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Honorable Frank Pallone, Jr.
Chairman
Subcommittee on Health
U.S. House of Representatives
Room 316, Ford House Office Building
Washington, DC 20515

Dear Congressman Pallone,

Thank you for the opportunity to provide my thoughts and opinions regarding a critical piece of legislation which would create a pathway to allow the FDA to approve generic biologic products. I too believe this is of paramount importance to the American patient and our health care budget both as a physician and as a Chief Executive of a biopharmaceutical company. Although I am a Board member of Biotechnology Industry Organization's (BIO) Emerging Company Section I want to note for the record that the comments and positions I have provided regarding follow on biologics legislation are my personal views and not that of BIO.

In addition to my answers to the questions provided I have taken the liberty of attaching several articles that present my integrated views on the key issues under debate for follow-on biologic legislation (period of exclusivity, degree of clinical trial requirements and interchangeability). In my view there is little economic or scientific evidence to support what some of the draft Bills have proposed such as prolonged periods of exclusivity, exhaustive duplication of clinical trials and the resistance to allowing follow on biologics to be substitutable or interchangeable with branded products. Specifically, Bain et al* in 2003 updated economic models of the cost of developing a small molecule drug from discovery through FDA approval providing factual support for justification for branded drug pricing and exclusivity protection given return on investment considerations. To my knowledge no such economic models have been constructed by independent third parties examining the cost, time and success rates for development of biologic drugs.

In my 15 years of industry experience, notably in the field of oncology drug development, the success rate and time to approval for biologic products

appears to be higher (higher percentage of biologics that enter human clinical trials are approved than small molecule drugs) with a shorter development cycle than their small molecule counter parts. This may be due in part to the unique targeted nature of the therapy and the lack of competition based on the unique nature of the product. As such the argument for prolonged exclusivity, non-interchangeability and quite frankly high prices does not appear justified by the argument of Companies needing to recover their return on investment. This is particularly true for modest innovative changes to formulation, like next generation ESA's, or next generation colony stimulating factors which demand a significant pricing premium despite marginal additional investment compared to the originator product, which in theory should have already captured their original return on investment.

I would be delighted to discuss further with the appropriate member of your staff at their convenience if desired.

Again thank you for including my views on this important and understandably controversial proposed legislation

Sincerely,

James A. Bianco, M.D.
President and Chief Executive Officer
Cell Therapeutics, Inc

Science/Safety

1. Immunogenicity is the ability of a particular substance (antigen) to invoke an immune response. Think of it like how foreign is the substance to what is normally in the body. Immune responses can range from being mild and of no clinical significance to a patient to a severe response which could lead to significant safety concerns. Different parameters like size or potency of antigens can influence the probability and severity of an immune response. This is relevant for biologics since they are predominately proteins which can be the strongest antigens among the various constituents that induce immune responses. The closer a engineered biologic is to the native body produced protein the less likely it will pose a safety concern for immunogenicity. In addition there are well documented and predictable what types of alterations to the native protein structure will increase or pose a potential to increase immunogenicity.

2. Immunogenicity testing should be determined by a scientific review body (i.e. FDA) on a case by case basis (see rational in #1) and not mandated through legislation. This would be, in my view, a bad precedent to place our legislative body in a position of dictating scientific decisions. If the Industry is pushing for such then it is a scare tactic that is not justifiable.

3. See answer 2. Immunogenicity testing both in animals and in limited clinical trials should be dictated by the science of each follow on biologic on a product by product basis.

4. The answer is not a simple yes or no as it will depend on the complexity of the biologic and the clinical endpoint for which it was approved. For example a reference ESA's were approved based on a simple primary efficacy parameter such as an increase in hemoglobin level to a clinically relevant threshold. If a follow-on ESA were structurally similar, deemed not to have additional immunogenicity concerns (or had acceptable immunogenicity testing), why would that product be required to undergo extensive clinical testing if that data exists from the reference product. While biologics are different than small molecules, those differences can be evaluated by the appropriate scientific experts who should be in position to determine the appropriate degree of clinical similarity testing. In the case of the ESA follow-on a simple bridging efficacy study could suffice. The same could be said for insulin. In contrast there are complex biologic proteins that have been tested with complex clinical endpoints (multiple sclerosis, rheumatoid arthritis). It may be appropriate given the complexity of the clinical benefit parameter upon which the innovator product was approved a more extensive clinical profiling for effectiveness may be required, albeit not to same extent as the innovator product. Again such decisions should be in the purview of the relevant scientific

committee. Extrapolation from one indication to another could be justifiable without requiring additional testing for each new indication. For example a biologic approved in treating lymphoma which is also approved for treating rheumatoid arthritis based on the same mechanism (anti-CD20 antibody for example) for the clinical benefit produced in each different disease then additional clinical testing may not be required. Once the safety and comparable effectiveness was determined for the first indication then scientific mechanism should be the guiding principle.

5. Why would post marketing studies be automatically required? That is not the case in Hatch Waxman Act. From a safety perspective all products are subject to post marketing surveillance and safety reporting.

6. I am not certain what scientific basis one could argue that FOB's should not be substitutable or interchangeable if they have been determined by the FDA to be safe and effective. I believe legislation similar to that in the Hatch Waxman Bill could justifiably be utilized for FOB. While it is true that the FOB will have different inactive ingredients than the reference product this should not solely be the basis for exclusion of interchangeability. Scientifically, it is not likely that these "inactive by-products" produced as a results of the difference between cellular systems from reference product manufacture will alter or affect the safety or efficacy of the underlying active protein.

7. Yes. Mechanism of action is a critical attribute to a biologic therapy and to some extent to all therapeutics including non-biologics. Given the current evolution of science and drug development the majority of therapeutics in development have well defined mechanisms of action. In the setting for a biologic the target may be of more, relevance than the mechanism of action. So if a mechanism of action is unknown or unconfirmed for a reference product then the FOB should at a minimum have the same target specificity. For example a biologic drug designed to target and bind to a receptor (CD-20) on a white blood cell (anti-CD20 biologic drug) determines the specificity of the biologic drug. If a FOB were to bind to a different receptor or an additional receptor in addition to CD20 receptor then scientifically it would be a different product and not an FOB. It would be unreasonable to have the FOB take on the burden of determining the mechanism of action when the reference product was not held to that standard for approval. As long as it targets the same target as the reference product they should be considered similar.

8. Biologics differ significantly in their structure, size, and complexity. With regards to batch-to-batch variability this, by regulation, has to be strictly controlled within required pre-determined boundaries. Batches that vary outside of FDA agreed upon specifications fail release testing and are not

subject for human use. The same requirements are implemented for changes in manufacturing processes. This used to be a more significant issue in the early days of protein production but over the past 30 years science, analytical technologies and control of clonal expression and infidelity etc have significantly improved making these less of a concern than in the past. If a product falls outside of validated specifications as a result of manufacturing changes then FDA may require additional human clinical testing before such lots are released for commercial use. This would have potentially minimal additional impact on FOB testing requirements, naming or interchangeability. If the FOB falls within similar characteristic/specifications as the reference product then it should be able to rely on that body of data without need for additional testing. If there are new constituents that may pose additional safety concerns that are not in the reference product then based on a scientific assessment as stated in 1 and 2 above, should determine what degree of clinical testing should be adequate to satisfy safety and efficacy similarity. If these "acceptable differences" have no clinical consequence then they should be deemed interchangeable. This is analogous to different incipient used in generic drugs where formulation or tablet composition differ from the reference product contributing no clinically meaningful or concerning difference in safety or efficacy.

9. FDA should be given the discretion whether such trials are needed on a case by case basis. What should be in the legislation is similar to the generic drug bill or a 505b.2 set of guidelines so that the FDA doesn't take an unreasonable position which essentially negates the intent of the legislation. Did the lack of requirement for generic Taxol (paclitaxel) to conduct human clinical studies create a difficult time for it to reach market acceptance. Paclitaxel is a complex semi-synthetic natural product and a decent analogy to a simple biologic like human growth hormone. Once generic the price of paclitaxel dropped 80% and saved the consumer and health care budget hundreds of millions of dollars while providing the same effectiveness and safety profile as the reference product. The more the legislation allows FOB's to behave like the regulations for generic drugs while letting science drive the decisions at the FDA the greater the saving and access to consumers will be realized. Similarly in the setting of where a novel paclitaxel formulation utilizing an albumin emulsion technology (Abraxane®) the FDA required comparable testing, pursuant to a 505b.2 application, to standard formulation paclitaxel to assure retention of reference product safety and efficacy.

10. I am unaware of any protein products that have been approved without some clinical trials. I am unaware of any approved biologics that could utilize the 505b.2 provision as it pertains only to drugs approved under an NDA

11. Omnitrope was only able to utilize the 505b.2 route because it was initially approved as a drug under an NDA prior to the establishment of CBER. The 505b.2 route could be a viable provision for a number of other biologics, albeit not all biologics and should seriously be considered as a provision in the propose FOB legislation. I am unfamiliar with a, b, c.

Regulatory/Administrative

1. Yes

2. Yes. Have not seen or read reports where there has been an adverse impact on safety

3. CBER

4. "Highly" similar is a subjective term and will potentially lead to a wide range of interpretive arguments from both sides. "As similar within available scientific parameters" at least attempts to make the definition objective and quantifiable. As they do other drugs. If the degree of dissimilarity is substantial then additional testing etc as noted in prior answers.

5. No. Not sure what that would add besides a strong lobbying effort by the innovator companies to protect their franchise. Same concern. I think it is reasonable that the Agency establish and utilize an expert Advisory panel for biologics that pose particularly challenging structural complexities like Enbrel for example where the description of scientifically similar may become challenging. Given the current state of affairs at the FDA public hearings, guidance review and establishment of new regulations and guidance for the industry would likely require 30 to 36 months.

6. I believe the user fee should be proportional to the complexity of the molecule. Should a simple application like Omnitrope be required to pay the same user fee as the reference product? It may be feasible to establish a scale based on degree of additional testing, characterization etc that scales the user fee.

Interchangeability

1. Yes, technology is currently available for most biologics in use.

2. I believe this has been addressed in the first section's questions

3. In general I believe that science should always dictate the guidance as that is the most reliable and least emotional or self serving parameter for our legislative body to rely on. I believe an independent panel could facilitate parameters and guidelines for interchangeability. Although stating the obvious this is one of the most critical aspects in the FOB legislation Without the ability to substitute or consider them interchangeable there will be less consumer access than desired along with less economic savings to the health care system. This is a provision you should strive to get right.

4. Product specific guidance should be driven by scientific evidence of clinically meaningful differences that require warning or guidance. I am not certain what you would obtain from a public comment period on interchangeability other than a voice from the competition. These are decisions best addressed by scientists and expert advisors.

5. If deemed similar for safety and efficacy by the FDA there should be no obvious risk to patients from interchangeability. There are always unforeseen, unanticipated safety issues that appear post approval when large populations of patients are exposed to any given drug let alone a biosimilar. The "fear" tactic of referring to the ESA approved in the EU that led to the immune destruction of some patients native erythropoietin could have been identified given the substantial difference in that particular product (hyper-glycosylation) which led to the production of anti-EPO antibodies. As I mentioned in #3 above this will be the single most important gatekeeper for patients' access (and cost savings).

6. Interchangeability was the single largest contributor for increased access for patients to lower cost alternative drugs under the generic drug bill. This provides consumer choice while at the same time permitting health care insurers and patients' ability to access lower cost alternatives. The argument in 1984 that the Hatch Waxman Act would stifle innovation, lead to a withdrawal of investment capital in the pharmaceutical sector and would destroy drug company returns on investment are all the same arguments that are being made from biologic drug manufacturers that are trying to protect their current franchises. FOB legislation that is driven by science, clear guidance, unbiased economic impact data coupled to the goal of improving access to lower cost alternatives so more American can benefit from these therapies will not affect the cost of future reference products and will lead to a substantial reduction in the cost of a FOB.

Patents

1. Approximately 12 to 16 years. Most companies work on deferring the issuance of US patents for their key drug/biologic candidates in development until the candidate is in final phases of clinical testing.

2. Yes as long as the same provisions under the Act are provided. I have seen proposed legislation mandating 14 years additional as opposed to "Up to" provision in the Hatch-Waxman Act depending on the regulatory review period. I am a proponent of following the Act's regulatory restoration provisions as they are fair and adequate to preserve innovation for the innovator. Anything beyond that is excessive.

3. Biologic patents can be considerably more complex than their small molecule counterparts and provide a variety of additional methods (expression vectors, conditions, sequence modifications etc) to secure exclusivity beyond the native sequence (i.e. NCE analogy) alone. Just examine the original G-CSF (Neupogen®) patent and the minor modification to pegylated G-CSF (Neulasta®).

4. Beyond my scope of expertise

5. Beyond my scope of expertise

6. Yes, this has been both appropriate, efficient and transparent, which in governmental agencies is a good thing

Incentives/Exclusivity/Investment

1. Why. What is the investment model data that supports an argument for additional period of marketing exclusivity? Shouldn't that decision be data driven? It certainly would have a significant impact on the degree of heath care cost savings. Let's take an example of a product that takes 9 years on average for regulatory review and the product at time of approval has 11 years left on the patent life. Under the Hatch Waxman Act the restoration incentive would provide 9 years additional protection. 20 years of market exclusivity in that example would appear adequate to justify the initial investment. It would appear that an additional period of exclusivity in excess of the restoration extension should not exceed 5 years. The concern for some of the proposed extensions of 15 years if applied would allow a single innovator to exclude from the market lower cost alternatives until such time that those alternatives could be rendered obsolete. A lot of new science occurs in a 35 year period of exclusivity such that the need for a product like an ESA may be obsolete when the exclusivity period expires.

2. Good question. There is certainly an abundance of data for small molecules, both probability of success by stage of development and cost by stage of development and total ROI and probability of achieving 15% or 30% ROI. This type of information is often referenced by biologic manufactures but never provided. A study should be conducted to determine these facts so that an economic argument can be made to guide the additional exclusivity period proposed.

3. Like they are in Hatch Waxman.

4. Data exclusivity prevents potential competitors from leveraging the work of the innovator.

5. This is one area where I would agree with the biologic innovator as much intellectual property creation stems from data exclusivity given the complex interactions of biologics in humans and in manufacturing processes.

6. Not certain

7. I already expressed my opinion on this issue. If a follow on pathway followed the framework of the Hatch Waxman Act I do not believe it would stifle innovation. If there is a strong economic rationale for additional incentives then that should be taken into consideration. Innovation at American Universities would not likely be affected by FOB legislation. I was an academic researcher at the University of Washington and the Fred Hutchinson Cancer Center and in my experience drug regulatory legislation was never a consideration in the direction of innovative scientific investigation.

Economic Impact

1. The savings will largely depend on whether or not they are deemed interchangeable and substitutable so that physicians and insurers won't deem a liability for choosing a lower cost alternative. For example in the Express Scripts February 2007 report, a generic interchangeable insulin could result in a $797 million cost savings with total cost savings across all biosimilars of $71 billion over 10 years. Similar conclusions were presented by the Pharmaceutical Care Management Association.

2. Not applicable

3. I do not believe it would adversely affect US competiveness and leadership re: protection of intellectual property rights but do believe if we do not have a biosimilar pathway we run the risk of having a divergence of

patient access to life saving medicines favoring ex US countries placing the US consumer health care delivery at a disadvantage to that of other countries.

4. Not certain

5. This was addressed in answers above

European Model (abbreviated approval pathway)

1. Yes. Product specific guidelines would potentially standardize across various biosimilars within a defined product class (i.e. ESA's). This could facilitate the scientific assessment of interchangeability across a product class than on a product by product basis

2. I believe, as noted in the economic argument discussion above, that any period of extended exclusivity beyond the restoration extension should be justified based on unbiased economic model data. US should be guided by evidence based information and not by the actions of EU regulatory agencies. One can not normalize the health care economic issues in EU countries to those in the US.

3. I do not believe it would have a major impact on US competitiveness since the US is the more attractive economic pharmaceutical market and will continue to set the innovation standards for rest of world. Even with shorter periods of exclusivity the pricing differences, expanse of patients with health care coverage and access favors the continued focus on the US as the primary market for these innovative therapies since ROI would still be substantially greater than that achievable in the EU.

4. I am uncertain of the specifics. What I do see as a substantial difference is the EMEA's position on interchangeability which they assert should be left to the central role of the physician-patient relationship for biotech derived drugs.....but not for small molecule drugs. That seems unusual to me as a physician. While it is clear FOB's are not identical but similar to the reference biologic, if deemed safe and effective they should similarly be deemed interchangeable as there is no scientific rationale that would not allow them to be interchangeable. In my opinion this is more a political issue than a scientific, regulatory or clinical judgment issue.