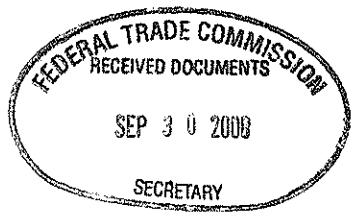
Talecris
BIOTHERAPEUTICS

P.O. Box 110526
4101 Research Commons
79 TW Alexander Drive
Research Triangle Park
North Carolina 27709

September 30, 2008



By Hand Delivery

William E. Kovacic, Chairman
Federal Trade Commission
Office of the Secretary, Room H-135 (Annex F)
600 Pennsylvania Avenue, NW
Washington, DC 20580

Re: Emerging Health Care Competition and Consumer Issues
Comment, Project No. P083901

Dear Chairman Kovacic:

Talecris Biotherapeutics ("Talecris") thanks the Federal Trade Commission ("Commission") for this opportunity to offer comments regarding Emerging Health Care Competition and Consumer Issues. We are a leading manufacturer of plasma-derived therapies, and our approach to quality patient care is simple. We support giving each patient and his or her physician access to the product most effective for that patient in a setting best suited for his or her individual needs.

For the Commission's consideration, we offer, in summary, these comments regarding follow-on biologics and quality:

- **Competition Provided By Developing an Abbreviated Regulatory Pathway for Follow-on Biologic Drugs**
    - Due to the complex and variable nature of plasma protein therapies, we urge U.S. policy-makers to follow the lead of European Medicines Agency ("EMEA"), the Food and Drug Administration's ("FDA") counterpart, by excluding these products from an abbreviated regulatory approval pathway. If, however, plasma protein therapies are included, we urge due consideration of interchangeability qualifications, sufficient data exclusivity, responsibility for manufacturing and immunogenicity data, and narrow information exchange. Critically important safety and efficacy issues and the potential to adversely affect innovation should give the FTC

pause in devising its policy on follow-on biologics, particularly with respect to plasma protein therapies.

- **Competitive Significance of Health Care Quality Information**

  - Effect of framing quality information on purchasers' decisions: All intravenous immunoglobulin ("IVIG") products vary, but until recently the Centers for Medicare and Medicaid Services ("CMS") treated all products the same for Medicare payment purposes. In doing so, CMS signaled to providers and beneficiaries that they should treat the products as clinically indistinguishable, despite the fact that the Food and Drug Administration ("FDA") has never made that determination, and it is not, in fact, correct. Grouping these products in this way framed providers' clinical decision-making and their selection of products to the detriment of patient access and the quality of care.

  - Development of reimbursement and payment reform and its effect on the development of quality matters: CMS' decisions regarding product comparability failed to appreciate important product differences. In doing so, CMS' implementation of a new payment metric provides an interesting case study about the potential impact of reimbursement on patient access and care. Before the Commission embarks on recommendations regarding health care quality, we encourage it to consider the unintended consequences that may occur when an agency acts without a full appreciation of the relevant market.

These comments are addressed more fully in the balance of this letter. We thank the Commission in advance for its consideration of them.

I. About Talecris

Talecris is a leading manufacturer of plasma-derived products. Collectively, our products are used to treat dozens of life-threatening conditions and enhance the lives of thousands of patients. We are perhaps best known for our IVIG product, Gamunex. Treatment with IVIG provides immune-deficient individuals with the antibodies necessary to prevent potentially fatal infections. Gamunex is indicated as replacement therapy for primary immuno-deficiencies along with other immune thrombocytopenic states. FDA recently approved Gamunex as a treatment for chronic inflammatory demyelinating polyneuropathy ("CIDP"), a debilitating neurological disorder that results in muscle weakness and fatigue, which can lead to severe impairment of motor skills. Gamunex now has the broadest set of FDA-approved indications of any liquid IVIG therapy and is the first and only IVIG therapy approved to treat any neurological disorder in the U.S. For these patients, Gamunex is lifesaving. Because Talecris is committed to providing quality products, we welcome the opportunity to offer our input to the Commission to help raise the quality of health care services and products nationwide.

We are a young company that is proud to have inherited a legacy of more than 60 years of providing lifesaving and life-enhancing plasma-derived therapeutic proteins. Following our 2005 acquisition of the assets of Bayer Biological Products' plasma business, Talecris is maintaining and building on a heritage of patient care innovations in therapeutic proteins that dates back to the early 1940s. Our products have long been recognized in the industry as innovative and of the highest quality. Talecris, having inherited a solid foundation of unparalleled expertise and experience, is now uniquely positioned to create a new standard of excellence in the field of biotherapeutics.

We produce our products from plasma pooled from thousands of blood plasma donors, which is processed to provide a high concentration of antibodies. Normal human blood contains antibodies, which help to protect us from a wide spectrum of pathogens. However, some individuals are unable to make functional antibodies, which renders them susceptible to recurrent and life-threatening infections. Treatment with IVIG, for example, provides immune-deficient individuals with the antibodies needed to prevent potentially fatal infections. Talecris is one of a handful of manufacturers that produce plasma protein therapies, like Gamunex. We are the only manufacturer that produces its IVIG product entirely in the U.S.

As you consider quality improvement, we encourage you to be mindful of the special commitments and enormous efforts that Talecris has made to preserve access to IVIG therapy. Talecris has taken extraordinary steps to substantially improve production of IVIG, dramatically increase investment in production facilities, ensure the availability of an emergency supply of product for patients, and conduct important scientific research. These efforts demonstrate our commitment to immuno-compromised patients, and we are justifiably proud of our record.

The nature of plasma-derived products demands that we adhere to rigorous quality standards underscored by continual inspection and improvement. We maintain the highest quality standards in each of our facilities and work with FDA to ensure the quality of our products. We offer the following comments in the context of our considerable commitment to quality improvement and consumer safety.

II. Competition Provided By Developing an Abbreviated Regulatory Pathway for Follow-on Biologic Drugs

In the production of biologics, like plasma protein therapies, comparability issues have immense importance. Even minor changes in the manufacturing process can have terrible consequences for the health and safety of patients, altering the resulting product and potentially making it both ineffective and unsafe. Those differences and the risks that they create, as well as other reasons, led EMEA to exclude plasma protein therapies from its abbreviated regulatory approval pathway:

> In view of the complex and variable physico-chemical, biological and functional characteristics of [blood or plasma-derived products

> and their recombinant alternative] products . . . it will not be acceptable to submit a reduced clinical dossier when claiming similarity to a reference medicinal product. As a result, applications for such similar products will still need to satisfy the safety and efficacy requirements described in these [Blood Products Working Group] guidelines for 'new products'.[1]

In our view, the EMEA's caution is well-advised and well-supported as a scientific and medical matter. Should U.S. policy-makers break from their European colleagues by advocating for an abbreviated pathway for plasma protein therapies, despite the risks, we would urge the FTC and other policy-makers to carefully consider the following critical issues: interchangeability qualifications, sufficient data exclusivity, responsibility for manufacturing and immunogenicity data, and narrow information exchange.

A. Interchangeability Qualifications

It is imperative for the Secretary of the U.S. Department of Health and Human Services ("HHS") to have the authority to establish the necessary scientific evidence to adequately support the determination that a biosimilar product is "interchangeable" with an innovator product. In the absence of this, we fear that safety and efficacy will necessarily be threatened. Cogent, unambiguous guidance regarding the qualifications for interchangeability, based on compelling scientific evidence designed to ensure safety and efficacy, would be critical to any attempt to develop and implement a follow-on biologics pathway for plasma protein therapies or other biologics.

B. Sufficient Data Exclusivity

Innovator companies must be afforded sufficient data exclusivity following marketing approval, which in no event should be less than 14 years when considering extensions for new indications and pediatrics. Data exclusivity must be afforded these critical protections to appropriately reward manufacturers for their investment into the critical and enormous research and development needed to demonstrate safety and efficacy of their product. We believe that innovator manufacturers need significantly longer periods of exclusivity than small molecule products to recover these investments. For example, where a drug has been developed for an orphan indication, as in the case of our CIDP indication, FTC should consider carefully whether any proposed policy would undermine the incentives necessary to encourage the development of orphan drugs. A policy that would inadvertently decrease the support offered for the development of orphan drugs would have serious negative consequences for some of the most vulnerable populations. Without sufficient protections, innovative biologics will not be developed.

[1] European Medicines Agency, Committee for Medical Products for Human Use, Guideline on Similar Biological Medicinal Products, 30 Oct. 2005, § 3.4 (available at http://www.emea.europa.eu/pdfs/human/biosimilar/043704en.pdf).

C. Responsibility for Manufacturing and Immunogenicity Data

For all biologics, but particularly for plasma protein therapies, non-innovators must be held responsible for critical manufacturing and immunogenicity data to independently determine the safety and efficacy of their products. Not only would it be manifestly unfair to permit non-innovators to rely on data generated by innovator companies and submitted to FDA, at great expense and risk to those innovators, it would, even more importantly, jeopardize consumer safety. Subtle differences in the manufacturing process will necessarily exist between an innovator and a non-innovator manufacturer. As a result, the innovator's data will not accurately reflect the characteristics of the biosimilar product and its manufacturing process. To protect the health and safety of patients, non-innovators must be required to submit independent immunogenicity information. Immunogenicity is of a special concern for biologics, since even the smallest change in the manufacturing process can alter the immunogenicity of the product, dramatically impacting consumer health and safety.

D. Narrow Information Exchange

Protections like the Uniform Trade Secrets Act and Freedom of Information Act are already in place to protect an innovator product's FDA master file. As an innovator manufacturer, we strongly support these protections and encourage policy-makers to consider their weight and purpose in the context of a biosimilar pathway. We urge that any necessary exchange of information narrowly include only the data that a non-innovator has unmistakably demonstrated as necessary to expedite the development of its biosimilar.

All generic biologics raise fundamental questions about their impact on innovation as well as their risk to consumer safety and effectiveness. This is especially true in the case of plasma protein therapies, which have a particularly long and expensive pathway for innovation. Accordingly, we urge FTC to appropriately consider and reflect these important issues in its work. The FTC should be careful to ensure that its policy does not inadvertently undermine safety, efficacy and innovation.

III. Competitive Significance of Health Care Quality Information

In reviewing the Commission's questions regarding quality, we note the apparent absence of inquiries soliciting manufacturer input. We urge the Commission to think more broadly about the question of health care quality. In fact, we implore it to heed the lessons learned by other agencies that regulate health care decision-making. For example, the fact that it recently took us seven years to secure the new CIDP indication for an already approved product is testament to the exacting review that FDA has found necessary to evaluate issues affecting drug safety and efficacy, which are, of course, critical components in any discussion of quality. Although FTC purpose and process would be different than FDA's, of course, we believe that, if the FTC addresses quality, it will have to invest an enormous amount of time and resources to addressing complex, science-based issues. Identification of all of the relevant obstacles and the variability of "quality" issues, which will depend on the product or service involved, the affected

market, and the relevant patient and provider populations affected, will be a tremendous task and will require all stakeholders to be involved in the regulatory or policy process.

If it chooses to proceed, Talecris urges the Commission to adopt a broad view of quality, as endorsed by the Institute of Medicine's report, *Crossing the Quality Chasm*, the seminal work by IOM in this area. Quality is one of many moving parts of the health care system. We suggest that the Commission follow the Institute's lead and identify precisely what is meant by the term "quality" and how to improve it before moving forward with any initiatives. We urge the Commission to take a broad view of consumer safety by accounting for access issues when attempting to enhance quality measures.

Despite years of effort by other federal and state agencies, there are no clear definitions and standards of "quality" for the wide variety of products and services that might be affected by the Commission's work. As such, the potential for the Commission's efforts to foster quality could have unintended consequences. In this regard, we ask that the Commission take note of Talecris's experience with CMS' attempts to influence plasma protein therapies based on a limited understanding of the marketplace and recognize how agency action can, unfortunately, produce unintended consequences that can have terrible effects on patients.[2]

We applaud CMS's efforts to address and ultimately resolve the access issue caused by its coding and reimbursement decisions. Nonetheless, we highlight this example as evidence of how regulatory actions can have a significant impact on consumer access and the quality of their health care. We believe that this issue could have been avoided if CMS had solicited input from the relevant stakeholders. Likewise, we urge the Commission to give full consideration to comments not just from providers and payors, but also from manufacturers and other stakeholders to gauge how the health care system might react to any quality improvement initiatives. Consumer safety is foremost on Talecris's agenda, and we are deeply concerned that moves by the Commission, even if well-intentioned, might jeopardize access to lifesaving therapies if it makes recommendations without consulting a full spectrum of stakeholders.[3]

---

[2] We commend, for example, CMS' growing appreciation for the importance of broad input on quality-related issues. In its Proposed Revisions to Payment Policies under the Physician Fee Schedule and Other Revisions to Part B for CY2009, CMS included a number of quality measures as part of its physician quality reporting initiatives ("PQRI"). *See* 73 Fed. Reg. 38,502 (Jul. 7, 2008). These are an important part of CMS' efforts to understand and improve the quality of care beneficiaries receive. CMS proposed to add a significant number of quality measures to the list of reported metrics; however, a number of the proposed PQRI measures would affect beneficiaries but either did not propose measures that could assist the relevant populations or suggested quality measures that would not be appropriate to apply to these populations. We applaud CMS for seeking stakeholder input on these measures. Because it did so, we were able to include specific remarks on each proposed measure before CMS finalized its proposals.

[3] Discussing quality comparisons between products may be difficult for manufacturers in the marketplace when providers use drugs or biologics, like Gamunex, for off-label indications. As a result of FDA regulation of off-label promotion, manufacturers would not be able to address quality issues in the marketplace in an unfettered and open fashion. This could distort the Commission's proposals as they are implemented. We encourage the Commission to

A. Purchaser Decision Making and Quality Information: How does the framing of quality information affect purchasers' decisions? (Question A-8)

Until recently, CMS treated all IVIG products the same for Medicare coding and reimbursement purposes. In doing so, the agency signaled to providers and beneficiaries that the products were clinically indistinguishable. But, IVIG products vary, and FDA has never stated that these products are therapeutically equivalent, the starting point in any attempt to compare products.

To fully appreciate the differences between IVIG products, it is important to have a fundamental understanding of the distinctions between pharmaceutical products and biological products. In contrast to traditional medicines, biological products are derived from a living organism and used for the prevention or treatment of disease. They are typically too complex for chemical synthesis. The quality assurance of biological products raises particular safety considerations due to the biological nature of the starting materials used, the manufacturing process involved, and the methods needed to characterize the production consistency. A biological manufacturer has a special appreciation for these quality issues and the issues they often pose for regulatory authorities.

The biological nature of human plasma provides particular challenges to obtaining safe starting material and manufacturing high-quality therapies. The process of collecting plasma and manufacturing plasma protein therapies is heavily regulated by FDA. The collection of source plasma from donors is closely scrutinized. And, plasma fractionation, the process of isolating specific proteins from human plasma to manufacture various therapies, is heavily monitored. We use a patented caprylate process that preserves more of the fragile IgG proteins compared to prior generation IVIG products made with a harsher solvent detergent purification process. The caprylate process maintains the integrity of the IgG protein by allowing it to remain in solution during processing, maximizing biologic integrity and purity. Different purification methods have been developed based on the individual physico-chemical properties of the protein classes. Following fractionation, the finished therapies are packaged for distribution. Each lot of manufactured therapies is reviewed before approval for release. FDA is instrumental in ensuring the safety and quality of all plasma products.

Each manufacturer relies on unique pools of source plasma and each has a distinctive, FDA-approved, manufacturing process. These differences are the fundamental reason that all IVIG products vary, and these differences impact clinical outcomes. For example, our IVIG product, Gamunex, has demonstrated differences that are *significant therapeutic distinctions* from any other IVIG product. FDA has recognized significant differences in IVIG products.

---

thoughtfully consider this structural barrier to thorough manufacturer participation in discussions of health care quality.

The differences between IVIG products include the following:

- *Excipients (sugar content)* – Sugars have the capacity to affect patient tolerability, as well as serious adverse event profile;
- *Osmolality/Osmolarity* – Measure of the osmoles of solute per liter of solution/per kilogram of solvent;
- *pH-* Low pH, such as in Gamunex, retains highest active monomeric content, preventing aggregation that can cause issues with efficacy and tolerability;
- *Method of Viral Inactivation* – All products differ in the mechanisms of viral inactivation, and all mechanisms have the capacity to affect the delicate structure of the IgG molecule;
- *Antibody Content* – Due to differences in plasma donors as well as differences in manufacturing that affect subclass distribution, all products have differential antibody titers;
- *Biologic Activity* – Not only is antibody content important and different between products, recent studies have shown in various models that the biological activity of products is also different; and
- *Clinical Outcomes* – The manufacturing process, including viral inactivation, can affect the final product in clinically significant outcomes which may vary depending on the disease state examined.

Grouping these products together for coding and reimbursement purposes framed providers' selection of products. We do not believe that it was CMS' intent to influence provider decision-making. Instead, this determination was apparently based on the agency's failure to fully appreciate important product differences and associated patient-specific issues. For example, as we explained above, we use a patented caprylate process that preserves more of the fragile IgG proteins compared to prior generation IVIG products made with a harsher solvent detergent purification process. The caprylate process maintains the integrity of the IgG protein by allowing it to remain in solution during processing, maximizing biologic integrity and purity. Unfortunately, in evaluating whether IVIG products were interchangeable, CMS did not apparently consider the effects of different purification processes. To lead to an improvement in health care decisions and utilization, agency decisions must appreciate the differences between drugs and biologics, including the differences in how those products are manufactured and utilized, and the populations that use and prescribe those products.

If the Commission elects to make a proposal in this complicated area, we encourage it to adopt a practical, transparent and flexible standard of quality, only after a thorough process where stakeholders' views and product, patient and provider-specific issues are considered and addressed. Though we caution against any process that defines quality without fully considering every necessary element of this complicated issue in a thoughtful manner that ensures safety, efficacy, and innovation, Talecris very much supports a meaningful and productive debate about the critical issue of quality.

B. Barriers to Developing and Implementing Quality Measures: How does the development of reimbursement and payment reform affect the development of quality measures? (Question B-4)

As discussed above, CMS' policies failed to appreciate important product differences. As a result, in 2005, Medicare beneficiaries began to experience difficulties accessing IVIG in the physician office setting.[4] The development of the IVIG access issue provides an interesting case study about the potential impact of agency action on patient access and care. Before the Commission embarks on recommendations regarding health care quality, we encourage it to consider the unintended consequences that other agency actions have had when acting without a full appreciation of the relevant market.

The chronology of the development of the IVIG access issue reveals its substantial link to Medicare coding and reimbursement. Pursuant to the Medicare Modernization Act, the average sales price ("ASP") payment system first became the basis of Medicare reimbursement for services in physicians' offices in January 2005.[5] Reports of beneficiary IVIG access problems in physicians' offices surfaced shortly thereafter, when, in implementing ASP, CMS determined a reimbursement rate for all products under a single payment code and not separate codes for each individual product. Based on the information that we received from patient advocates, these reports were essentially localized in physicians' offices and limited to Medicare beneficiaries. In the case of IVIG, where there were multiple products in a HCPCS code, the ASP for this code was an average of all prices that all manufacturers reported for the products CMS fit within that code. Accordingly, the reimbursement failed to cover the acquisition costs of all products.

In establishing one reimbursement rate for all IVIG products in a code, CMS failed to appreciate the pharmacologic and therapeutic differences among competing products. When CMS averaged all the prices reported by manufacturers, by definition, some manufacturers' prices were above that reimbursement. Since each IVIG product is therapeutically distinct, setting one reimbursement rate for all products meant that some products were under-reimbursed and could not be utilized. The disparity between Medicare reimbursement rates and provider acquisition costs led to significant beneficiary access issues.

Because physicians were unable to acquire IVIG at or below the Medicare reimbursement rate, many stopped offering the infusions in their offices. A report by the Department of Health and Human Services ("HHS") at the time showed that 85 percent of physicians reported that they could not purchase IVIG at prices below the Medicare

[4] Letter from Daniel L. Levinson, Department of Health and Human Services Inspector General, to Nancy L. Johnson, Chairman, U.S. House of Representatives Committee on Ways and Means Subcommittee on Health (Nov. 16, 2006).

[5] Although the Medicare Modernization Act is perhaps best known for its establishment of Medicare Part D prescription drug coverage, it also made significant changes to the reimbursement mechanism for physician-administered drugs under Medicare Part B. *See* Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173 (2003).

reimbursement amount.[6] Furthermore, 61 percent of physicians indicated they had not been able to provide IVIG therapy to at least some patients. The same study showed that physicians were paying, on average, 24 percent above Medicare reimbursement per gram of IVIG.[7]

As a result of these access issues, beneficiaries who normally received their Gamunex infusions at local clinics were shunted to hospitals for therapy where they faced time delays, added cost and increased health concerns. Since Gamunex patients are immuno-compromised, the added burdens of traveling to another site for therapy, where infections are prevalent, presented serious health risks. Often, the hospitals where they eventually received their infusions did not stock Gamunex, but rather another brand with a different therapeutic and side-effect profile, further complicating the care of patients who had long-tolerated Gamunex. As a result of the failure to appreciate the IVIG market in implementing the ASP reimbursement metric, patient care was inadvertently jeopardized.

Significantly, throughout 2005, Medicare continued to reimburse hospital outpatient facilities without using the ASP methodology, while Medicare services in the physician office setting were being transitioned to the ASP methodology. Patient groups did not report any significant access issues at the time in the hospital outpatient setting. Indeed, the patient groups reported a migration of a significant number of patients from the physician office setting to the hospital outpatient setting.

In 2006, however, Medicare hospital outpatient reimbursement transitioned to the ASP payment system. Soon after, patient groups began to report that Medicare beneficiaries were experiencing IVIG access problems in hospital outpatient departments as well. During this time, it is important to note that reports of IVIG access issues were primarily focused on Medicare beneficiaries; commercially insured patients were generally not claiming similar access issues. Significantly, at a town hall meeting that HHS hosted regarding IVIG on September 28, 2006, many participants provided the same analysis about the link between multiple source coding and the access issues.

In mid-2007, CMS, to its credit, issued all liquid IVIG products separate HCPCS codes. This provided for ASP-based Medicare reimbursement equal to the price that each IVIG product's manufacturer reported. Shortly thereafter and following the creation of an add-on payment to reflect costs associated with the use of IVIG products, complaints of beneficiary access issues subsided.

This experience with Gamunex reimbursement demonstrates the enormous impact that payors, like Medicare, can have on quality and access through their reimbursement schemes and untested notions about the interchangeability of products. When CMS opted against

[6] U.S. Department of Health and Human Services, Office of the Inspector General, *Intravenous Immune Globulin: Medicare Payment and Availability*, OEI-03-05-00404, 5 (Apr. 2007). (hereinafter, "OIG Report")
[7] Id.

assigning different IVIG products separate HCPCS codes, providers were unable to differentiate the product within the market, and, in our view, serious quality and access issues were created.

Before CMS satisfactorily resolved the IVIG access issue last year, it was the subject of a Congressional hearing, an Office of Inspector General investigation, and a study by the HHS Office of the Assistant Secretary for Planning and Evaluation. Had greater steps to fully understand the impact of coding and reimbursement decisions been taken earlier, much debate and numerous access issues could have been avoided. Accordingly, should the Commission endeavor to make recommendations regarding health care quality, we encourage it to consider carefully the unintended consequences that other agency actions have had when acting without a full appreciation of the relevant market. Again, we encourage input from a broad range of stakeholders as part of the Commission's efforts.

IV. Conclusion

Talecris appreciates this opportunity to submit comments regarding Emerging Health Care Competition and Consumer Issues and thanks the Commission in advance for its consideration of the above comments. We welcome the opportunity to assist the Commission in avoiding the pitfalls and unintended consequences of agency actions. As such, we respectfully request an opportunity to participate in the Commission's upcoming Workshop on this matter. In sounding this cautionary note, Talecris urges the Commission to focus on these issues only after fully appreciating patient, provider and product specific issues like those affecting plasma protein therapies. Too narrow a focus may cause unintended and negative consequences that could undermine patient access, care and safety.

We urge the Commission to proceed with caution only after consultation with all stakeholders. Talecris would be happy to discuss any or all of the aforementioned issues further.

Respectfully submitted,

Bruce Bunyan
Vice President, Corporate Communications and Public Policy