

Me-too drugs: is there a problem?

Aidan Hollis

Department of Economics
University of Calgary
ahollis@ucalgary.ca

December 13 2004

Introduction

This brief note presents an economic perspective on “me-too” drugs (sometimes also called “follow-on” drugs). Me-too drugs are products which largely duplicate the action of existing drugs. Several recent books (such as Angell (2004), Avorn (2004) and Goozner (2004)) have heaped criticism on the drug industry for the increasing extent to which investment appears to be focused on developing drugs which have a similar mechanism of action to pre-existing drugs. Others, such as Calfee (2000) and diMasi and Paquette (2004) have defended me-too drugs, as providing more therapeutic options and enhancing competition. diMasi and Paquette have also observed that many me-too drugs enter development long before the first drug in a new class is approved, so that in many cases me-too drugs are the result of parallel development rather than of imitation.

The key problem with me-too drugs is that, *to the extent that they are similar to pre-existing drugs*, they diminish the incentives for innovation in pioneering drugs without adding therapeutic value. Me-too drugs also absorb R&D resources, which is wasteful if they are undifferentiated from pre-existing drugs. On the other hand, the more differentiated me-too drugs are from pioneering drugs, the greater their potential benefits, and the less they harm the incentives for pioneering research. Defined very narrowly as drugs which have more or less identical clinical outcomes to pre-existing drugs, me-too drugs are likely of little value – indeed in this case they effectively undermine the intent of patent protection, without even providing much benefit from price competition. But drugs which are more differentiated in clinical outcomes are also sometimes described as me-too drugs, and such drugs may create value without substantially harming incentives for pioneering innovation – indeed, to the extent that a drug is differentiated, it becomes more of a pioneer and less of a me-too.

It would be useful in any discussion of me-too drugs to be clear about the meaning of the term. I would suggest that a me-too drug is one that is approved after a pioneering drug and which is the “same”, in the sense of the US Orphan Drug Act, and is not clinically superior (Milne, Kaitin and Ronchi, 2001, p. 7). “Same” in the Act is normally defined as comparable or similar. Examples of me-too drugs which fit into this definition could be Nexium and Clarinex.¹ Obviously, however, there is a continuum of drugs within and outside this definition which may be to a greater or lesser extent me-too

¹ Other plausible examples are Crestor, Levitra and Lexapro. However, I do not pretend to have any competence in such an assessment and I leave determining which drugs fit into this definition to others.

drugs. The key is the degree to which a drug adds incremental therapeutic value. I will use the term “follow-on drugs” for drugs which are similar but would not necessarily fit into this definition.

In the following, I begin by considering some of the benefits of more competition within a therapeutic class, i.e. of me-too drugs, relying heavily on diMasi and Paquette’s very thorough analysis, and examine the costs of me-too drugs. I then consider two additional points: first, whether it makes any difference if drugs were developed simultaneously or sequentially; and second, whether there is anything to learn from the case of orphan drugs. I conclude with a discussion of the proposal to require a demonstration of clinical superiority for approval.

Benefits of me-too drugs

The primary benefit of what diMasi and Paquette label “follow-on” drugs is the increased therapeutic choice they present. Some follow-on drugs are better than the pioneer drug for most patients, while others are better for a substantial fraction of patients. The increased choice between drugs can be very valuable, particularly for patients for whom the pioneer drug is ineffective or entails undesirable side effects.² In addition, for some classes of drugs, such as antibiotics, having more drugs can help to protect against resistance (Calfee, 2000). diMasi and Paquette observe that around 33% of the follow-on drugs they identify received a priority rating from the FDA, indicating that there was considerable expectation that the follow-on drugs would likely create some significant therapeutic benefit. Another way of viewing this finding is that around 67% of follow-on drugs were thought unlikely by the FDA to confer a significant benefit, and indeed, many of the drugs listed as second to enter in Table 1 of diMasi and Paquette appear not to have been better than the pioneering drug. Of course, to the extent that new drugs do confer significant benefits, they are less likely to meet the suggested definition of me-too drugs.

The second major benefit from me-too drugs is that they would be valuable if they led to substantial price reductions, although in practice price competition between therapeutically similar drugs does not tend to lead to significant price reductions. Lu and Comanor (1998) using American data, and Ekelund and Persson (2003) using Swedish data, have shown that drugs categorized by the FDA as having “little or no therapeutic gain” are typically introduced at around the same price as existing therapies in the US and at about twice the price of existing therapies in Sweden.³ Lu and Comanor calculate the effect of entry on prices and find that the average effect of adding an extra competitor is a price reduction on the order of 2%. (The average number of competitors in their data is approximately 3 or 4, which seems to suggest that the effect of going from pure monopoly to four firms with very similar products is a reduction in price of only 6%.)

Other data from very large drug markets shows how the entry of me-too drugs may not work according to the standard expectations. Cockburn and Anis (1998) examine

² Angell (2004, p. 90) argues that many me-too drugs are never tested at equivalent doses to show that there are significant differences in outcomes for some patients, and claims that “the idea that patients respond differently to me-too drugs is merely an untested – and self-serving – hypothesis.”

³ Lichtenberg (2004) finds that drugs which the FDA lists as “priority review” create a significant impact on population longevity, while “standard-review” drugs, which have therapeutic properties the FDA considers to be similar to those of already-marketed drugs, have no discernible effect on longevity. Prices of standard-review drugs are, however, typically similar to those of the previously introduced priority-review drugs.

pricing of anti-arthritic pain-relievers before the Cox-2 inhibitors Celebrex and Vioxx entered. Their regressions of price on therapeutic quality show exactly the “wrong” relationships: efficacy is negatively correlated with price, while toxicity is positively correlated. They do at least find that market shares go in the “right” direction. Azoulay (2002) shows that in the H2 stomach ulcer market, Tagamet’s price *increased* when its first competitor Zantac entered, rather than going down. Prices for both drugs continued to increase when new competitors (Pepcid and Axid) entered. Such strange results from pharmaceutical markets are not intended to show that price has no effect on sales in pharmaceutical markets, but that me-too drugs very frequently not only fail to increase price competition but may even lead to price increases. In summary, the evidence on price competition from me-too drugs suggests that it confers little benefit to consumers.

Costs of me-too drugs

Given the therapeutic (and small price) benefits from me-too drugs, why is there a problem? There are three important issues. First, me-too drugs reduce the incentive to undertake pioneering innovation. Second, me-too drugs may have an unacceptable benefit/risk ratio, if their incremental benefits are relatively small. And third, me-too drugs may be using up more resources than they are worth. I discuss these points below.

Incentives for innovation

Me-too drugs harm the incentives to undertake pioneering innovation because they make pioneering innovation less profitable through taking market share from pioneers. As Lichtenberg and Philipson (2002) have shown, competition between therapeutic substitutes reduces innovator profits at least as much as competition from generics. While their study includes a broad set of substitutes, “me-too” products are likely to be most important in reducing the profitability of pioneering drugs because their only effect is market-splitting (as opposed to market expansion). And it appears that me-too drugs may be having an increasing impact on pioneer returns: diMasi and Paquette (2004) point out that the average period of marketing exclusivity of pioneer drugs shrank considerably from the 1970s to the 1990s. While these me-too drugs may bring some benefit to the market, they undoubtedly lessen the incentives to undertake pioneering drug research.⁴

According to Lichtenberg and Philipson, generic drugs, which bring unquestionable benefits to consumers through price reductions, cause less reduction in the incentives to pioneering innovation than therapeutic substitutes. We should therefore expect that the gains to consumers from me-too drugs should be at least comparable in magnitude to the gains to consumers from generic drugs. We can get some sense of how large the benefits of generic drugs are by simply examining the savings they generate: in 1994, generics were estimated to save consumers at retail drug stores between \$8bn and \$10bn in the US. Including other buyers and updating the numbers, one might guess that currently generics save consumers on the order of around \$40bn annually in the US. So we should expect me-too drugs to generate on the order of \$40bn in net benefits to consumers every year in order for them to compensate for the harm they cause to the

⁴ In this context, it is hard to understand the standard industry defence of me-too drugs, which consists of arguing that they are good *because* they lead to price reductions and competition before patent expiry (Kaitin 2004). If price reductions are desirable in themselves before patent expiry, why are patents so desirable?

incentives for innovation. This seems improbable, since me-too drugs offer relatively little therapeutic benefit over pioneering drugs. This is, however, ultimately an empirical question. One perspective on this question is the following: if consumers highly value me-too drugs over pioneers, they should be willing to pay more for them. Instead, according to Lu and Comanor (1998), me-too drugs of comparable therapeutic effect tend to enter at about the same price as pioneer drugs in the US. In Sweden, in contrast, drugs of comparable therapeutic value enter at higher prices (Ekelund and Persson 2003). (Drugs with “modest therapeutic gain” tend to enter in the US at about double the price of existing drugs. Given the small number of drugs in this category, of course, the incremental revenues from better follow-on drugs are not even close to \$40bn annually.)

From an economic perspective, the concern about me-too drugs is a question of whether there is excessive entry. It is well known that monopolistic competition can lead to too much or too little product diversity (e.g. Spence, 1976; Dixit and Stiglitz, 1977; Anderson, de Palma, and Nesterov, 1995). In general, it is not possible to determine whether there is too much or too little entry. However, for some specific cases, it is possible. For example, consider a me-too drug which is a perfect substitute for the pioneer drug. The only effect of the me-too is to create additional costs of product development, testing, and promotion, as well as to split the market and lower the profits of the pioneering drug. From a social perspective, the prospect of such a me-too drug is harmful since it reduces the incentive to invest in developing the pioneering drug. The more differentiated the me-too product is from the pioneer, the greater the likelihood that the social value of having more product diversity will compensate for the harm to the incentive for pioneering R&D. This suggests that there is a strong reason for restricting approval of me-too drugs which do not offer a significantly different clinical profile than pre-existing drugs. (It is important to emphasize that the harm is principally to the incentive for pioneering innovation. The concern here is exactly the same that motivates the existence of the patent system: competitive returns may be inadequate to stimulate investment into R&D.)

In other markets, excessive entry tends not to be a concern, since competitive entry will at least bring consumer benefits through both price reductions and product diversity. But in pharmaceutical markets, while me-too drugs may bring product diversity, they do not seem to bring price reductions to the same extent. The result is that in pharmaceutical markets competitive entry obtains relatively high rewards, while creating relatively little social value. Part of the reason for the extent of me-too entry is the peculiar nature of the pharmaceutical market, in which therapeutically similar drugs tend to compete in marketing, rather than in price. (Generic drugs, in contrast, compete much more in price, which explains why generic drugs typically enter at a significant discount to the innovator drug, while me-too drugs do not.) The result of this is that me-too drugs can obtain substantial profits, even if they are second or third in a class.

Another argument which has been made in support of me-too drugs is that they enable firms to finance their R&D activities in breakthrough drugs. It is hard to understand how this would work, since it is the *prospect* of gains which mainly induces investment. Me-too drugs harm the returns to breakthrough drugs, and use up the cash flow of the industry in costly competitive marketing campaigns, which hardly seems like a recipe for increased spending on breakthrough R&D.

Risks of new drugs

A second point which is important to draw out is that while, as diMasi and Paquette observe, having more drugs in a class can confer greater therapeutic choices which may be advantageous, it is also true that drugs bring risks to consumers as well. Consider a me-too drug which we will assume has failed to demonstrate clear clinical advantages and which arrives five years after the pioneering drug. What is the benefit/risk ratio for this new drug? In clinical trials, the new drug has failed to demonstrate significant clinical improvement over the older drug, so the incremental benefit of the new drug is at best small. Several years of additional experience with the older drug have demonstrated very clearly what its side effects are and it is increasingly unlikely that a discovery will be made of some hidden, long-term toxicity. The new drug, however, has only its clinical trials to recommend it. In such a case, it clearly presents relatively high risks, compared to the older drug. This point alone suggests that there is a solid rationale for requiring clinical superiority of new drugs at approval: in any case, the relevant comparison is between the incremental benefits of the new drug over well-understood therapies, and its incremental risks. When the incremental benefits over existing medicines are small, this should be a cause for concern. From the perspective of investors, note that this approach does not decrease industry profits or discourage innovation, since me-too drugs which are substantially similar to existing drugs will tend to cause costly market-splitting rather than increasing the total market.

Research Costs

The fact that me-too drugs do not increase price competition substantially can also lead firms to invest in me-too drugs even when they have little expectation of developing a drug which is better than existing therapies. Estimates of R&D spending in pharmaceuticals consistently show that a large fraction of expenditures are targeted at products offering little or no therapeutic improvement over existing drugs.⁵ In part, this is a function of the fact that it is difficult to develop new and highly effective drugs, of course; but it is also the case that firms find it profitable to imitate successful drugs. It is not clear what proportion of research spending is devoted to these so-called “me-too” products, as the industry does not release data on spending by product. It is possible to obtain some insight into this question by examining data on clinical testing, which consumes over 50% of drug R&D spending (DiMasi, Hansen, and Grabowski, 2003). Public data on the number of subjects in clinical tests suggests that only 20% of the R&D budget allocated to clinical testing is used for drugs which the FDA categorizes as offering a “significant improvement” compared to marketed products – the other 80% is used for products which do not offer a significant improvement (Love, 2003). Recognizing that much me-too drug research is undertaken before approval of the first drug in a category, not all me-too drug research should be seen as wasteful. However, some waste may be incurred when firms observe a successful drug and then imitate it.

When me-too drugs are the outcome of parallel development

One of the points raised by diMasi and Paquette is that many me-too drugs (and likely all of those which enter shortly after the pioneer) were already in development when the pioneer was approved. If two firms are engaged in a race, only one will arrive first at the finish line. The perspective suggested by diMasi and Paquette seems to be that in order to

⁵ Love (2003), Lexchin (2003), and National Institute for Health Care Management Research and Educational Foundation (2002).

stimulate drug development in an area, me-too drugs may be desirable. But it is not quite clear why this should be the case. Consider the following: if drug A comes to market alone, it captures \$1bn in sales and, say, \$500m in profit per year. But if drug B arrives in the market after a year, it will take some of the sales, so that between them total sales remain at \$1bn. Total profits, however, must be less, because additional money will have to be spent on marketing. Firms would prefer to race toward a market in which they have exclusivity and monopoly profits, rather than possibly ending up in a competitive situation. So if we want to encourage the largest possible investment in R&D, we should reward entry with the largest possible profits, which is of course consistent with monopoly. There is also a downside to this: as diMasi and Paquette observe, if only the first to arrive earns the prize, this increases the financial risk of firms, which can also raise costs. It is hard to imagine, however, that the prospect of unalloyed monopoly would, as they suggest on p. 13, entirely dissuade firms from investing in developing a drug for a market.

A comparison with orphan drug legislation

One of the most important features of the US Orphan Drug Act is a seven-year period of marketing exclusivity for classified drugs for rare diseases: a me-too drug without any discernible clinical benefit over the older drug will not be approved for sale in the US. This key aspect of the Orphan Drug Act appears largely responsible for the substantial increase in introduction of drugs for rare diseases after the act was passed (Milne, Kaitin and Ronchi, 2001). The benefits of this exclusivity provision are that it protects the investment of pioneering drug developers from me-too copiers.

Thus some relevant questions to consider are the following. If the exclusivity provisions of the Orphan Drug Act are successful, what does this suggest about the effect of me-too drugs on development of new drugs generally? Does the threat of me-too drugs harm incentives to invest in development of pioneering drugs? Are the short exclusivity periods described by diMasi and Paquette really desired by the industry, and are they good for innovation or for consumers? Given that the exclusivity period provided by the Orphan Drug Act is only 7 years, would it be fair to conclude that most of the protection provided by the 7 year period is against drugs that were developed in parallel with the first approved drug?

Conclusion

The key question which should follow from a discussion of me-too drugs is whether any of the policy responses which have been suggested are worthwhile. I will only consider one: the suggestion made by Marcia Angell and others that the right standard for FDA approval should be evidence not only of efficacy compared to placebo but also of clinical benefits compared to pre-existing therapies.

There are advantages and costs of switching to such a standard. First, such a standard would tend to increase the returns to pioneering or breakthrough innovation by leading to longer exclusivity periods. Higher returns would increase investment. Second, such a policy would reduce the need for wasteful promotional activities and wasteful investment into research and development for me-too drugs. Third, such a policy would lessen the likelihood of consumers taking drugs with small (or zero) incremental therapeutic benefits but large and unknown risks.

Such a policy would require greater investment by firms developing follow-on drugs since they would be required to demonstrate clinical superiority as well as efficacy. (Such a demonstration might not be all bad: it would help to clarify which drug a consumer should be taking.) It would reduce the number of close substitute drugs, and this in turn would lead to less therapeutic choice for consumers as well as a slight increase in prices. (Recall, however, that higher prices would be good for inducing more investment in R&D into truly pioneering drugs.)

diMasi and Paquette also conclude their paper by considering the suggestion that me-too drugs should be approved conditional only on showing clinical superiority to pre-existing therapies. They offer two main criticisms of this approach. First, they argue that this could increase the uncertainty of drug approval and therefore lead to fewer firms actually entering a market. However, as I discuss above, since the prize for a single entrant will in general be larger than the sum of prizes for two entrants with very similar offerings, the incentives should work in exactly the opposite direction from the one they have suggested. (On the other hand, if the later drug is clinically superior, then it will obtain approval and expand the market.) Second, they argue that such a policy could create a moving target for drug approval, where a firm which was hoping to be the pioneer suddenly finds itself having to conduct new clinical tests against a drug which arrived first. This is a very reasonable criticism. Fortunately there is a solution: a reasonable compromise might be to require firms to show clinical superiority only in comparison to drugs which were marketed for more than, say, 18 months before the firm sought regulatory approval. This would largely solve the problem of the moving target.⁶

References

- Anderson S, A de Palma, and Y Nesterov, 1995, "Oligopolistic Competition and the Optimal Provision of Products" *Econometrica*, 63 (6): 1281-1301.
- Angell, Marcia, 2004, *The truth about the drug companies*. New York: Random House.
- Avorn, Jerry, 2004, *Powerful medicines*. New York: Knopf.
- Azoulay, P. 2002, "Do Pharmaceutical Sales Respond to Scientific Evidence?" *Journal of Economics & Management Strategy* 11(4): 551-594.
- Calfee, J.E., 2000, *Prices, Markets, and the Pharmaceutical Revolution*. Washington DC: American Enterprise Institute Press.
- Cockburn I, Anis AH, 1998, "Hedonic Analysis of Arthritis Drugs." NBER Working Paper 6574.
- diMasi J and C Paquette, 2004, "The Economics of Follow-on Drug Research and Development Trends in Entry Rates and the Timing of Development." *Pharmacoeconomics* 22 (Suppl. 2): 1-14.

⁶ A related problem is that when a drug enters a relatively crowded market, it is not clear what the standard for approval should be. Should it be comparison to the most recent entrants, to the first entrant, or what? Requiring a demonstration of clinical superiority to six other drugs would be very expensive. Perhaps a reasonable requirement would be comparison to (at most) two therapies deemed to be most similar by the regulator.

- DiMasi, J., R. W. Hansen, H. G. Grabowski, 2003 “The price of innovation: new estimates of drug development costs,” *Journal of Health Economics* 22: 151-185.
- Dixit A and J Stiglitz, 1977, Monopolistic Competition and Optimum Product Diversity; *American Economic Review*, 67(3): 297-308.
- Ekelund, Mats, and Björn Persson, 2003. “Pharmaceutical Pricing in a Regulated Market.” *Review of Economics and Statistics* 85(2): 298-306.
- Goozner, M. 2004, *The \$800m pill: The truth behind the cost of new drugs*. Berkeley: University of California Press, 2004.
- Kaitin KI, editor, 2004. “Incremental R&D creates safer, more effective drugs & fosters competition.” *Tufts Center for the Study of Drug Development Impact Report* 6(6).
- Lexchin, Joel, 2003, “Intellectual Property Rights and the Canadian Pharmaceutical Marketplace: Where Do We Go From Here?” Canadian Centre for Policy Alternatives discussion paper. Available at <http://www.policyalternatives.ca/publications/ipr.pdf>, last accessed June 22, 2004.
- Lichtenberg, FR, 2004, “Pharmaceutical Knowledge-Capital Accumulation and Longevity.” In Carol Corrado, John Haltiwanger and Daniel Sichel, Editors, *Measuring Capital in a New Economy*. Chicago: University of Chicago Press.
- Lichtenberg F and T Philipson, 2002, “The Dual Effects of Intellectual Property Regulations: Within- and between-Patent Competition in the U.S. Pharmaceuticals Industry.” *Journal of Law and Economics* (Part 2) 45 (2): 643-672.
- Love, James, 2003, “Evidence Regarding Research and Development Investments in Innovative and Non-Innovative Medicines,” mimeo, available at <http://www.cptech.org/ip/health/rnd/evidenceregardingrnd.pdf>, last accessed June 22, 2004.
- Lu, Z.J. and W.S.Comanor, 1998, “Strategic Pricing of New pharmaceuticals.” *Review of Economics and Statistics* 80(1): 108-118.
- Milne, C., K. Kaitin, and E. Ronchi, 2001, “Orphan Drug Laws in Europe and the US: Incentives for the Research and Development of Medicines for the Diseases of Poverty.” CMH Working Paper Series, Paper No. WG2: 9.
- National Institute for Health Care Management Research and Educational Foundation, 2002, “Changing Patterns of Pharmaceutical Innovation,” NIHCM, Washington.
- Spence M, 1976, “Product Selection, Fixed Costs, and Monopolistic Competition.” *Review of Economic Studies*, 43(2): 217-235.