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From maturity to value-added innovation: lessons from the pharmaceutical and agro-biotechnology industries

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1 **Abstract:**

2 The pharmaceutical and agro-biotechnology industries have been confronted both by

3 dwindling product pipelines and rapid developments in life sciences, thus demanding a

4 strategic rethink of conventional R&D. Despite offering both industries a solution to the

5 pipeline problem, the life sciences have also brought complex regulatory challenges for

6 firms. In this paper, we comment on these industries' response to the life science

7 trajectory in the context of maturing conventional small-molecule product pipelines and

8 routes to market. The challenges of managing transition from maturity to new high-value

9 added innovation models are addressed. Further, we argue that regulation plays a critical

10 role in shaping the innovation systems of both industries and, as such, we suggest

11 potentially   useful   changes   to   the   current   regulatory   system.

Introduction to the new life science industries

The new molecular life sciences have transformed a range of R&D-driven industries over the past two decades, particularly in pharmaceuticals and agriculture. Both industries are susceptible to "technological shocks" as new scientific knowledge and path-breaking technologies broaden the spectrum of options for R&D and strategic management. The complexity of the life sciences, and the different implications of biotechnology and genomics for various parts of the R&D process, have created distributed innovation systems and company networks in both sectors [1-3]. Firm strategy is shaped by robust, though ever-changing, multi-layered and sometimes cumbersome regulatory systems that are located outside the core innovation system, but which continue to influence innovation at all times [4]. The success of multinational companies depends on a continuous flow of new, innovative products with clear routes to market and established, well-understood value systems. In pharmaceuticals, these have traditionally been small-molecule blockbuster products in core therapeutic franchises. Similarly, until the early 1990s, the dominant innovation model in the agricultural sector was global commodity crops. In both industries, new technologies, such as high-throughput screening and combinatorial chemistry, were embraced enthusiastically and brought product and process advances in the identification, validation and formulation of new chemicals.

Rapid developments in the life sciences in the late 1980s and early 1990s brought new opportunities and challenges for both industries, and continue to do so today. Just as conventional product pipelines began to reach maturity, the new life sciences offered hope of developing radically different types of product and markets. For the pharmaceutical industry, recombinant proteins in the 1980s, monoclonal antibodies in the

35   1990s, and more recently stem cells, emerged as potential alternatives to blockbuster

36   small molecule drugs. Similarly, in the late 1980s GM crops presented the agro-chemical

37   industry with a radically new product portfolio disruptive to its prevailing R&D strategy.

38   However, the life sciences also brought new competition for incumbent firms as smaller

39   biotechnology companies with unique knowledge and expertise emerged. The path-

40   breaking nature of the new technologies and products, many with unknown risk profiles

41   and without established routes to market, engender new regulatory hurdles that increase

42   the cost of R&D and generate uncertainty.

43   Our aim is to explore the evolution of the pharmaceutical and agro-biotechnology

44   industries in the context of emerging life science innovation and new regulatory systems,

45   and suggest key lessons for future governance. We use the term agro-biotechnology in

46   this article to refer specifically to those agrochemical companies that linked with seed

47   companies to produce GM crops. We highlight the opportunities and challenges of

48   managing transition from maturity to a new high-value-added innovation model subject

49   to high regulatory hurdles and hope to spur a broader discussion about the systemic

50   aspects of R&D-driven industries and the role of regulation in shaping innovation.

51

52   **From maturity to value-added innovation: challenges and opportunities**

53   Developments in the life sciences have reshaped the pharmaceutical and agro-

54   biotechnological industries. During the 1980s and early 1990s, the largest multinational

55   chemical firms had relatively integrated and complementary R&D strategies. Indeed,

56   some had both health and agriculture divisions. This period of innovative activity was

57 characterised by a series of mergers and acquisitions as multinationals sought "buy-in" to

58 new technology platforms [5].

59 However, this "combination strategy" ended around the late 1990s. The two

60 sectors separated their capabilities and pursued autonomous strategies of innovation

61 through both merger and acquisition activities and strategic alliances. It became clear to

62 senior managers that synergy between agriculture and pharmaceuticals at the discovery-

63 level was profitable only when both sectors were primarily interested in the source of

64 chemical novelty, but not in the "gene" area [5,6]. Functional genomics could benefit

65 both sectors, but disparities in profit margins [7] and technological and economic

66 differences [8] did not make for long-term positive synergies.

67

68 *Responding to the "problem of maturity"*

69 In the early 1990s, both sectors struggled as conventional chemical-based products

70 reached maturity and R&D pipelines narrowed. By "maturity", we mean molecules had

71 already been developed for easy targets and were now off-patent, so no longer generating

72 large profits, and industry was concerned about the long-term sustainability of

73 conventional blockbuster R&D models. Both sectors searched for new R&D options. In

74 agriculture, strategic planning focused on 'a combination of chemical and biotechnology

75 developments with varying degrees of synergistic interaction' [9,10]. Companies

76 embraced diversity in technological development [11]. As product pipelines matured,

77 three distinct company strategies emerged to exploit the new life science trajectory (Box

78 1).

79   Innovation strategies are cumulatively dependent on a company's past history

80   [12,13], and the resources and 'dynamic capabilities' of a firm influence its patterns of

81   innovation [13]. The innovation strategies of agro-biotechnology companies in the 1980s

82   and 1990s varied, depending on their existing strengths in product development and

83   technology trajectories along with their overall vision for the future. GM crops were a

84   disruptive technology for most multi-national agro-biotechnology companies still

85   benefiting from patented agro-chemical products, but were attractive to firms that had

86   reached the limits of small molecule chemical innovation.

87   In pharmaceuticals, the maturity problem and desire to move to high-value-added

88   biotechnology-based products was also a driver of organisational change and

89   restructuring. Traditionally, pharmaceutical R&D was a serendipitous activity in which

90   chemical compounds were randomly screened and tested on known disease targets. Lead

91   molecules were then optimised to produce lead candidates for further development. In the

92   1980s and 1990s, advances in molecular biology, synthetic chemistry and screening

93   technologies reshaped this R&D process [14] and created economies of scale and scope

94   [15]. The emergence of potentially transformative life science technologies led to major

95   industry restructuring, through internal reorganisation and merger, acquisition and

96   strategic alliance activity [2,16,17]. Firms now coordinate an increasingly diverse range

97   of R&D capabilities alongside the "normal" processes of organic growth [18]. However,

98   despite the promises and strategic visions presented by the life sciences, various factors

99   challenge large firms' dominance in therapeutic innovation (Box 2).

100   Together, these challenges, amongst others [24], continue to shape the evolution

101   of the pharmaceutical sector and strategic management of R&D within individual firms,

102   with new R&D models and product development strategies emerging. For example, GSK

103   developed Centers of Excellence for Drug Discovery in 2000, leading to its current

104   decentralised R&D Hub structure [25,14], and most multinationals exploit public-private

105   partnerships in both research and development. A good example is Pfizer's current

106   investment in Scotland's Translational Medicine Research Collaboration (TMRC);

107   focused on the identification and validation of novel biomarkers for drug development.

108   Both the pharmaceutical and agro-biotechnology industries have been forced to

109   confront the challenges and opportunities of the molecular life science paradigm in the

110   context of maturity of conventional product pipelines. For pharma, life science

111   investment and attendant organisational restructuring has been primarily a response to the

112   challenges of therapeutic innovation, rather than a revolutionary, pro-active attempt to

113   fully embrace a life science-based innovation trajectory. Innovation spending in agro-

114   biotechnology has moved towards GM seed technology, with total agro-biotechnology

115   R&D expected to equal agrochemicals in 2009 [26].

116   Our research on both the agricultural and pharmaceutical industries has shown

117   that multinationals do not always share common objectives and strategies; rather, strategy

118   is an evolutionary process based on firms' unique histories, internal competencies and

119   routines, market position and future expectations [2,9,14]. The long-lead times in

120   pharmaceutical and agro-biotechnology R&D mean that the precise benefits of any

121   restructuring initiative and implantation of new strategy take time to emerge.

122   Nevertheless, product innovation and company strategy is also determined by the

123   regulatory environment and it is to this important aspect that we now turn.

124

Regulation and its impact on innovation strategy and product development

Regulation has significant impact on R&D-driven industries, such as pharmaceuticals and agro-biotechnology, and partly explains the long product lead times that distinguish these industries from most others, although even without formal regulation firms would still need to invest time and resource to establish product safety. Nevertheless, changes in standards for safety and efficacy do have time/cost implications for industry [27]. A significant effect of regulation in agro-biotechnology has been to increase costs, over conventional non GM varieties, by approximately 0.5 to 13.5 million USD [28]. We argue that regulation is the dominant shaper of both the innovation system and markets for innovative products in pharmaceuticals and agro-biotechnology. Specifically, it can constrain life science innovations through the complex, expensive and lengthy requirements imposed on developers of new drugs or pesticides. It has been recently suggested that clinical trials required by European regulators to compare biosimilar products with corresponding biologic brands are unnecessary and may impede the development of biosimilars of more complicated biologics [31]. Although this particular example is focused on biosimilars rather than novel biologics, it does highlight how regulation impacts on innovation. The nature of the regulatory system for any given product can dictate the type of firms able to develop such products [4].

To highlight the role and influence of regulation on both sectors, we look briefly at two "disruptive technologies"; GM crops in the agro-biotechnology sector; and stem cells/regenerative medicine in the pharmaceutical sector. The systemic interactions of regulation and innovation for these two sectors and technology platforms are highlighted. A background to life science regulation is provided in Box 3.

148

Path-breaking Versus Path-Dependent Products and Regulation

Scientific knowledge and technological advances in biotechnology have led to radically new path-breaking products in health and agriculture, including GM crops and stem-cell-based therapies. In both cases, regulation has been considered crucial, but with no precedent for establishing a robust governance framework. In cases of new technologies, one can either look for existing regulatory regimes within which to place new product ranges, or design new path-breaking regulatory frameworks to meet the specific properties of the new technology. Based on our research [28-30], we consider it important to question the relationship between the emergence of path-breaking innovations and the putative need for path-breaking regulatory systems.

Path-breaking innovations do not always require novel regulatory mechanisms. GM crops were a path-breaking technology - the agro-biotechnology industry expected that they would be disruptive and move the sector onto a new high value-added innovation model - but it was unclear for quite some time after heavy investment what the nature of the regulatory regime would be. While companies can cope with radical changes to their innovation systems, when these challenges are coupled with uncertainty in markets and regulatory systems that are outwith their control, disruption to the entire sector can be magnified [4].

Innovation that is "path-breaking" for one company or sector may of course be "path-dependent" for another. For example, it was not inevitable that GM crops would be developed and marketed only by what were then agro-chemical firms, for which they were clearly path-breaking; GM crops disrupted the prevailing innovation model,

171   simultaneously impacting company R&D strategy (i.e. requiring a shift from chemistry-

172   to biology-based development and production systems), markets (i.e. seed markets are

173   very different from pesticide markets), and regulatory systems. In the 1980s and early

174   1990s, it was equally likely that food and seed companies would develop the technology.

175   For these companies, the technology was path-dependent [4,30].

176   A complex set of interactions between policymakers at European, U.S. and

177   international levels, as well as among the agro-biotechnology, food production and

178   distribution, and seed industry sectors, contributed to the overall framing of GM. It would

179   have been beneficial to guide policymakers to adopt the regulatory system that applied to

180   the industry sector for which the technology was path-dependent; in this case the seed

181   companies. The regulation of GM crop varieties would have been easier (perhaps

182   regulated under plant breeders' rights) if the initial developers had been seed firms. This

183   path-dependent regulatory approach may have made a difference to the direction of

184   innovation in GM crops today and also to European public perception of the technology.

185   This analysis also applies to the pharmaceutical sector in the case of stem cells

186   and regenerative medicine. Stem cells, like GM crops, are potentially highly disruptive of

187   prevailing pharmaceutical R&D systems, markets and regulatory systems. They require

188   modification of company R&D strategies, moving from small-molecule innovation to

189   complex biologics, and markets, which are very different to conventional blockbuster

190   drug markets (smaller patient populations and delivery mechanisms for the product are

191   far more complex, expensive and uncertain). The nature of the regulatory requirements

192   also determines whether such products are developed by conventional multinational drug

193   companies or smaller tissue engineering firms. In parallel with the GM crop example,

194 stem cells would be path-breaking for pharmaceutical multinationals, but path-dependent

195 for smaller tissue engineering companies. Comparison with GM crops would suggest that

196 if regulation of stem cells could be framed to be path-dependent for the smaller

197 companies, we might see faster and more innovative development and uptake of novel

198 therapies. However, if regulation continues to align more closely with the sector to which

199 the technology is path-breaking (multinational pharmaceutical firms), which appears to

200 be the case with the Advanced Therapies Regulation in Europe

201 [http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:P

202 DF], we could see delays in the development of therapies and few small, innovative

203 companies independently developing stem cell products. Whilst it is of course essential

204 that stem cells and regenerative medicine products meet the key requirements of safety

205 and efficacy, the question is whether the conventional regulations that apply to small

206 molecule blockbuster products, and more conventional biologics, are appropriate for stem

207 cells; especially when they may be a barrier to innovation. Whilst there are myths and

208 uncertainties about the regulatory gaps and barriers to regenerative medicine [32], there is

209 as yet no clear route to market for many small companies developing the technology and

210 regulatory guidelines can be vague and ambiguous. Lessons from the regulation of GM

211 crops may help us to develop regulatory processes for stem cells that encourage, rather

212 than impede, those companies best placed to innovate in this area.

213

214 **Conclusion: key lessons for new "smart" approaches to regulation**

215 Regulatory systems tend to evolve incrementally over long time periods, which make

216 them susceptible to becoming inflexible and out-of-step with the latest innovations and

217 technologies. Furthermore, regulation can become so complex that modifications to one

218 set of regulations have unforeseen consequences for other parts of the regulatory system

219 and for the innovation community. However, *de novo* creation of path-breaking

220 regulation for path-breaking technology also poses difficulties and challenges and could

221 just as easily discourage innovation as encourage it.

222 From our extensive research exploring innovation and regulation interactions in the

223 pharmaceutical and agro-biotechnology sectors [2-6; 9, 10, 14, 30] we consider there to

224 be a number of key lessons for better governance of innovative life science technologies,

225 such as GM crops and stem cells [Box 4].

226 The life sciences continue to be of high strategic importance to both developed

227 and emerging economies and shape many innovative industries. But life science

228 innovation is largely dominated by a relatively small number of multinational companies,

229 and regulatory systems often serve to maintain the status quo. Regulation is an

230 insurmountable barrier to many small start-up companies with innovative ideas that

231 challenge prevailing orthodoxy. Whilst it would of course be inappropriate to lower

232 safety and efficacy standards for life science-based products, the development of a

233 smarter approach to regulation, which we have outlined, could bring about a more

234 favourable climate for innovation.

235

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241

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350 **Box 1. Agro-biotechnology company strategies**

351 Distinct strategies were employed by leading agro-biotechnology companies. These

352 strategies were conceived in response to external pressures, including low farm

353 commodity prices and income; erosion of profit margins; more aggressive competition as

354 a result of agribusiness restructuring; and the emergence of new technologies, such as

355 genetic modification and molecular marker technologies, which challenged conventional

356 farming practice. The narrowing of chemical pipelines also crucially drove this need for a

357 new strategic vision. Companies employed these different strategies to respond to

358 maturity and pressures in the innovation environment.

359

360 *"Buying the route to market"*

361 Monsanto (from the 1980s) and Dupont both invested heavily in building the GM

362 technology base for the world's major commodity markets: corn, soya and cotton.

363 Moving from selling agrochemicals to selling seeds required a new marketing strategy,

364 and both companies invested large sums in acquiring seed companies. Monsanto invested

365 $8bn alone between 1996 and 1999 and DuPont purchased Pioneer in 1999 for $7bn [9].

366

367 *"Collaboration along the route to market"*

368 AgrEvo, Zeneca, Novartis, Rhone Poulenc and Dow also invested significantly in

369 building a GM technology base throughout the 1980s, but they focused more on

370 collaboration with seed companies rather than on outright purchases. This was a more

371 incremental strategy which gathered momentum in the mid 1990s.

372

373   *"Jumping on the bandwagon"*

374   BASF and Bayer were intentionally several years behind other agro-biotechnology

375   companies in investing in GM technology, preferring to wait and to benefit from the

376   experience of other companies. BASF began investment in the mid-1990s and Bayer in

377   the early 2000s.

378

379 **Box 2. Key challenges facing the pharmaceutical industry (1990s – present day)**

380 **1. Decline in productivity** despite increases in R&D investment. The problem of product

381 maturity coupled with low productivity led to perception of "innovation deficit" that

382 continues today [19]. Since 1996, the number of small molecules approved by regulators

383 has been in decline and the number of new active compounds discovered has remained

384 constant. Companies are not generating enough new compounds in-house for sustainable

385 growth [20].

386

387 **2. High attrition rate of compounds**, particularly during Phase II clinical trials. Lack of

388 demonstrable safety and efficacy has been the principal cause of attrition, which partly

389 explains why companies experiment with new "translational sciences" [21,22],

390 particularly those centred on identifying and validating novel biomarkers.

391

392 **3. Rising overall costs of drug discovery** owing to the need for new, experimental

393 methodological approaches to R&D; increasing internationalisation of research and its

394 competitive environment, and increasing demands from regulators and healthcare

395 providers. In 2007, the cost for a firm to bring one product to market was estimated to be

396 $800 million USD [23].

397

398 **4.** Some early biotechnology firms were successful in **transforming themselves into**

399 **large multinationals** (Amgen, Genzyme, Genentech and Geron); but later growth in

400 biotechnology has been slow. Today the chances of a small biotechnology firm becoming

401 a large, independent company appears bleak given the high barriers to entry.

402

403   **5.** There are now more **partnerships between public and private institutes** to pool

404   information and attempt delivery of niche products, including orphan drugs and products

405   vaccines for developing countries. Nevertheless, the dominant model continues to rely on

406   "blockbuster drugs" rather than targeted drugs for niche markets. Despite the promises of

407   the life sciences, multinational pharmaceutical firms did not seek to fully transform

408   themselves into biotechnology companies; in contrast to some of the agro-biotechnology

409   companies like Monsanto. Indeed, there has not yet been a pharmaceutical equivalent to

410   Monsanto.

411

412 **Box 3: The nature of regulation in the life sciences**

413 Whilst it is obvious that regulation impacts product development, we suggest that the

414 impact of regulation is much more far reaching than just ensuring goods are safe,

415 effective and high-quality – [28]. It determines overall company strategy, the types of

416 firm that will succeed in bringing products to market, and the structural dynamics of the

417 sector as a whole. For example, if we compare the lightly regulated Information and

418 Communication Technologies ICT sector with the heavily regulated life sciences, the

419 former has a much greater turnover of products and capabilities arising from

420 technological innovation. In ICT, small start-up companies can quickly become major

421 players by developing innovations that challenge the status quo. Most candidates for

422 product development in the health and agricultural sectors will fail (only one out of

423 approximately 200,000 molecules initially screened will make it to product launch);

424 therefore, innovation in life sciences appears far more linear than industries such as ICT

425 [29]. Life science innovation is dominated by a small group of multinationals, which we

426 argue is partly due to the fact that the regulatory system poses an insurmountable barrier

427 for many new entrants with innovations that threaten to disrupt the status quo.

428 The markets for life science products are also different from most other industries,

429 inasmuch as few are marketed directly to consumers. Pesticides and GM crops are sold to

430 farmers, and new medicinal products are mainly sold to health services [10]. The unique

431 combination of regulation and markets for life sciences has therefore had major impacts

432 on the structural dynamics and strategic management of both the pharmaceutical and

433 agro-biotechnology sectors.

434

435

Box 4 : Key lessons for good governance of the life sciences

(1) Regulatory initiatives can have significant, rapid and positive influences on the innovation system. Such insights on successes should be used as exemplars when designing regulatory systems for new innovations.

(2) Regulations appropriate for one area can have unexpected and/or negative impacts when applied to other areas. Application of conventional clinical trial systems to stem cells could be a major constraint, with adaptations to mechanisms such as the 'hospital exemption route' for the development of therapies for named patients perhaps a better way to facilitate innovation. This problem becomes more likely and significant when regulators lack knowledge and understanding of the new technologies.

(3) A regulatory policy that is *enabling* in that it encourages positive change in industry strategies and appropriately *discriminates* among products on the basis of socially and economically relevant criteria, will generally be more effective and efficient than a policy that is *indiscriminate* and seeks to *constrain* what it considers undesirable behaviour.

(4) The *enabling* criterion affects the rapidity with which a particular regulatory policy can exert influence, while the range, scope and appropriateness of its *discrimination* among products and processes will determine its effectiveness in guiding desirable product development.

(5) Path-breaking regulation for path-breaking technology should not be the norm but the last resort once all other options have been exhausted. Other options might

458   include a focus on 'substantial equivalence'. If the new technology or product is

459   substantially equivalent to an existing product, path-breaking regulation should

460   not be necessary.

461   (6) In considering which regulatory precedent is most appropriate for a new

462   technology, a useful approach would be to prioritise the regulatory system for the

463   industry sector for which the innovation is path-dependent rather than path-

464   breaking. This would ensure the sector better positioned to quickly take forward

465   the product to market is encouraged to do so.

466