Recent Studies of Follow-On Biologics Are Based on Seriously Flawed Assumptions:

PCMA Study – *Potential Savings That Might Be Realized By the Medicare Program From Enactment Of Legislation Such As The Access To Life-Saving Medicine Act (H.R. 6257/S. 4016) That Establishes A New cBLA Pathway For Follow-On Biologics*

and

Express Scripts Study – *Potential Savings of Biogenerics in the United States*

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This paper was prepared by Ted Buckley, PhD, the Biotechnology Industry Organization's (BIO's) Director of Economic Policy. It consists of an assessment of two recent analyses that predicted savings from proposed Congressional legislation to establish a pathway for the approval of follow-on biologics. The first, a Pharmaceutical Care Management Association (PCMA) analysis, purported to examine potential savings for biologics covered by Medicare Part B, and the second, an Express Scripts study, claimed to examine potential savings for biologics in four specific therapeutic categories. We have determined that these analyses contain conclusions of potential savings based on a demonstrably flawed set of assumptions that contradict current experience and lack credible evidentiary support. These assumptions undermine the validity of their findings.[1]

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[1] BIO believes that approval of follow-on biotechnology products must be based on the same rigorous standard applied by the FDA for the approval of pioneered biotechnology products. Patients should not have to accept greater risks or uncertainties in using a follow-on product than when they use an innovator's product. Please see http://www.bio.org/healthcare/followon/ for BIO's position statement on Follow-on Biotechnology Products.

This paper identifies some of the analytical flaws that lead to significant overestimation of potential savings from follow-on biologic products (FOBs) in these studies.

1. **CLAIM – Interchangeability:** The two studies assumed that follow-on products will be designated by the FDA as interchangeable beginning in 2007.

   Facts: <u>To date the U.S. has not accepted interchangeability of complex biologics and Europe has rejected an "interchangeable generics" approach.</u> The Food and Drug Administration (FDA) has noted that it has not determined how interchangeability can be established for complex proteins.[2] FDA has also stated that "Different large protein products, with similar molecular composition may behave differently in people and substitution of one for another may result in serious health outcomes, e.g., generation of a pathologic immune response."[3] The European Medicines Agency (EMEA) has rejected the generic approach in favor of a biosimilars model applied on a case by case basis. According to the EMEA, "[d]ue to the complexity of biological/biotechnology-derived products the generic approach is scientifically not appropriate for these products."[4] EMEA also noted that biological products are usually more difficult to characterize than chemically derived medicinal products, and can be significantly altered by manufacturing changes that may initially be considered 'minor.'

   Result: In the face of these regulatory decisions, the studies failed to provide any credible basis for calculating savings based on interchangeable products. This led to a significant overestimation of savings if, in fact, these products are not interchangeable in a way that would result in the extremely rapid market penetration that appears to be presumed. These differences do not appear to have been taken into consideration in either the PCMA or the Express Scripts studies. In addition Express Scripts' statement with respect to interferons that "there was no substitutability among products" coupled with their statement for this category of products that their analysis "assumed that only chemically equivalent biogenerics would be used in place of brand-name biologics" casts serious doubt on <u>$13.8 billion</u> of its claimed savings.

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[2] U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars (September 1, 2006), accessed at <u>http://www.fda.gov/cder/news/biosimilars.htm</u>.

[3] Ibid.

[4] Guideline on Similar Biological Medicinal Products, EMEA Committee for Medicinal Products for Human Use (October 30, 2005), p. 4, accessed at <u>http://www.emea.europa.eu/pdfs/human/biosimilar/043704en.pdf</u>.

2. **CLAIM – Timelines for Patent Expirations:** The PCMA study relied upon a biotechnology trade newsletter's patent expiration dates for a sample of biotech products to determine the percentage of spending on biologics under Medicare Part B that would lose patent protection each year over the 10 year period. PCMA then applied the resulting annual percentages to the total spending of all biologics covered under Medicare Part B. This methodology resulted in PCMA claiming that 30% of all biotechnology spending under Medicare Part B would lose patent protection by 2007. The Express Scripts study did not even cite its source for patent expiration data, and modeled its savings calculations on the assumption that the patents for most of the products it analyzed have already expired.

   Facts: <u>The studies' claims regarding patent expiration timelines appear to be inaccurate, internally inconsistent, and/or inconsistent with other credible analyses.</u> For example, a recent Citigroup report, "A Global 'Generic Biologics' Guidebook" estimates that expiring patent protection during 2007 may affect at most 5% of the spending on the top ten Medicare Part B biologics.[5] Further, the Express Scripts report was internally inconsistent because it acknowledged that patent protection exists for many of these products but then estimated "savings" as if those patents did not exist. For example, the report noted that "additional patents have been granted, which may extend the protection of Procrit and Epogen," but then made the unexplained statement that "[t]his model assumes that these patents would not be a barrier to biogeneric entry in this therapeutic area." In contrast, the Citigroup report also states that Epogen is protected by matter, process and product patents that extend the patent life out to 2012 - 2015. Further, inconsistencies concerning patent expiration were made by Express Scripts with respect to other products as well.

   Result: The incorrect patent expiration dates led to significant overestimates of savings. The Express Scripts' assumptions surrounding epoetin alfa casts serious doubt on at least <u>$40.7 billion</u> of its claimed savings.

3. **CLAIM – Market Penetration in the First Year:** Even if one falsely presumes that there were no other problems with the assumptions of the PCMA study, the study incorrectly applied its own method for estimating savings. That is, the study assumed that market penetration by the follow-on products would immediately reach 30% for products coming off patent in the later years.

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[5] These 10 biologics account for 87% of the Medicare Part B spending on biologics.

Facts: **The PCMA study incorrectly applies its own method for calculating savings.** That is, the PCMA study incorrectly applied the erosion curve that it selected by assuming that the market penetration of the follow-on products would immediately reach 30% for products coming off patent in the later years. Instead of applying the curve independently to each individual FOB that might gradually capture an increasing share of the market, it assumed that the savings from those FOBs marketed in 2012 and beyond would immediately generate savings of 30%. Actually, the savings for a FOB first marketed in 2012, according to the PCMA methodology, should be 5% - not 30%. This resulted in a major mathematical miscalculation that led to a dramatic and false compounding of potential savings.

Result: This incorrect application of PCMA's stated methodology led to an overestimation of savings by 40%, even if all of PCMA's other assumptions were correct.

4. **CLAIM – Market Penetration Rates.** The Express Scripts study made dubious assumptions about market penetration rates for follow-on products.

   Facts: **The market penetration rate used in the Express Scripts study was based on Express Scripts' 83.4% generic fill rate for nonbiologic drugs with narrow therapeutic index.** However, given the complexities of biologics manufacturing and the fact that follow-on biologics will likely be different from the innovator product – and, therefore, not designated as interchangeable – the studies presented no credible evidence to justify or explain this adoption rate for follow-on products. Thus, using a non-biologic generic equivalent fill rate is inappropriate for this analysis.

   Result: This assumption, once again, has likely led to a significant overestimation of savings in the Express Scripts study.

5. **CLAIM – Timing of Savings:** The studies implausibly assume that the law would be implemented and that savings would begin to accrue at the beginning of 2007.

   Facts: **Clearly, no law has been passed, nor have any regulations or guidances been issued at this time. It will take time to consider, develop and implement any legal and regulatory systems for FOBs.** Experience with FDA shows that this often takes a considerable amount of time. Even after regulations and guidances could be established, FDA would still need time to receive, review and consider the safety, efficacy and quality aspects of each application, creating an additional delay to potential market entry. These studies presumed that a certain sequence of events would happen almost immediately. With the approval of Omnitrope the FDA took approximately 2 years to consider the application.

Result: Failure to include a reasonable time frame for the legal and regulatory processes of drug review resulted in a significant overestimation by both studies of potential savings during the period assessed.

6. **CLAIM – A Pathway Under One Law Will Generate Savings for Products Approved Under Another Law.** The Express Scripts study discussed savings from hGH and insulin associated with passing a follow-on biologics law.

   Facts: **Both hGH and insulin were approved under the Food, Drug and Cosmetics Act as new drugs, and FDA has already approved under that existing law numerous competitive versions of such products.** Therefore, there is no credible basis for assuming that the establishment of an abbreviated pathway under the Public Health Service Act would generate any savings in these product categories that would not otherwise be achieved under existing law.

   Result: This inaccurate inclusion resulted in an overstatement of savings of almost $17 billion.

7. **CLAIM – All Biologics Will Have Follow-Ons in the Near Future:** The PCMA analysis assumed that for every biologic that comes off patent there will be an associated FOB.

   Facts: **There is no credible evidence to suggest that it is scientifically possible to develop a FOB for every biologic that is currently on the market**, and, in fact, many in the scientific community suggest it is not possible at this time to make follow-ons for many highly complex products such as monoclonal antibodies. Further, many biologics have a limited market, and therefore, it will probably not be economically attractive for companies to develop and market an FOB for many of these products.

   Result: Assuming that every biologic would have an associated FOB, when many will likely not, would result in a further overestimation of savings.

8. **CLAIM – Excess Manufacturing Capacity:** The PCMA analysis assumed that there is excess manufacturing capacity to produce FOBs.

   Facts: <u>A recent analysis appears to contradict the assumption of excess manufacturing capacity.</u> "The recent wave of biologic approvals and expanded pipelines suggests that there might be limited idle manufacturing capacity in the near future."[6] Thus, producers of FOBs would face either significant time delays or significant upfront costs to develop FOBs that would likely negatively impact any potential price differential and therefore lower the savings.

   Result: By not including these costs and/or time delays in the analysis, the PCMA study likely overestimated the amount of savings.

9. **CLAIM – Next Generation Products:** Both studies implausibly assumed that the current market share of individual biologics would not evolve over time but rather would remain unchanged; that is, the utilization of current biologics does not change over time as next-generation products become available. The Express Scripts study further assumed that patients on next-generation products would switch back to first generation products.

   Facts: <u>This assumption is not supported. Experience has shown that in an dynamic marketplace products are replaced by newer, more innovative products.</u>

   Result: By failing to take into account the dynamic nature of an innovative marketplace, the PCMA and Express Scripts studies have likely overestimated the potential savings.

In conclusion, the studies by PCMA and Express Scripts relied upon flawed assumptions and lack credible supportive evidence. These flaws raise serious questions and doubts about their validity.

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[6] Grabowski, Henry, Iain Cockburn and Genia Long. "The Market for Follow-On Biologics: How Will It Evolve?" <u>Health Affairs</u> 25(5).