The Economics of Follow-On Drug Research and Development: Trends in Entry Rates and the Timing of Development – The Authors’ Reply

Joseph A. DiMasi and Cherie Paquette
Tufts Center for the Study of Drug Development, Tufts University, Boston, Massachusetts, USA

Hollis[1,2] discusses so-called ‘me-too’ drug development and comments on our paper[3] recently published in this journal, which presented evidence on the entry rates and development histories of first-in-class and follow-on drugs in therapeutic classes defined by mechanism of action or chemical similarity. While the discussions by Hollis are interesting and provocative, we believe that to some extent he mischaracterises our views and the relevant literature. We also believe that his strong conclusions are neither the inevitable implications of economic theory as he seems to suggest, nor are they supported by empirical evidence. DiMasi[4] offers a comprehensive critique of the antecedent [1] to Hollis’ comment[2] in PharmacoEconomics. Our comments here will be brief, but we refer the reader to DiMasi’s posting[5] for a more detailed discussion of many of our points.

Hollis[1,2] maintains that follow-on drugs decrease innovation incentives, and that we claimed that they increase innovation incentives. We never made such a claim, and framing matters in this way makes little sense to us. Institutional and policy environments, interacting with scientific and economic conditions, determine innovation incentives. The level and type of entry into a market is a consequence of the incentives and disincentives inherent in institutional and policy structures. It makes sense to examine the incentive and market entry effects of a particular policy change, but general statements claiming that multiple entrants to a market increase or decrease innovation incentives are not particularly useful.

The empirical results in our paper[3] are not tests of hypotheses about innovation incentives. However, our discussion did remark on some of the potential implications of a proposal to use drug registration authorities to erect entry barriers for follow-on drugs in therapeutic subclasses.[5] DiMasi[4] expands on that discussion in relation to claims in Hollis’ earlier posting.[1] The basis for Hollis’ claim about incentives was made in his earlier posting in the context of a model that, in its starkest form, makes extreme assumptions. Specifically, the underlying explicit and implicit behavioural and market assumptions for the model are that firms in the current environment seek to develop drugs that are perfect substitutes for one another, there is no price competition among the perfect substitutes (other things being equal, relaxing this assumption will strengthen his argument about private incentives if demand is inelastic), marketing among competitors...

1 We believe that a much more value-neutral term, such as ‘follow-on’, is more appropriate for scientific and scholarly discussions of the issues than is the clearly pejorative term ‘me-too’, but we recognise that the latter term is very widely used.

2 The policy would forbid regulatory authorities from allowing a new drug in an existing class from entering the market unless it was proven in pre-market testing to be ‘better’ than existing drugs. The definition of what constitutes a ‘better’ drug is left undefined.
can only result in cannibalisation of other firms’ sales (i.e. shifts only in market share, with no market expansion possible), and (implicitly, because it is ignored) the policy shift will not result in any changes in risks or expected research and development (R&D) costs. In practice, none of these assumptions is likely true individually, let alone in combination. It is worth examining each of these assumptions in turn.

1. Perfect Substitutes or Horizontal Differentiation

As noted above, an underlying assumption in Hollis’ framework for analysing innovation incentives is that firms in the current environment are willing to compete consciously in the development of perfect substitutes. However, pharmaceutical company executives routinely comment that they are not interested in developing what are effectively identical products. Observations of how drug development tends to proceed appear to be consistent with these characterisations. As Scherer has noted, “If there is no future in me-too drugs, what companies do is to seek an unpopulated niche. Given the long lead times in drug discovery and testing, however, they may inadvertently end up with a me-too drug. But they are not trying consciously to duplicate the output of one or more known racing partners.” Scherer further describes a type of racing that characterises drug discovery and development, “Drug discovery and development are more like a marathon than a 400-meter dash. In a marathon, the runner mostly has to pace himself, or he will drop from exhaustion. But there may be key stages at which he comes into head-to-head rivalry. Moving from that analogy to a closer approximation, firms in the pharmaceutical industry are racing to horizontally differentiated niches in what economists call product characteristics space. If that is true, and I believe it is, it is not an ‘either he wins or I win’ race. It can be an ‘everybody wins’ race – one, to be sure, in which some win more than others.”

2. Price Competition

Hollis and Comanor paper disputes Hollis’ conclusion that there is nearly no price competition from the introduction of new drugs in a class. A number of points about the data and results in the paper show why. First, the data used for the Comanor and Lu paper are now quite old. They refer to new drugs introduced from 1978 to 1987, a period during which price discounting was limited relative to what we see today. As the authors themselves note, “The period covered in this study largely predates the rapid growth of managed care, which is relevant because it led to much greater price discounting. For this reason, the results presented here may not fully represent current conditions in pharmaceutical markets.” On the other hand, we discussed in our paper results from a study that DiMasi conducted on pricing trends for drugs approved from 1995 to 1999 that showed an average launch price discount of 14% for new entrants relative to the weighted mean price of existing drugs in the class. Furthermore, the results do not include the impact of widely-acknowledged rebates (which were unavailable).

Second, the impact of additional entrants to a class in the Lu and Comanor study was measured by multivariate statistical analysis. Lu and Comanor ran a number of regressions to examine the extent of competitiveness for their study period. Contrary to Hollis’ conclusion, the authors themselves concluded that market entry of a new drug induces a significant amount of price competition. As they note in their abstract, “In addition, the number of branded substitutes has a substantial negative effect on launch prices, which reflects the importance of competitive pressures.” For a quantitative assessment, their regression results imply that, “increasing the number of direct substitutes from one to two leads on average to a 38% decline in the ratio of a product’s launch price to the average price of its predecessors; while increasing the number of substitutes from two to three leads to a 19% decline.” Similarly, they also used regression analysis to evaluate the impact of market entry on pricing dynamics and concluded that “More numerous rivals have the expected effect of slowing price increases.” In sum, a full reading of the Lu and Comanor study strongly supports the hypothesis that therapeutic class com-
petition in a relatively unregulated market induces a significant amount of price competition.3

The Ekelund and Persson study9 was designed to examine price competitiveness in a price-regularized market. They attempted to replicate the Lu and Comanor8 analysis for drugs launched in Sweden from 1987 to 1997. Their regression results show that the impact of additional entrants on launch prices has the expected sign (negative) but that the effect is not statistically significant. The message from the Ekelund and Persson9 study is not that drugs in a therapeutic class cannot compete on price. The message (to the extent that one can even embrace a null hypothesis) is that price regulation suppresses price competition.

Hollis2 also alludes to two studies12,13 each covering one therapeutic area, as a basis for concluding that “me-too drugs very frequently not only fail to increase price competition but may even lead to price increases.” Even if one takes Hollis’ comments about these two studies at face value, they could hardly constitute proof for such a broad claim. However, it is worth examining these two studies in more detail.

The Cockburn and Anis12 study does not test directly for price competition, but rather, in part, examines the relationship between price and quality. The authors examine demand for so-called disease-modifying antirheumatic drugs (DMARDs) using quality measures based on the results of published clinical trials. Their price variable (wholesale prices) does not account for discounts and rebates. The authors acknowledge that measurement error or confounding with other factors determining prices may have affected the pricing results. Furthermore, their preferred explanation for the weak statistical results for price and quality is that prices were largely exogenous to the rheumatoid arthritis market because the primary uses of many of the drugs examined were for other conditions.4 It is not surprising, then, to find that price is not related to quality in the expected way if prices are set in other markets. We would still expect that quantity demanded is dependent on quality, and that is what the authors found.

The Azoulay13 paper examined the H2-antagonist market before these drugs went over-the-counter, before patents expired and before the proton-pump inhibitors rose to dominance. The period studied predates the era during which discounts and rebates became more substantial. Also, the descriptive pricing data in Azoulay13 shows that Pepcid® and Axid® entered at prices below the price leader (Zantac®). The upward price trend for covering one therapeutic area, as a basis for concluding that “me-too drugs very frequently not only fail to increase price competition but may even lead to price increases.” Even if one takes Hollis’ comments about these two studies at face value, they could hardly constitute proof for such a broad claim. However, it is worth examining these two studies in more detail.

3. Failure Risk and Innovation Incentives

Hollis1,2 claims that follow-on drugs decrease innovation incentives because a monopolist will take the whole market, while, with entry, profits must be shared. However as shown in DiMasi,4 keeping within the confines of Hollis’ model and making reasonable assumptions, from a pre-innovation perspective the advantage of being the only seller in the market is completely offset by the risk of being one of the losers in a race to the marketplace in the winner-take-all scenario induced by the policy of restricting market entry to follow-on drugs. In addition, it may also be the case that firms are not risk-neutral over all sets of potential risk/

---

3 This is not to say that the entry of therapeutic class substitutes will induce the type of intense price competition seen with generic entry, where products essentially compete just on price. Branded drugs will compete on quality attributes and supporting promotional efforts as well, a notion that is also supported by data in Lu and Comanor8 and DiMasi;4 the results on pricing by therapeutic rating at least suggest that prices tend to adjust, to some extent, to quality differences.

4 The drugs examined were heterogeneous in terms of chemical structure and mechanism of action (which was not well understood for most of them). They would not have constituted a subclass as defined in our paper.

5 The use of trade names is for product identification only and does not imply endorsement.

6 Hollis does note that he does not mean to claim that prices have no effect on pharmaceutical sales. Indeed, Azoulay13 finds that the three follow-on entrants to the H2-antagonist class had price elasticities of demand between 1.4 and 1.6. The first entrant, Tagamet®, with a lengthy exclusivity period in which to build first-mover brand loyalty, had a price elasticity that was slightly less than unity (0.9).
reward outcomes, but that they could become risk averse if the distribution of risks across outcomes becomes skewed enough. That is, firms may not be willing to take a ‘fair bet’ or even a somewhat better than fair bet if there is a sufficiently high risk of a substantial loss. This is one reason why innovation incentives could in fact be diminished under a regulatory policy change that erects entry barriers for follow-on drugs in therapeutic subclasses.

Hollis cites a Lichtenberg and Philipson study[14] and uses it to support his conclusion that me-too drugs reduce incentives for innovation because they take market share from pioneers. However, it is worth noting that the data used in the Lichtenberg and Philipson study were quite broad in comparison to the kinds of groupings we used for our study.[3] We noted in our article that the classes we used were conservative from a full economic perspective. Drugs compete in the marketplace across, as well as within, classes of the type we analysed. It was not our purpose to characterise and analyse demand in complete markets for drugs; our focus was on evidence on the development and entry of drugs in what many would think of as me-too groupings. Hollis recognises that the empirical analysis in the Lichtenberg and Philipson study used very broad categories, but he largely dismisses the distinction. He argues that nearly all of the lost value for new drugs comes from later entry in the same class. In that regard, it is instructive to note just how much broader the classes are in the Lichtenberg and Philipson study than anything we are discussing here. In our study, the mean number of entrants (including the first-in-class) was four and the median was three. In the Lichtenberg and Philipson analysis, at the time the average new entrant was launched, the mean number of drugs in the class that were already on the market was 25.

Lichtenberg and Philipson have firmly in mind the kind of creative destruction of value that comes from improved products (“… the demand for a given innovation is often destroyed by the entry of new, superior products long before patent expiration”). In their empirical analysis, additional competition after entry in their empirical analysis can come from drugs in newer classes, not just new entrants to the same class. In theory, if the advances are large enough, new and improved classes can destroy more value than additional entrants to an older class. In any event, as noted above, given the particulars of the proposed regulation-induced monopoly policy, offsetting risks of failure to reach the market must be considered.

4. Marketing and Innovation Incentives

Hollis[1,2] essentially offers just two reasons to justify his conclusion that innovation incentives will increase with a regulation-induced monopoly policy. One is that firms in the current regulatory environment have to share markets, as opposed to capturing the entire market in the induced monopoly scenario. As we have seen, this factor is offset by the increased risk of incurring R&D costs and failing to reach the marketplace in the induced monopoly case. Hollis’ other reason for concluding that innovation incentives increase derives from his claim that aggregate marketing expenses are greater in the multiple entry scenario than in an induced monopoly scenario, while aggregate market sizes are fixed. If so, industry profits would be higher for the induced monopoly scenario. In his discussion of marketing, Hollis[2] claims that DiMasi[4] ‘defends’ the promotion of drugs as market-expanding. This is a puzzling characterisation. DiMasi[4] neither defends nor attacks promotion (either in terms of innovation incentives or social welfare). The discussion in DiMasi[4] was intended primarily to make just two technical points about how the impact of Hollis’ claim[1] about differential aggregate marketing expenditures in the current versus the induced monopoly scenarios should, in theory, be adjusted.

One of the factors that should be considered is that from a pre-innovation perspective lower aggregate marketing expenditures under an induced monopoly scenario (and so higher aggregate profits) must be tempered by the fact that there is a lower probability that any potential entrant will succeed in making it to the market and actually achieve higher profits. The second technical point relates to the Hollis assumption that aggregate market sizes are fixed, and so marketing by follow-on entrants can only affect market share. That is, marketing with multiple entrants will have no market-expanding effects beyond those that would occur under monopoly.
DiMasi[4] notes results from much more of the literature on promotion than just those from the Rosenthal et al.[15] study mentioned by Hollis.[12] The empirical literature on the existence of market share effects is very weak for direct-to-consumer advertising (DTCA), but much stronger for other forms of pharmaceutical promotion.[7] However, this is largely beside the point. Undoubtedly, there are market-share effects for pharmaceutical promotion in general. However, the issue that DiMasi[4] was addressing was whether entry in therapeutic classes is associated with market expansion. If so, then the negative impact on aggregate profits resulting from higher aggregate marketing expenditures in the multiple entry scenario is attenuated to the degree to which markets expand.

There are a number of reasons, some subtle, why markets can expand with multiple entrants. Inventions do not immediately diffuse fully. It would take a monopolist some time to capture the full quasi-rent potential of a market. If there are a number of competing firms in the marketplace, the movement towards the capture of maximum quasi-rents will likely be much quicker. Thus, the present discounted value of aggregate quasi-rents (total profit potential) will be larger in the multiple entry than in the monopoly scenario. In this way, we can say that a market can expand with entry. Furthermore, the market will expand if additional indications are approved, or at least approved more rapidly, under rivalry.[8] It is also thought that compliance rates are poor for many drugs (even for those individuals with insurance coverage). Marketing in a multiple-entry scenario could improve compliance rates in general for the class.[11]

Market expansion may or may not be good from a societal perspective (it depends largely on whether drugs would otherwise be under- or over-utilised in each of their uses), but it increases private incentives, and so works against Hollis’ conclusions. As noted, the issue in DiMasi[4] regarding market size was simply whether Hollis’ claim about the effect of marketing on incentives needs to be qualified (and potentially reversed), because marketing by later entrants to a class can result in some market expansion. Much of the analysis and data on pharmaceutical promotion is suggestive of market-expanding effects from entry in pharmaceutical markets. Direct evidence of this type of effect was provided in a careful econometric analysis by Berndt et al.[18] In the context of the H2-antagonist market (for which marketing was perceived to be intense and highly rivalrous), the authors directly tested the hypothesis that, other things equal, entry was associated with market expansion. They found that while the effectiveness of an entrant’s advertising on expanding industry demand generally declines with the number of entrants, market-expanding spillovers remained positive with entry. That is, for the H2-antagonist anti-ulcer market, they strongly rejected the hypothesis that the only impact that marketing by additional competitors had was on market share with no effect on overall market size.

Apart from any effects on innovation incentives, much of the criticism of follow-on drugs flows from assumptions made about the nature of the effects that marketing has on demand for these products. The argument is often made that these drugs do not really differ much from the first entrant, but marketing is used to create perceived, but not real, differences in the minds of physicians and patients. In other words, marketing efforts increase product differentiation beyond that which would exist if consumers and/or their agents (physicians) had been presented only with the most impartial and comprehensive information that existed at the time. However, to the extent that this is true, it can be largely

---

7 The Kravitz et al.[16] study that Hollis[12] cites was published after DiMasi[3] was posted. It provides strong support for the hypothesis that patients can affect physician prescribing. However, it offers little support for market-share effects with DTCA since all of the actor-patients in the study who mentioned a brand name drug used for the conditions considered. In addition, their results are consistent with a market-expansion hypothesis given their statistical evidence that physicians differ systematically in their propensity to prescribe antidepressants.

8 The pursuit of different indications by rivals can occur prior to original marketing approval, as well as later. For example, although Celebrex® and Vioxx® were approved just 5 months apart, Celebrex® was originally approved for osteoarthritis and rheumatoid arthritis, while Vioxx® was originally approved for osteoarthritis, acute pain and dysmenorrhea.
remedied, as we suggest in our study,\(^9\) by improved information on drugs already in the marketplace (e.g. pharmacoepidemiology studies, disease management programmes, pharmacoeconomic analyses, so-called pragmatic clinical trials, and, occasionally, additional randomised controlled clinical trials [not necessarily conducted by manufacturers]).

5. Restricted Entry and Research and Development Costs

When considering innovation incentives from a proposed regulation-induced monopoly policy, any effect on expected profits that higher industry marketing expenditures (net of higher industry demand from market expansion) has in the multiple-entry scenario must be weighed against any higher expected costs in the induced monopoly scenario. A cost to the proposed regulatory change that we noted in our study\(^3\) is the impact on expected R&D costs that the regulatory change would engender, from both increased approval standards and moving targets. These are costs (potentially quite substantial) from the regulatory change that would have to be added to the costs noted above that arise from a higher risk of sinking large expenditures into R&D programmes of the type that exist under the current system that will now not yield any returns. Here, we also need to consider that the more stringent approval standards will result in higher expected development costs for the average programme, even if the approval targets are known in advance (i.e. which drugs will serve as comparators). This is so because there is some likelihood that firms that lose the race to be first will shift focus and spend additional funds to try to demonstrate superiority. This strategy may be perceived to be a worthwhile risk because at that point in time much of the firm’s R&D expenditures to develop the drug are sunk costs. In addition to higher expected development costs from testing to show superiority against a known comparator, the expected costs for firms considering entry will be still higher because there is a likelihood that part of the development programme would have to be stopped and begun again as other drugs reach the marketplace (i.e. firms would be faced with the prospect of a moving target). This latter scenario may be replicated a number of times during development. Aside from directly increasing R&D costs, this will delay the introduction of follow-on drugs. Delays in entry can substantially reduce expected profits.\(^9\) All of these factors serve as strong disincentives to development when viewed from a pre-development perspective.

Hollis\(^{1,2}\) acknowledges the moving target problem and proposes, as a solution, restricting the drugs to be used as comparators to those approved prior to an 18-month window leading up to regulatory submission of an application for marketing approval of an investigational drug. This solution appears completely arbitrary. Or, at the least, one can say that Hollis has not provided any rationale for why 18 months is the right figure to “largely solve the problem of the moving target.” However, what we can note, is that historical development time data indicate that the phase II testing period has averaged about 3 years.\(^{19}\) This is an average, so there are drugs for which phase III testing has lasted longer than 3 years. In addition, arguably, at least some phase II trials might be affected by whether testing against comparator drugs is to be undertaken, for what purposes, and which comparators will be used. So, should we make the window say, 5 years, 7 years, 8 years, etc.? What would be left to test against with such lengthy windows for narrowly defined classes? Our data showed entry from therapeutic substitutes in the same class occurring relatively rapidly for recent periods.\(^{19}\)

Investigational drugs that would have to be tested against comparator drugs in the same class with windows this lengthy would be very late entrants to the class. It is highly likely that firms with such late entrants would not bother pursuing entry unless they already had reason to suspect that they could demonstrate superiority for some attributes (even if this is done post-approval) or could find some niche that is not already well served. One would have to

---

\(^9\) Of course, from a pre-innovation perspective, the effects of delays must be weighted by the likelihood that they will be incurred.

\(^{10}\) We also note that while firms do project timelines for the development of their drugs, early projections often turn out to underestimate the subsequent reality as a consequence of a variety of unexpected circumstances.
wonder, then, if a proposal of the type suggested by Hollis\(^{[1,2]}\) with a window lengthy enough to “largely solve the problem of a moving target” is a solution for which there is no problem.

6. Safety Risks

Hollis\(^{[1,2]}\) maintains that, independent of innovation incentives, therapeutic benefits or costs to the system, the potential risk that a follow-on drug will have unanticipated serious safety problems (that a first-in-class drug that has been on the market for many years is less likely to have) argues strongly for a much more stringent approval standard for follow-on drugs. However, without evidence on real-world outcomes it is impossible to know whether this should be viewed as so serious a concern that it alone constitutes a strong argument for higher approval standards.

To provide some evidence along these lines, we examined the drugs used in our study on therapeutic subclasses\(^{[3]}\) for safety withdrawals. The first-in-class drugs for our 72 subclasses had a 2.8% safety withdrawal rate. This rate is similar to safety withdrawal rates that have been found for new drugs as a whole.\(^{[20-24]}\) If we include all of the follow-on drugs in our dataset, we find a safety withdrawal rate of 3.0%. The difference in safety withdrawal rates is not statistically significant. In fact, including all of the follow-on drugs in this analysis can overstate the risk for follow-on drugs. The reason is, that because we wanted to have enough time to find follow-on approvals for relatively recent first-in-class approvals, there are more recent follow-on drugs in the dataset than first-in-class drugs (first-in-class approvals run through 1998, but follow-on approvals run through 2003). If we try to correct for this by including for analysis only follow-on approvals from the same period as first-in-class approvals, the difference disappears entirely (follow-ons have a 2.8% safety withdrawal rate).

Safety withdrawals reflect a safety extreme. Drugs may have serious adverse effects that are nonetheless not serious enough to warrant withdrawal from the market. Hollis\(^{[1,2]}\) cites a study by Olson\(^{[25]}\) to support his concern over the relative safety of follow-on drugs. However, a close reading of the study suggests the opposite conclusion. Olson found that reports of serious adverse drug reactions were substantially higher for novel than for other new drugs.\(^{11}\) Her definition of novelty was that the drug had received a priority review rating from the US FDA. While this does not exactly mirror a first-in-class versus follow-on distinction, it strongly suggests that follow-on drugs were associated with many fewer safety problems.\(^{12}\) Why might this be so? Two possible explanations occurred to us.

One reason is that experience with first-in-class and other early entrants can help better define for physicians and patients risks and rational use for drugs in the class, thereby resulting in improved prescribing and utilisation patterns for later entrants to the class. A second reason is that some of the later entrants may have had better safety profiles. Indeed, this could have been a reason why firms found it worthwhile in the first place to pursue entry into established classes where they are naturally disadvantaged by virtue of order-of-entry effects and less time before both generic entry of some members of the class and the emergence of newer classes.

These results suggest that, in practice, relative safety issues for follow-on drugs are not nearly as much, if any, of the issue that Hollis contemplates. Our results on rapid entry of follow-on drugs in recent periods also indicate that lengthy prescribing experiences with first-in-class drugs are not available before most entry occurs. Finally, Hollis ignores the benefits of having follow-on drugs in a class available when a first-in-class drug is withdrawn for safety reasons or does not work well or safely for individual patients.

\(^{11}\) Results from Olson’s\(^{[25]}\) regressions suggested that, other things equal, adverse drug reaction reports submitted to the FDA (for cases where causation was suspected for the drug), were 60%, 45% and 61% higher for novel new drugs than the average new drug for the serious-, hospitalisation- and death-reporting categories, respectively.

\(^{12}\) Priority ratings are highly positively correlated with first-in-class status. We found that 80% of the first-in-class molecules in our dataset had received a priority rating, while 33% of the follow-on drugs had received such a rating from the FDA.
7. Lessons from Orphan Drug Regulation?

Hollis[1,2] points to US orphan drug regulations, and their perceived impact on the development of drugs for orphan indications, to argue that therapeutic class competition should be precluded along the lines discussed above. The US orphan drug legislation affords a number of incentives for orphan drug development, including tax credits, clinical trial grants, advice from regulators, waiver of user fees in some instances and marketing exclusivity. This last factor is usually thought to be the most powerful of the incentives. However, it is important to understand just what problems this solution addresses.

During the period of marketing exclusivity, orphan drug regulations preclude approval of other drug products that are the “same drug for the same indication.”[3] Under orphan drug regulations, for a small-molecule product to be considered the ‘same’ as another drug product that has received orphan drug marketing exclusivity, it must contain the same active ingredient. Therefore, for small-molecule drugs, the orphan drug regulations do not prevent the type of therapeutic class competition that Hollis seeks to inhibit.[4]

The issues for macromolecules under the orphan drug regulations are a little more complex. It was about 10 years into implementation of the Orphan Drug Act before the FDA established rules that provided industry with clear guidance on what constitutes ‘sameness’. The delay led to some high-profile conflicts in the biotechnology sector over whether variation in particular characteristics of the physical/chemical structure of a macromolecule yielded a ‘different’ drug. In late 1992, the FDA provided guidance on what constituted sameness for macromolecules. The presumption under the rules is that macromolecules with small changes in amino acid sequences, glycosylation patterns and a number of other small differences in structure for a variety of types of macromolecules do not have any clinical effect and so the molecule would be considered the ‘same’ as the drug with exclusivity.[5] However, such follow-on macromolecules could be considered different drugs if the manufacturer of the later drug demonstrates ‘clinical superiority’ for its product.[6]

The rationale for orphan drug marketing exclusivity has to do principally with providing protection against free-riding on research for drugs that were unpatentable (a particular concern for biopharmaceuticals) or that had patents that had expired or would expire prior to regulatory approval or shortly thereafter. The regulations on ‘sameness’ effectively protect firms against early generic or

13 For purposes of this discussion I will refer to both drugs and biologics as drugs.
14 Although the share of new drug orphan approvals that are for small-molecules has trended downward, small-molecule drugs still constitute a majority of these approvals over the entire history of the implementation of the Orphan Drug Act.
16 For example, in a dispute between Genentech and Lilly about their versions of human growth hormone, the FDA ruled that Lilly’s product was not the ‘same’ drug as Genentech’s earlier approved product, even though Lilly’s product differed structurally only by the addition of a single amino acid to a sequence of 191 amino acids. The ruling made Lilly’s product eligible for approval and orphan drug exclusivity.
17 These differences in large molecular structures might be viewed as something akin to differences in excipients in small-molecule formulations. They are not expected to have clinical effects, but in highly uncommon cases they might. Thus, without evidence to the contrary, these molecules can be viewed as essentially generic versions of existing drugs. In theory, clinically different outcomes might result not from these structural variations, but rather from differences in formulation, route of administration or frequency of administration.
18 Under the regulations, clinical superiority means that the manufacturer has demonstrated a significant therapeutic advantage with regard to some aspect of efficacy or safety, or in unusual cases by showing that the product “makes a major contribution to patient care”. It does not mean that the new product is ‘better’ than the original product in some overall sense for all patients, or even on average.
Commentary

8. Conclusions

The discussions in Hollis,[1,2] DiMasi and Paquette[3] and DiMasi[4] all illustrate various economic considerations that impinge on the incentives to develop new drugs. However, Hollis’ analysis of the effects on incentives for developing new drugs from creating higher regulatory hurdles for potential second and later entrants to a therapeutic class ignores, or does not give due weight to, such factors as the risks of failure, risk aversion, market expansion under rivalry, racing to horizontally differentiated niches, expected R&D costs and expected delays in marketing. These factors argue against Hollis’ conclusion that inhibiting therapeutic class competition through creating regulatory barriers of the type he discusses will inevitably increase drug development incentives. Thus, theory does not predict the effect on incentives that Hollis claims, and he does not provide the empirical evidence to support it.

One of the difficulties with assessing proposals such as those made by Angell[5] and others is that they are made without offering any operational details. The costs of such proposals depend critically on the details. Hollis[2] does not provide such detail either.21 These authors[2,5] simply assert that a new drug in a class should be proven ‘better’ than existing drugs before it be allowed to enter the market. If we interpret the proposal as literally meaning that sponsors of follow-on drugs would need to prove that their drugs were at least no worse in all drug attributes and superior in at least one attribute, then development costs could be increased substantially. In comparing drugs, there are potentially dozens of adverse effects that one might consider (although some are more important than others) with differing frequencies of occurrence, a plethora of potential drug/drug interactions, and even multiple efficacy endpoints and indications. Powering randomised controlled clinical trials to provide definitive answers to all comparisons where clinically significant differences might exist and against all competitor drugs in a class could be enormously expensive and often not feasible.22

Such proposals also have the potential to distort drug development practices in ways that are hard to assess. The proposals can lead to excessive haste in trying to get to market first. In particular, it can result in a shift towards more parallel testing and less sequential testing than is optimal from the perspective of minimising drug development costs. Regulatory approvals for marketing are also highly specific. They are not usually a general approval for some broad disease or condition, but will often specify the stage or type of the disease or condition, the patient populations for which the drug is indicated, and the level of therapy (e.g. first-line, second-line, etc.). Under a high regulatory hurdle policy, strong incentives will be created for firms to strategically alter development plans towards approval for a label that is only slightly different from that of the existing drugs in the class or towards minor indications with a consequent reliance on off-label use.

19 In the absence of regulations precluding the approval of drugs that are the ‘same’, firms seeking marketing approval for macromolecules that are the ‘same’ as products already on the market would avoid some discovery and other costs, but some clinical trial testing would still be necessary. The situation is similar to that which was required to obtain approval of a generic drug in the US prior to the enactment of the Drug Price Competition and Patent Term Restoration Act of 1983.

20 The protection is somewhat weaker than patent protection on drug substances. Even with orphan drug marketing exclusivity, it is possible for other firms to get the same drug substance approved during the exclusivity period for other uses (either non-orphan or other orphan indications) if there are no other relevant intellectual property protections for the original manufacturer.

21 However, in his initial posting[1] on this topic, Hollis did suggest that me-tooism be defined according to the notion of ‘sameness’ in the orphan drug regulations and that drugs not be approved unless they meet the ‘clinical superiority’ standard in those regulations. Given the discussion above, this reflects a misunderstanding of those regulatory concepts. They would not achieve what Hollis wants to achieve.

22 If such comprehensive testing were actually done, we would likely also be left often without a dominant outcome (i.e. comparisons where, on average, some attributes turned out better and some turned out worse), and the difficult problem of precisely weighing the relative benefits of numerous attributes.
Given the potential costs and inherent uncertainties from using pre-market approval requirements as a kind of industrial policy that would enforce monopoly positions, it would seem that more predictable beneficial outcomes could come from improving information on the demand side of the market. As we note above (section 4) and in our study, much useful information about the comparative properties and rational use of drugs can come from the generation of knowledge after drugs have been in widespread use. This would have an impact not only in improving the use of existing drugs, but it would also reach back and affect the decision-making processes of drug developers who would have to factor into their plans the anticipated preferences and demands of informed patients, physicians and payers.

Finally, Hollis\(^{1,2}\) often moves back and forth between claims about drug innovation incentives and what may be called some of the social welfare aspects of follow-on drug development. For example, Hollis refers to R&D expenditures on follow-on drug development as wasteful, with a distinction made between ‘pioneering’ research and follow-on research. We have shown in our study\(^{3}\) that the bulk of development for follow-on drugs happens before the first-in-class drug is approved. It is problematic, then, to label most follow-on R&D as non-pioneering. In any event, success, in the sense of finding a drug with an acceptable benefit/risk ratio, is not assured for any new class of compounds, or even for every compound in a class where some compounds are approvable. In general, it is useful to have multiple independent organisations pursuing different compounds in a new class. The likelihood of finding at least one compound in a class that has an acceptable benefit/risk ratio increases with the number of independent development efforts.\(^{23}\)

**Acknowledgements**

We thank Ernst Berndt and William Comanor for helpful comments.

The Tufts Center for the Study of Drug Development is supported in part by unrestricted grants from pharmaceutical and biopharmaceutical firms, as well as companies that provide services and products to this industry. Sponsoring companies have no direct access to any of the Tufts Center’s proprietary databases, and they have no direct influence on the group’s research agenda. No financial support was provided for this reply.

The authors have no other conflicts of interest directly relevant to this manuscript.

**References**

2. Hollis A. Comment on “The economics of follow-on drug research and development”. Pharmacoeconomics 2005; 23 (12): 1267-72

\(^{23}\) For examples, see discussions by Scherer\(^{28}\) and Scotchmer\(^{29}\) regarding innovation in general. To put the matter formally in a simple context, suppose that N firms pursue different independent approaches to developing a drug in a new, but unproven, class, and that the probability of failure, q, is the same for all firms. Then, the probability that at least one investigational drug will be found that has an acceptable benefit/risk ratio is 1–qN. Thus, the likelihood of at least one success increases with the number of firms pursuing different molecules in a class. This observation alone does not tell one what the socially optimal number of experimental approaches is, but we would certainly expect that generally it is greater than one.
Commentary 1203


25. Olson MK. Are novel drugs more risky for patients than less novel drugs? J Health Econ 2004; 23 (6): 1135-58


Correspondence and offprints: Joseph A. DiMasi, Tufts Center for the Study of Drug Development, Tufts University, 192 South Street, Suite 530, Boston, MA 02111, USA.
E-mail: joseph.dimasi@tufts.edu

© 2005 Adis Data Information BV. All rights reserved.