Competition Issues Involving Follow-on Biologic Drugs

Submission to the FTC by Adrian Towse, Office of Health Economics

Our responses to the FTC questions draw on the paper we published in October 2008 (Chauhan et al 2008). I attach a pdf of the full paper which is also available to be downloaded at http://www.ohe.org or can be obtained by sending an email request to cdevaney@ohe.org.

Our research covered ground that addresses questions 1 and 2 in section A and accordingly we have only responded to these questions. I listened with interest to the Workshop via the web link where issues relating to these two sets of questions were raised.

By way of note - in our research paper we use the term "biosimilar" which equates to the FTC definition of a follow-on biologic (FOB) drug. We also use the term "interchangeable" in our research paper to refer to *physician* willingness to use one drug instead of another in the expectation that they have the same efficacy and safety profile, reserving the term "substitutable" to refer to *pharmacy level* willingness to regard two drugs as having the same efficacy and safety profile. In our response below, however, we use the term FOB and use the term interchangeability in the sense used by the FTC.

I. Competition Issues Involving Follow-on Biologic Drugs

A. Regulatory Exclusivities and Follow-on Biologic Drug Competition

1. *What is the likely competitive effect of the market entry of a follow-on biologic competitor? Are there empirical models that predict the nature of this competition based on existing biologic drug product competition? How has competition developed between referenced and follow-on products in European markets? Would referenced product manufacturers lower their prices, offer discounts, and/or engage in enhanced marketing activities?*

Likely competitive effect

The likely competitive impact of an FOB will be limited unless it is able to establish credibility with physicians that it can be used interchangeably with the referenced innovator product. We do not think it sensible, however, to seek to establish interchangeability/substitutability with the reference product at the licensing stage for reasons we set out below. Evidence from generic and non-pharmaceutical markets also indicate that more than one entrant is usually required to produce strong competition for market share through price or other means.

Our expectation is therefore that the penetration achieved by an FOB will initially be low reflecting physician caution given the lack of cumulative safety data on the products and data on their interchangeability with the reference originator product and that the high

costs of entry and the need for different skill sets relative to chemical generics will, at least initially, limit the number of entrants.

There is a need for post-launch data that indicates that the efficacy and safety profile of the FOB is in practice the same as that of the referenced originator product. We term this in our research paper "Patient Safety Year" (PSY) data. As safety data is accumulated, more new patients will be commenced on FOBs. The critical point may be two to three years after entry when enough data may have been accumulated to encourage clinicians to opt for routine interchangeability in some markets. This will lead to much greater FOB penetration and to greater price competition.

Are there empirical models?

We are not aware of empirical models. However, we adapted the Frank and Salkever model of generic entry (Frank and Salkever, 1997) to consider how individual companies might in theory respond. This is a market segmentation model where the products are differentiated. The market segments into two when the FOB enters: a price-sensitive segment where the differentiated products compete on price and a price-insensitive or loyal segment where demand for the originator product does *not* depend on the price of the competitor.

We assumed the originator can only charge one price across segments, so this price will affect its demand in both market segments. This might make it attractive for FOB entrants to offer large price discounts to win market share. Originators will be reluctant to match these discounts if they have also to offer them to their loyal customer base. However, lack of perceived similarity and safety data may mean discounts are not sufficient to generate customers for the FOBs.

Experience of use of the FOB and the accumulation of safety data can be expected to lead to a reduction in the degree of differentiation between the originator and the FOB. At given prices this reduces the size of the "loyal" market for the originator and increases the market share of the FOB product in the price-competitive segment. The originator has to cut price or see an erosion of its market – until eventually it has only the (now small) "loyal" market left – at which point it may choose to increase price as in conventional chemical generic markets.

We can drop the assumption of a single originator price. The originator company can seek to charge different prices in different market segments depending on price sensitivity. It may be willing to accept a lower price in one market segment in order to reduce the ability of the entrant to gain market share and so to further safety data. In other words heavy discounting by an FOB entrant may be matched in key market segments by the originator, reducing the benefits to the entrant of doing this. It may therefore make more sense for FOB entrants to find non-or limited price cutting routes to gaining market share and to generating safety data.

Experience of competition in Europe

Experience of FOB competition in Europe is limited and the analysis in our paper pre-dates some more recent FOB entry. The Growth Hormone market was always likely to be difficult to enter successfully in the absence of good safety data demonstrating interchangeability with the reference originator product as it is a market where the patients are children, the delivery device matters, and training patients to use the device is important. Our understanding is that FOB entrant market share is below 5%. Experience in the EPO market is different with several FOB entrants recently coming in at around 20% - 25% below list price in Germany (the largest European market) and, we understand, gaining market share greater than 5% on this basis. A responding price cut by the originator was matched by the FOBs. EPO is a market in which in many countries there has been a history of aggressive discounting from the list price by competing originator products. Physicians and pharmacists have gained enough experience of use of competing originator products to regard them as interchangeable. This may mean that it is easier for FOBs to establish credibility with physicians and pharmacists that they also can be used interchangeably with reference products.

It is difficult to draw conclusions from the limited experience to date of FOB competition in Europe, other than to note the obvious – the market does not behave as if chemical generics have been introduced. FOBs seem to have entered at a discount of around 20% which may or may not lead to a price response from the originator. Some FOBs have gained market share, others not. Our modeling has suggested a number of competitive scenarios depending on both the extent to which safety data is available that convinces physicians and pharmacists that an FOB could be used interchangeably with its reference product, and the extent to which other non-price factors are important to prescribers.

Potential Savings

Our analysis leads us to conclude that many estimates of potential savings from the use of FOBs are far too high. This is because they commit one or more of the following errors:

- take the list price of the originator product as the starting point, whereas in many cases there is already price competition from competing originator drugs leading to discounting from list price;
- assume the FOB has the same cost structure as a generic and can stay in business over time whilst offering discounts of around 80%. This is unrealistic. Biotech manufacturing processes can be high and entrants will incur pre-launch clinical trial costs; post–launch study costs and marketing costs that chemical generic manufacturer companies do not incur. The cost base is different to that of a chemical generic.
- assume physicians and pharmacists treat the FOB from the point of product launch as identical in clinical effect and safety to the reference originator product in the way that they would for a chemical generic. This will not happen for reasons we discuss below.

- assume there will usually be multiple entry leading to strong price competition. This ignores the different skill sets, higher costs, and other factors we discuss above which will lead, at least initially, to less entry and less price competition than in the case of chemical generic markets of a similar size.

2. *What is the likely impact of a follow-on biologic product being designated "interchangeable" (i.e., receiving an approval that would permit pharmacists, without physician authorization, to fill a prescription for the referenced product with the follow-on product)? What are the prospects for the use of "authorized follow-on biologics" in these circumstances? Do the answers to these questions differ based on the type of biologic product involved?*

The EMEA does not accept that FOBs are direct substitutes for the referenced original product. It has said that FOBs are not necessarily interchangeable. It is not the objective of its licensing process to establish interchangeability with the referenced originator product, but to establish that there is comparable safety, quality and efficacy. The extent of clinical development required varies from case to case. The absence of EMEA indicated interchangeability means that pharmacy substitution laws in EU Member States do not cover FOBs. Some countries (France and Spain) have, additionally, explicitly ruled out the inclusion of FOBs in pharmacy substitution.

Requiring the FDA to designate an FOB as interchangeable in the sense of substitutable at the pharmacy level is likely to substantially raise the regulatory hurdle set by the FDA in terms of clinical development work required. This will in turn significantly delay the entry of FOBs. It is far more efficient from a public policy point of view to license FOB products as "biosimilars" in the EMEA sense and encourage data on interchangeability to be collected *post-launch*.

The public policy challenge is how to generate post patent expiry entry of FOBs that enables competition to deliver savings to health care systems in a way that does not jeopardise patient safety or future innovation. It is not in our view possible to "jump start" a "biogenerics" market by forcing down prices (which would deter FOB entry) or by imposing interchangeability / substitutability at the pharmacy level, which would substantially raise the licensing hurdle, pushing up costs and delaying entry.

It seems to us to make sense for the US to follow the European "biosimilar" approach with licensing requiring some clinical development work on a case-by-case basis and to facilitate the collection of post-launch Patient Safety Year and other data. Information on the degree of interchangeability /substitutability is needed to make this market work efficiently and competitive pressures will encourage FOB entrants to collect this, perhaps in alliance with payers. However, there is a case for government agencies to help fund, set up, or create infrastructure to facilitate these studies occurring.

Over time post launch data collection arising from the use of FOBs will impact on subsequent licensing hurdles and on the potential for allowing pharmacy level substitution. As more knowledge accumulates about the interchangeability (or otherwise) of a FOB with its reference product then the requirement for studies by the licensing authority (EMEA or FDA) for subsequent FOB entrants may change. If the post-launch data indicates interchangeability between a FOB and its reference product then it may be possible at this point to allow pharmacists to substitute the FOB for its reference product without physician authorisation. However, this can only happen with the accumulation of information, it cannot pre-empt the collection of information.

References

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Frank R G and Selkever D S. 1997. Generic Entry and the Pricing of Pharmaceuticals, Journal of Economics and Marketing Strategy, 6(1): 75-90.