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VIA HAND DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Comments on Behalf of Barr Pharmaceuticals, Inc. and Its Subsidiaries, Barr Laboratories, Inc., Duramed Pharmaceuticals, Inc., and Duramed Research, Inc.
Docket No. 2004N-0355 (Follow-On Proteins)

Dear Sir or Madam:

On behalf of Barr Pharmaceuticals, Inc. and its subsidiaries, Barr Laboratories, Inc., Duramed Pharmaceuticals, Inc., and Duramed Research, Inc. (collectively, "Barr"), we submit the attached comments in connection with Docket No. 2004N-0355 relating to so-called follow-on protein products.

As the Agency is aware, Barr was represented at FDA's September 14-15, 2004 public workshop on scientific and technical considerations related to the development of biogenerics. We appreciate the opportunity to comment on this issue, which is important to Barr, the pharmaceutical industry, and the public.

Should you have any questions regarding these comments, please do not hesitate to contact me.

Very truly yours,

RAKOCZY MOLINO MAZZOCHI SIWIK LLP

Christine J. Siwik

CJS/cd
Enclosure

2004N-0355 C10

Comments on Behalf of Barr Pharmaceuticals, Inc. and Its subsidiaries, Barr Laboratories, Inc., Duramed Pharmaceuticals, Inc., and Duramed Research, Inc. (Docket No. 2004N-0355)

I. Compelling Public Policy Reasons Exist For Approving Biogenerics – Generics Control Costs And Spur Innovation.

Biologics represent a major part of health care expenditures in the United States each year. In 2003, as we understand it, just six biologic pharmaceutical products generated sales of more than $9.5 billion. Three of the top biotech pharmaceuticals can cost as much as $24,000, $10,000 and $20,000 per patient, per year.[1] Another product, a biologic drug approved for an enzyme deficiency, costs over $170,000 per patient per year.[2] While the regulatory and patent system should incentivize and reward true innovation in the biologics arena, the market exclusivity on such compounds should not last forever. Allowing generic competition would ensure increased access, lower prices, and greater innovation.

The need for increased competition is particularly acute for off-patent biologics. According to one source, "[t]hrough 2006, over $10 billion worth of branded biologics are scheduled to go off patent."[3] Once a biologic loses patent protection, consumers should not be forced to continue paying monopoly prices. Instead, there must be an expedited approval process for biogenerics, just as there is for traditional generic drug products, which will encourage competition and price rationalization. Market competition with respect to traditional drugs has saved Americans literally tens of billions of dollars.[4] Today, generic drugs represent 51% of the total prescriptions dispensed in the United States, but less than 8% of all dollars spent on prescription drugs.[5] An effective program for biologics would yield similar, much-needed savings. Indeed, generic competition for biologics has the potential to offer health care providers and consumers dramatic and substantial savings, lowering America's overall healthcare bill.

In addition to controlling costs, competition also stimulates innovation. Competition from biogenerics will spur brand companies to develop new products, as happened with respect to traditional small molecule drugs.

Without competition, brand companies have little, if any, incentive to develop truly innovative products. Rather than invest significantly in entirely new products and product lines (which carries financial risk), they can simply rely on the generous revenue stream that their on-going monopolies on older products generate. But competition from generic products pressures brand companies to develop new products and improve existing ones to maintain profit

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[1] *See* DESERET NEWS, December 15, 2002 (Neupogen®, $15,000 to $24,000) (Ex. A); ST. PETERSBURG TIMES, July 22, 2003 (Procrit®, $7,000 to $10,000; Humatrope®, $12,000 to $20,000) (Ex. B).

[2] THE NEWS & OBSERVER, May 13, 2003 (Cerezyme®) (Ex. C).

[3] Generic Biologics: The Next Frontier at 4 (June 2001) (Ex. D).

[4] According to a 1998 study by the Congressional Budget Office, generic drugs save consumers approximately $8 to $10 billion each year. *See* CBO Study, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry" at ix, xiii (July 1998) (Ex. E).

[5] *See* GPhA, "Generic Pharmaceutical Facts at a Glance," *at* http://www.gphaonline.org/aboutgenerics/factsabout.html (last visited Dec. 13, 2004) (Ex. F).

margins. Consider, as one example, the development of drug products to treat gastric ulcer disease.

Brand companies developed H_2-receptor antagonists such as cimetidine (Tagamet®) and ranitidine (Zantac®) first to treat gastric ulcer disease and then for the treatment of gastroesphageal reflux disease (GERD). These products, while protected by patents and regulatory exclusivities, generated billions of dollars in sales. As generic companies began to develop competing versions, brand companies responded by developing the next class of treatment, proton pump inhibitors. AstraZeneca's omeprazole (Prilosec®), once a multi-billion dollar product, is perhaps the most well known of these drugs. Many touted this new class of drugs as a more effective treatment for GERD. But as generic competition for omeprazole loomed, AstraZeneca developed a new product, esomprazole (Nexium®). Patients taking esomeprazole reportedly experience better healing rates of esophageal erosions than patients taking omeprazole. Without question, brand companies will be looking for the next, improved GERD treatment as generic competition for esomprazole begins to take shape.

The fact is, the growth of the biologic drug industry may owe itself in large part to generic competition. After Congress passed Hatch-Waxman in 1984, brand companies knew that they would face increased competition for sales of traditional small molecule drugs. Many began investing their resources in what was then a fledgling industry, developing biologic drug products. These investments brought about numerous new life-saving drugs, as well as significant advances in the technology needed to produce and characterize these drugs. Hundreds of additional products currently are in the pipeline. While these investments might eventually have been made, no one can seriously doubt that the competitive pressures that generics created provided the incentive for this research and development to be done sooner rather than later.

The market dynamic created by generics thus benefits consumers in two important ways. First, generics provide the public with quality, lower-priced alternatives to brand name drugs, saving consumers and taxpayers billions of dollars a year while increasing access to those with restricted income. Second, generics provide the urgency for innovation, forcing brand companies to constantly strive for new and revolutionary treatments.

Finally, and significantly, creating a pathway for the approval of less-expensive biogenerics should not unfairly deprive brand companies of legitimate rewards for innovation. Barr believes that brand companies should be rewarded with a period of regulatory exclusivity for undertaking and accomplishing the development program necessary to obtain approval of their biologic drug products, in addition to any patent protection that they might obtain under existing law. Strong brand companies are critical to the continued improvement in public health, as well as to the continued success of the pharmaceutical industry as a whole. But the marketing exclusivity on biologics that brand companies currently enjoy cannot and should not last indefinitely. The need for brand companies to recoup research and development expenditures

must be balanced against the undeniable benefits that generic products produce, both in terms of cost savings and as a motivating force behind future advances.

II. Science Supports Approval Of Biogenerics.

Perhaps it is fitting that much of the discussion surrounding FDA approval of biogenerics takes place this year – the 20th anniversary of the Hatch-Waxman Amendments. In the discussions leading up to the passage of Hatch-Waxman, brand companies expressed many of the same concerns raised today when attempting to block efforts to develop a generic drug approval pathway. Twenty years later, the success of traditional drug products amply demonstrates that those concerns never materialized. With a well thought out and scientifically-based process, the same will be true for biogenerics.

With regard to feasibility, the issue is not biologic versus small molecule. Rather, the issue is the approval of simple versus complex drug products. Rational development programs need to be and can be designed to address the complexity of a specific compound. The brand companies have focused on a small number of particularly complex biologic products when arguing that science cannot support an abbreviated biogeneric pathway. But there also are relatively simple biologic products (insulin, human growth hormone, and the like), just as there are simple traditional drug products (Tylenol®) and more complex traditional drugs (Premarin®).

When deciding to approve a drug product, the Agency must focus on the complexity of the scientific issues involved with that particular drug product. FDA cannot allow the entire process to be driven by a few atypical products that might require special consideration. The fact is that for the vast majority of biologics, comparability can be demonstrated using some or all of the following parameters: *in vitro* studies, pharmacokinetics, surrogate markers, and/or clinical outcomes depending on the nature of the protein. By demonstrating therapeutic interchangeability, safety and efficacy profiles between the biogeneric and the reference biologic will be comparable. Traditional generic drugs do not require full pre-clinical and clinical trials because of well-defined, publicly available safety and efficacy data generated as health care providers used these products over the years. The same is true of biogenerics. As Novartis readily acknowledges: "Old models and mantras are inhibiting progress – **the product *is no longer* the process**."[6]

Moreover, innovators do not hold a monopoly on "know how" or experience with complex drug applications. Generic companies have decades of experience developing and manufacturing complex drug products – substitutable for brand name drug products – in full compliance with GMP's. The Chemistry, Manufacturing and Controls ("CMC") section of a generic drug application is, for example, every bit as complete and complex as the information

[6] Statement of Mathias Hukkelhoven, Ph.D., Senior V.P., Global Head, Drug Regulatory Affairs, Novartis, Sept. 14-15, 2004 FDA Public Workshop at 3 (emphasis in original) (Ex. G).

submitted by an innovator company. Companies like Barr validate their own processes and generate their own stability data and impurity profiles, among other things. Many companies even have full clinical development capability, which they use to develop generic products that require clinical endpoint studies and branded products that require full New Drug Applications. Biogenerics, therefore, will not be "follow-on" proteins which utilize the innovator's proprietary process, specifications, or clinical data. Biogenerics are drug products fully supported by independent analytical testing capable of ensuring their safety and efficacy.

Finally, a willingness to take certain risks, in light of the potential benefits, is an inevitable component of FDA's review and approval process. Approving a new chemical entity always requires the Agency to conduct a risk/benefit analysis, weighing the known against the unknown. FDA considers, among other things, the pre-clinical and clinical trial data submitted with the application. However, this limited safety data does not necessarily represent the entire population of patients who will ultimately be treated with the product. Indeed, at the time of FDA approval, information about a given compound often is incomplete. But if the Agency refused to approve any product until all questions had been answered and no risks existed, few, if any, drug products would ever get approved. Pharmaceuticals products do, after all, carry risk. Yet, as time passes and a broader patient population uses the product, health care providers obtain more information and experience with the product. FDA uses this experience to, among other things, modify labeling, thus ensuring appropriate and safe use of these products. Because of this broader and more complete understanding of these products, generics – drug or biologic – do not need to regenerate the same information. Consequently, an abbreviated development program targeted at demonstrating comparability can insure the safety and efficacy of biogeneric products.

In the end, generic companies, like their branded counterparts, remain fully committed to producing safe and effective drugs. No one benefits from short cuts that would put the consuming public at risk. Generic companies stand ready to utilize the significant scientific advances available today to make quality biogeneric products readily available to the public. It is incumbent upon FDA to establish the necessary approval pathway for biogenerics. The science necessary to support such approvals exists today. The need for such products exists today. Any bright-line distinction between biologics and traditional drugs is wholly artificial and ultimately unhelpful in advancing the cause of biogenerics.

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Barr urges FDA to act swiftly and decisively in approving biogeneric products, and appreciates the opportunity to comment on these important issues.

Respectfully submitted,

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