Service Act (42 USC 262, *et seq.*; 21 CFR Part 600).
3. ANDAs are authorised under the Federal Food, Drug & Cosmetic Act (FFDCA) 21 USC 355(j); CFR 314.92.
4. See NDA 21–047.
5. *Serono Labs v Shalala*, 158 F.3d 1313, 1320 (DC Cir. 1998).
6. FDA/DIA jointly sponsored workshop 'Scientific Workshop on Follow-on Protein Pharmaceuticals' 14th–16th February, 2005.
7. NDA 505(b)(2)s are authorised under FFDCA 21 USC 355(b)(2); 21 CFR 314.52.
8. Dudzinski, D. M. (2005) 'Reflections on historical, scientific, and legal issues relevant to designing approval pathways for generic versions of recombinant protein-based therapeutics and monoclonal antibodies', *Food and Drug Law Journal*, Vol. 60, pp. 143–260.
9. Currently Director of the Office of Pharmaceutical Science at FDA's CDER.
10. 'Generic Medicines: A Global Market, A Global Industry', 19th–22nd June, 2005, Malta.
11. This comes from private communication with several companies. Once approved, the BLAs will have details on the actual number of patients used.
12. See http://www.tev-tropin.com.
13. 8th Annual IGPA Conference, 'Similar Biological Medicinal Products Regulatory Perspective' Malta, 19th–22nd June, 2005.
14. BioPartners submitted alpha interferon on 25th October, 2004 for hepatitis C and then somatropin on 30th November, 2004.
15. Survey by Technology Catalysts 2005 unpublished data.
16. See Insulin CHMP/32775/05, somatropin CHMP 94528/05, EPO CHMP 94526/05 and G-CSF CHMP/31329/05.
17. For EPO, as an example, CHMP 94526/05 states 'safety data from at least 300 patients treated with the biosimilar is sufficient.'
18. Shelton, D. M. (2005) 'Whither biogenerics: An update', at: 3rd Annual Generic Pharmaceuticals Global Summit, 2nd August, 2005.
19. NDA number 21–406.
20. Citizen's Petition 2004p-0015.
21. 10th Annual EGA Conference, Amsterdam, November 8th–9th, 2004: The Generic Medicines Industry Meeting the Challenge of European Healthcare, 'Presentation of EGA's Internal Review of National Measures Affecting the Marketing of Generic Medicines'.
22. Kox, S. (2005) 'Other regulatory developments in the European Union related to ''biosimilars''', 3rd EGA Annual Symposium on 'Biogenerics': Moving Forward with Biosimilar Products in Europe, 27th May, 2005, London, UK.
23. Author's personal communication with Dr Raffaella G. Balocco Mattavelli, Responsible Officer, INN Programme, Quality Assurance and Safety: Medicines, Dept. of Essential Drugs and Medicines Policy, World Health Organization, 26th July, 2005.
24. http://www.egagenerics.com: Facts & Figures: Pricing and Reimbursement Systems.
25. Mike Brownlee, Head of Medicines Pricing & Supply Branch, Dept. of Health, UK.
26. Mehta, N. M. (2004) 'Oral delivery and recombinant production of peptide hormones, Part II: Recombinant production of therapeutic peptides', BioPharm International, July 2004.
27. Investor's Conference Call, 15th August 2005. http://www.unigene.com.