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The EC Pharmaceutical Inquiry: Behind the Headlines, What is the Real Story on Innovation and Generic Competition in Pharmaceuticals?

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While the pharmaceutical sector waits for the European Commission's interim report and hearing scheduled for November 28, 2008, there is an opportunity to step back and examine critically the premise of the inquiry—started infamously with dawn raids on January 16, 2008—that, as Commissioner Kroes announced, “if innovative products are not being produced, and cheaper generic alternatives ... delayed, then we need to find out why and, if necessary, take action.”¹

I. THE PROGRESS OF THE INQUIRY AND CURRENT STATUS

Dubbed by officials “the most thorough sector inquiry ever conducted,” the dawn raids were followed by a huge exercise in information gathering. Initial questionnaires to around 100 innovators and generics were sent on March 28, 2008 and were soon supplemented by further and broader requests. DG Competition proceeded to issue weekly requests for further information, with seven day return dates, throughout the summer and beyond even the date for inter-service consultation on the draft findings. Wholesalers, parallel traders, marketing authorization authorities, antitrust regulators, and even doctors and patient groups have received broad-ranging requests. The research-

*Thomas Cueni is the Chairman of the EFPIA Sector Inquiry Task Force.

¹*Commission launches sector inquiry into pharmaceuticals with unannounced inspections*, European Commission Press Release, (Jan. 08) available at <http://europa.eu/rapid/pressReleasesAction.do?reference=IP/08/49&format=HTML&aged=0&language=EN&guiLanguage=en>.

based industry, represented by the European Federation of the Pharmaceutical Industries and Associations (“EFPIA”), and the European Generics Association (“EGA”) have also made submissions. The interim findings are currently with national authorities and other Commission services, ahead of publication and a public hearing on November 28, 2008. After a round of consultation on the interim report and, no doubt, follow-up questionnaires, a final report is scheduled for the second quarter of 2009.

II. INNOVATION

As to innovation, the Commission says its concerns were triggered by a perceived decline in output: “From 1995 to 1999 an average of 40 novel molecular entities were launched. From 2000 to 2004 the figure was only 28. The Commission wants to investigate the reasons for this.”² It suggests that possible causes might be patent portfolios that block other innovators’ research, litigation, or restrictive agreements between innovators.

Intuitively, industry watchers felt that this approach was misplaced.³ It was contrary to all the economics of the industry. With development times for pharmaceuticals of between 10 to 12 years, average costs estimated to exceed EUR 1 billion, and every day of delay to commercial launch eating into the innovator’s limited patent exclusivity period, no company would adopt a strategy of retarding the commercial launch of its innovations. The economic research commissioned by EFPIA

²ANTITRUST—SECTOR INQUIRY INTO PHARMACEUTICALS—FREQUENTLY ASKED QUESTIONS, European Commission, (Jan. 08), available at <http://europa.eu/rapid/pressReleasesAction.do?reference=MEMO/08/20&format=HTML&aged=0&language=EN&guiLanguage=en> (hereinafter Sector Inquiry FAQs).

³K. Bernard, *The EC Sector Inquiry Regarding Pharmaceuticals*, 2(1) GCP MAGAZINE (Feb 2008), available at <http://www.globalcompetitionpolicy.org/index.php?id=841&action=907>.

from Charles Rivers Associates (“CRA”) in response to the inquiry bore this out.⁴ It concluded there was “no clear evidence of a marked decline in innovation.” In fact, approvals of new active substances by the European Medicines Agency (“EMA”) had increased from 28 to 40 over the last three years. Judged qualitatively—the Commission’s comparison of simple molecule numbers does not differentiate between successful or failed medicines—there was, indeed, some cause for optimism. There was a slight increase in the proportion of products with novel modes of action. Higher “innovative” or priority ratings, assessed by the US Food and Drug Administration (“FDA”), were accorded to a greater percentage of products. Innovative ratings by the French Haute Autorité de Santé showed consistent levels of innovative value (or even a modest upward trend). There was also evidence that biotech products tended to meet a more diverse variety of unmet patient needs.

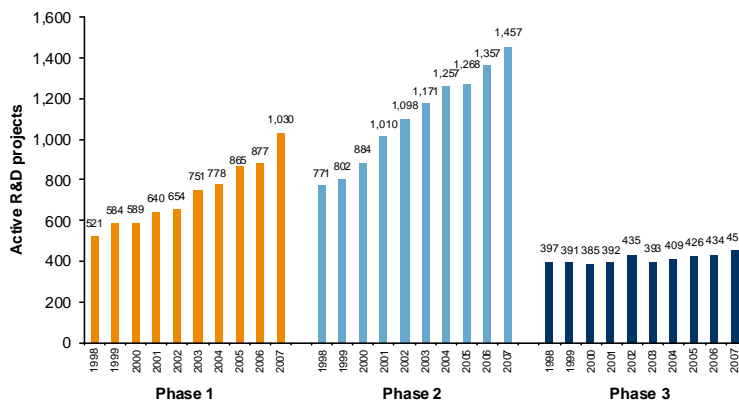
But just as interesting for the industry were the findings on productivity. While industry spending on Research and Development (“R&D”) and new projects entering development increased relentlessly over the period under investigation (Figure 1)—again, hardly consistent with a theory of cartelization—output in terms of approved medicines did not keep up. There was a decline in productivity with fewer medicines being approved per Euro spent on R&D. The reasons for this were insightful.

⁴Charles River Associates, THE CURRENT STATE OF INNOVATION IN THE PHARMACEUTICALS INDUSTRY, (June 2008) (www.efpia.org/content/Default.asp?PageID=563).

Figure 1: Projects Entering Each Development Phase

Increasing number of products in development but concern regarding bottleneck in phase III continues

Trends in the total number of global R&D projects by stage of development



Source: PharmaProjects as reported in Parexel's Biopharmaceutical R&D Sourcebook 2007-08

First, industry retooling to meet the biotech revolution has caused substantially increased costs in the short term, but as yet no increase in the number of approved molecules. A second factor was rising regulatory costs—the well observed phenomena of bigger and more expensive trials being required, higher costs per patient, and companies looking at more challenging and costly therapeutic areas for development, such as oncology. The third factor is particularly revealing. The evidence suggested changing productivity was the industry response to pressure from state purchasers. Member states’ cost-effectiveness assessments effectively set a price cap on the level of innovation that

member states are prepared to fund. Therapeutic reference pricing—classing innovator and generic products within the same reference group for a particular therapy, regardless of the innovative nature of the patented product—as used in the key German market and spreading to other states, also acts as a chilling signal for investment in innovation.

Accordingly, there was increased focus on new mechanisms of action (a riskier focus which increases attrition rates) and increased commercial attrition (terminating a project because the product is insufficiently differentiated from existing therapies to the standard required by national authorities). Although projects entering phase one development increase, higher attrition rates affect progression to later phases (Figure 1).

This response is economically rational. Companies do not wish to invest in developing innovative products that states will not fund. As CRA concludes, productivity decline “is at least partly due to changes in returns to innovators offered by pricing and reimbursement regimes and this is an increasingly important contributory factor.”⁵

It is to be regretted, in light of these findings, that the Commission has excluded the effects of state regulation from the inquiry. The functioning of a market cannot be reviewed piecemeal. State regulation controls every aspect of competition in Europe by way of restrictions on price, supply, and access. This is a missed opportunity to build upon all the policy initiatives undertaken by DG Competition’s sister services and member states—the Frankfurt/Bangemann Round Tables on Completing the Single Pharmaceutical Market, the High Level Group on Innovation and Provision of Medicines, the High Level Pharmaceutical Forum, and the Innovative Medicines Initiative—in their

⁵*Id* at 5.

commitment to create a framework to foster innovative medicines and a resilient healthcare sector in Europe. It suggests a lack of joined up regulation that, in contrast to prior sector inquiries, DG Competition has not involved its sister services in launching this investigation.

III. GENERICS

Turning to generics, the principal focus of the inquiry is the allegation that innovators delay generic entry. “The Commission has indications that the entry of such medicines ... is ... delayed.”⁶ The Commission lists possible concerns as “[m]isusing public procedures and regulations,” “patenting or the exercise of patents ... litigation (which may be vexatious) and agreements which may be collusive, such as settlement agreements.” It points to the decision in *AstraZeneca* [2006] OJ L332/24, by way of example of allegedly unlawful tactics to delay generic entry.

The EGA has also raised concerns. Its focus has been primarily on state incentives to encourage generic dispensing/subscribing and perceived weaknesses in the patent system that allegedly block generic access. As to patents, it argues that examiners are under-resourced and too quick to grant patents. Complainants’ views are given insufficient weight. Applicants are not required to give sufficient information. Opposition procedures—challenging the validity of a patent after its grant—are too lengthy and time consuming. Subsequent use or allegedly uninventive formulation or process patents

⁶Sector Inquiry FAQs *supra* note 2.

should be circumscribed. It calls for reforms to patent procedures, a centralized patent court, and a Community patent.⁷

IV. THE DATA ON GENERIC ENTRY

These allegations are highly contentious, raising policy issues that reach far beyond the pharma sector, and will no doubt be hotly debated. But is the premise—that generics are blocked or delayed—consistent with the data? EFPIA worked with IMS Health and CRA to examine the speed of entry of generics for molecules losing exclusivity during the period investigated.⁸ In the big five markets—France, Germany, Italy, Spain, and the U.K.—it found generic competition for 41 to 58 percent of those products. At first sight this may seem low. In well-functioning markets, what would hamper entry for the other products? But the answer becomes clearer when considering the value of the drugs. That 41 to 60 percent of molecules represented the vast majority of the market—80 to 90 percent of the pre-patent expiry sales, when measured by value.

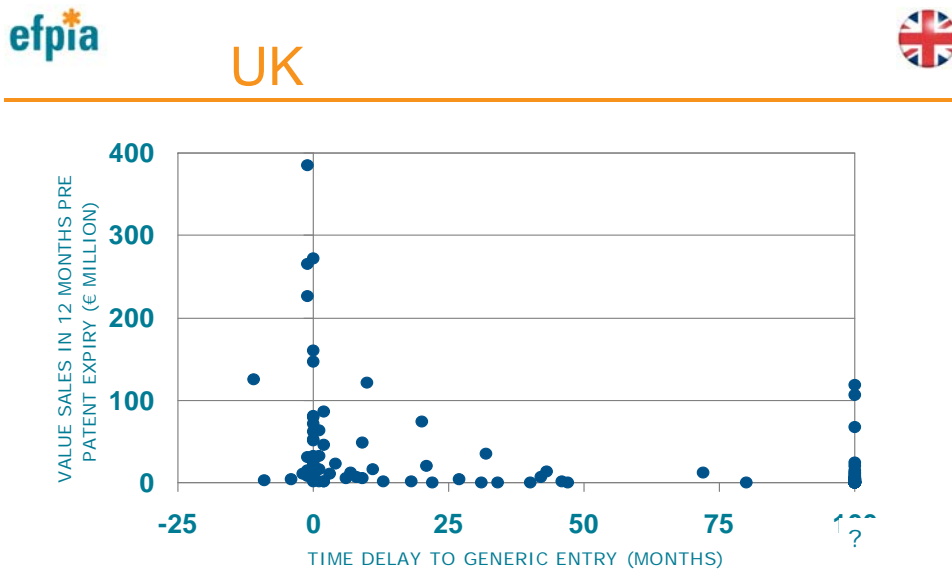
The implication seemed to be that generics followed the commercial opportunity. Plotting the date of entry of generics against the pre-expiry value of the drug showed exactly this. Entry was almost instantaneous for high value drugs, but far slower for low value opportunities (Figure 2). There was a threshold of sales value, generally between EUR 5 to 10 million in the major markets, below which generics would not tool up to

⁷Prof Dr Steven Simoens, SUSTAINING GENERIC MEDICINES MARKETS IN EUROPE, Katholieke Universiteit Leuven, (Apr 06); PATENT-RELATED BARRIERS TO MARKET ENTRY FOR GENERIC MEDICINES IN THE EUROPEAN UNION, European Generic Medicines Association (“EGA”) *available at* http://www.egagenerics.com/ega-barriers_rpt.htm, (May 08); BETTER PATENTS, BETTER MEDICINES: RECOMMENDATIONS ON HOW TO IMPROVE THE EUROPEAN PATENT SYSTEM, EGA, (Oct 08) *available at* http://www.egagenerics.com/doc/ega_position_patentquality_2008-10-01.pdf.

⁸Charles River Associates, FACTORS AFFECTING GENERIC ENTRY IN EUROPE, (June 08) *available at* www.efpia.org/content/Default.asp?PageID=563).

enter. Of course, other factors were important. The analysis showed that, after market value, other factors included: manufacturing complexity (complex manufacturing discourages entry), simultaneous loss of exclusivity in multiple national markets (the larger opportunity attracts entry), existing competition for the product (making entry less attractive), associated delivery mechanisms (again, making entry more complex), and brand loyalty (entry less attractive).

Figure 2: Plotting Speed of Entry Against Product Value (UK)



Source: IMS Health MIDAS January 2008

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Source: IMS Health (note: outliers include molecules which lost exclusivity at the end of the observation period without generic entry, so do not capture entry which occurred immediately after the observation period)

The evidence of entry was not only that it was effective where the commercial opportunity allowed, but also that it was becoming faster over time over the period investigated. Between 60 to 80 percent of drugs (by pre-expiry value) exhibited generic

entry within three months of loss of exclusivity. Bearing in mind the time required for regulatory approvals in many countries, that is almost instant entry.

In short, generics responded perfectly rationally to commercial incentives. High value, easy markets would readily be entered, but entry was delayed into lower value, higher cost markets. One might add that this observed pattern is consistent with the expected operation of market forces, rather than anticompetitive conduct. Any putative conspiracy or abusive conduct would rationally be aimed at protecting the highest value markets from generics. That would be where the innovator has the most to lose. Yet it is precisely there where we observe the fastest entry.

V. THE PERIOD OF EFFECTIVE PATENT PROTECTION

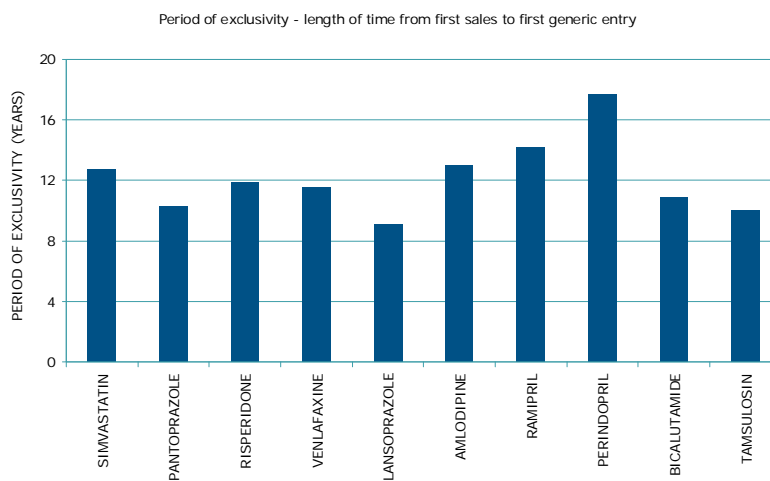
The pattern is similar when one considers not just speed of entry after loss of exclusivity, but the duration of the innovator's protection. Assuming 10 years spent in development, the protected life of a patented drug might be expected to be around 15 years (20 year patent protection plus five years supplementary protection certificate, less 10 years development).⁹ For the 10 best selling 2007 drugs, which came off patent during the period under investigation, the time between launch and first generic sale is for the most part between 10 to 14 years, with one of 17 years and one of 9 years. The concern that weak or cumulative patents extend the protected life of drugs seems implausible on this basis. Far from showing an extended life span, the protected life of

⁹The 15 year effective period of protection was contemplated by the legislature when introducing the supplementary protection certificate. Council Regulation 1768/92/EC concerning the creation of a supplementary protection certificate for medicinal products (as amended) [1992] OJ L 182/1 (“[T]he duration of the protection granted by the certificate should be such as to provide adequate effective protection; whereas, for this purpose, the holder of both a patent and a certificate should be able to enjoy an overall maximum of fifteen years of exclusivity from the time the medicinal product in question first obtains authorization to be placed on the market in the Community.”).

this sample of pharmaceuticals—precisely those high value opportunities that generics wish to copy—appears close to the 15 years of protection that would be expected.

Figure 3: Effective Patent Protection from Launch to First Generic Entry in the EU 15 and Switzerland

efpia Period of exclusivity – Length of time from first sales to generic entry



Source: IMS Health MIDAS Database (Retail Panel except Denmark and Sweden where retail and hospital panels are combined).^[1] Note: combinations and biologics excluded.

^[1] IMS Health reaches its own view on loss of exclusivity; IMS Health's views on loss of exclusivity may be different to other companies.

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Source: IMS Health retail panel, biologics and combinations excluded.

VI. THE GENERIC TO GENERIC DYNAMIC

A notable omission in relation to generics is the generic to generic dynamic, which officials say will not be examined in the inquiry. In addition to investigations of collusion among generics in some member states,¹⁰ there is the more straightforward concern that Member States' price controls do not seem to be reaping the efficiencies offered to them by a genericized market, with huge variations in the degree of penetration

¹⁰See, eg, *R v GC plc and others* [2008] UKHL 17.

of generic products. So too, economic analysis suggests generic price controls achieve less competitive prices.¹¹ While price controls have swiftly reduced the price of generics, they have also acted as a focal point for generic pricing, discouraging price competition below the regulated ceiling. As the commercial opportunity is reduced, excessive price regulation appears to reduce the incentives for generics to enter the market. The failure to maximize the efficiencies of the generic segment means that healthcare budgets forego the significant savings that might be achieved through a properly functioning generic market place which would allow them to fund investment in innovative medicines.

VII. CONCLUSION

Taking a step back, then, from the furor surrounding the dawn raids and the hugely intrusive information gathering, policy makers and regulators must look at the bigger picture. There is an important story behind the headlines. The productivity decline in innovative pharmaceuticals should be of genuine concern. The chilling effect of excessive and distorting price and access controls must be addressed if innovators are to receive the right buying signals from state purchasers to reinvigorate productivity. EFPIA's work with the Commission, Member States, and other stakeholders has sought to create an emerging consensus around best practice for state purchasers which it believes should achieve this objective.¹² The generics market is there to be used by state purchasers—the data shows generics actively and effectively chasing the high value opportunities—and used wisely it can generate real savings, available to be plowed back

¹¹Panos Kananos, Joan Costa-Font, & Elizabeth Seeley, *Competition in off-patent drug markets: Issues, regulation and evidence*, 23(55) ECON. POL. 499-544 (July 2008).

¹²EFPIA, POLICY PRINCIPLES FOR A COMPETITIVE HEALTHCARE ENVIRONMENT (Nov 07), available at (www.efpia.org/content/Default.asp?PageID=563).

into innovation. Fundamentally, generics respond rationally to economic incentives and generic policies based on sound economics are likely to produce the most competitive outcomes. It is enormously disappointing that the inquiry excludes state regulation and off patent competition from its review. A report which does not take account of these features will be fundamentally flawed. After an inquiry of this intensity, the key questions that have vexed policy makers will remain unanswered and stakeholders will still be left without a comprehensive roadmap for the pharmaceutical sector.