

Legislating to death

Impact of legislation on the EU Pharmaceutical Fine Chemicals Industry

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Abstract

In Brussels the right hand spares no effort to legislate to protect the environment whilst the left agonises as to the weakness of European biotechnology and how the EU falls behind in the R&D league tables. Brussels worries about what it does not have but takes for granted the jewel of its manufacturing industry, and does everything in its power to stifle its growth and destroy its competitive advantages. The EU fine chemicals industry is the cradle and the powerhouse of the industrial development and commercial manufacturing of new pharmaceutical chemical entities. Half of all FDA foreign inspections take place in Europe and address the compliant production of Active Pharmaceutical Ingredients (APIs). 75% of all medicines in US pharmacies contain APIs made outside the USA, mostly in Europe. Were it not for the EU fine chemicals industry, the US pharmaceutical industry there would have been unable to launch as fast many of the HIV protease inhibitors: Viracept, Sustiva, Crixivan, Sequinavir, Indinavir, Ritonavir, etc.. Europe has by far the largest share of the API market and it has the best people – but EU policies are killing this industry stifling it with multiple legislative actions:

- Patents: SPCs and lack of Waxman-Hatch rules
- Legislation on Environment matters such as ELINS/PORD/IPPC/EPER

European API manufacturers, whether manufacturing generic compounds or supporting the innovators' need for commercial manufacture or clinical quantities see their flexibility, their ability to respond fast and their cost being hurt to a level such that manufacturing is migrating at an accelerating rate to the US, Mexico, Singapore, India and China. New Greenfield investment in Europe is down to zero; and were it not for the high demand growth our sales would be dropping.

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1. The Pharmaceutical Fine Chemicals Industry

The European pharmaceutical fine chemical industry is a major creator of wealth, employer and net exporter¹. It is a high value, low volume business characterised by a high content of science, a profound understanding of its processes and intense regulation. Europe is both the cradle of Chemistry and of Pharmacy – it stands today as the powerhouse of pharmaceutical fine chemicals – and yet its future is grim.

How can the future be grim for an industry that is clearly the crown jewel of European Industry. $\frac{3}{4}$ of the active pharmaceutical ingredients (APIs) that make up the medicines found in the shelves of US pharmacies are manufactured outside of the USA, over half come from Europe². The two key antibiotics that Americans used to fight Anthrax were either made by Bayer in Europe (Ciprofloxacin) or by Hovione in Macau (doxycycline).

Even though the North American Pharma market is much larger than Europe's, it grows at almost double the rate³ – on the other hand Europe's capacity, breadth and depth of know-how and technologies are unrivalled and the EU enjoys today a significant positive trade balance in pharmaceuticals with the rest of the World (including the USA). When the first

computer modelled HIV protease inhibitors first went into clinical development, cryogenic reactions -a key technology for these complex molecules- was nowhere to be found except in Europe⁴.

In Biotechnology, because we are loosing the race to the Americans, the EU spares no effort to stimulate and support European efforts, both state and private ones, in this area. Yet in pharmaceutical fine chemicals -an area where Europe is light years ahead of anyone else- the EU is legislating a stifling environment that provides the Industry with the dilemma of locating elsewhere or disappearing.

2. Helpful legislation sits side-by-side with unwise and stifling regulation

The competitive position of Europe's Pharmaceutical Fine Chemicals industry is subject to an extensive, dense, complex, rigorously supervised body of legislation in force at both National and EU levels, at international level (WHO and ICH) and at the export markets: the USA and Japan. Most of it is embraced by the industry as a necessary driver for a level playing field but others appear to be nothing more than a European idiosyncrasy that serves no other practical purpose but to diminish the advantages of a European location.

The legislation that is embraced as innovative, common sense and has the benefit of world harmonization is that connected with the registration and approval of new pharmaceutical products. The key examples are the ICH⁵ guidelines (turned into law through Directives in the EU and into Guidelines to Industry published in the USA's Code of Federal Regulations, with similar solutions in other countries: Australia, Japan, Switzerland, etc.,). The basis for the ICH is the global standardization of best practices that have the double aim of 1) enabling the faster and quasi-simultaneous access to patients in all countries of new medicines and 2) the reduction of costs by avoiding duplication of tests and studies. ICH is notable by the degree of collaboration and consultation between authorities and industry. Additional components of these international harmonized legislative initiatives are the Mutual Recognition protocols between regulatory authorities and the Common Technical Document⁶.

On the other hand the last 10 years have seen in Europe a plethora of legislation that markedly interferes with the international market and distinctly affects the competitive advantage of the European Pharmaceutical fine chemical industry. The impact in the market place is one of distortion, the actions of the players are to take measures to meet the new legislative demands in ways that are totally opposite to the intent of the legislator, the net effect is that Europe loses jobs, manufacturing capacity, exports and -worst- know-how.

The legislation that most distorts the markets is that which is connected with the innovation process. The issues that must be addressed include:

- The SPC and the lack of Roche Bolar amendment type law
- The existing and proposed controls of registration, evaluation and authorization of Chemicals (both existing and new)

Other areas of legislation that will be reviewed are:

- IPPC: Integrated Plan for Pollution Control, an industrial licensing process
- EPER: European Pollutant Emission Register

We shall show how the application of this legislation is hurting the industry, having an effect opposite that that intended by the legislator and often that its application within the EU presents inexplicable inconsistencies.

3. Generics

Generics are big business, they are a very fast growing business. *In the next 10 years the pharma industry will see patent expiries of drugs currently generating some €91 billion sales*⁷. The timing and the strategy for the development of a generic pharmaceutical involves being ready with an approved marketing license on the day the patent expires so that the product may be put on the market then. Today this already is the case in the USA; Canada, Australia, Israel. In those countries a Roche Bolar amendment type law exists which provides that all acts necessary to apply for a marketing license (development work, validation batches, stability and bio-equivalence tests) do not constitute infringement. In Europe this is not the case, so anyone what wants to develop a generic in Europe will be a loser because he will start 4-6 years too late – in deed it takes about 2-4 years to do the necessary work to develop a manufacturing process and the data for registration – in addition in takes 2-3 years after the data is complete for the average EU authority to conclude its review of a generic.

A further EU piece of legislation is the SPC (supplementary patent certificate) exacerbates the lack of Roche Bolar type provision as it extends the life of the patent-holder's monopoly beyond patent expiry. SPC assures the patent holder of an actual market exclusivity to 15 years from the first European registration. Further national complexities mean that Generic firms in Italy and France at an especial disadvantage, to the point that a large number of Italian API firms have moved their development and manufacturing capabilities abroad⁸.

The Generic industry is relatively young and its management style if traditionally entrepreneurial. However a consolidation process has led to the emergence of several companies whose strategy includes the systematic development of all generic opportunity APIs. There is not a single EU company among them⁹ ! The traditional players, the original builders of this industry, usually Italians, are falling by the way-side.

The reality is that the legislation has not stopped the Europeans to develop their generics, it has merely pushed them to do so outside Europe¹⁰. There is a steady stream of brain- and manufacturing-drain away from Europe in the key skills of developing and registering new generics. Roxythromycine¹¹ is a typical example of what has been called patent-tourism. In reverse the foreign companies rich of know-how imparted to them by their EU-constrained clients grow, prosper so the point where they venture into Europe on the acquisition trail¹².

The original intent of the legislator was to encourage R&D in Europe. This has failed; NCEs are developed either by Large Pharma (the top 20 firms are all located outside of Europe, except GSK and AstraZeneca that regularly threaten to move to the USA) or by Small Pharma. The Nasdaq Biotechs are way ahead of Europe's across every possible parameter.

4. Controls over the production and of (new) chemical substances

The new EU White Paper Strategy for a future Chemicals Policy has recently caused much stir in the wider industry, though it contains little news for the Pharmaceutical Fine Chemical sector. The wider industry is concerned with the "burden of the past"¹³, in pharma chemicals we are concerned with the future, with innovation – and our capability to support the drug development process is being systematically hurt.

It is well known that the richest, largest, most highly regulated, most profitable and fastest growing pharma market is the USA – it is also the most innovative. But whenever a Giant pharma multinational or a NASDAQ quoted Biotech need to outsource some chemical

synthesis process they invariably used to go to Europe – no longer – why not is the question we should address as it should shed some light on the White Paper debate.

No area of the chemical industry is more at the leading edge of innovation than pharmaceutical chemistry – therefore the “burden of the past” is more to do with polymers than with life-saving drugs. Those involved in making chemicals that are the active ingredients in pharmaceuticals have had to cope with the need to register new compound with ELINCS and with PORDs for some time. This is costly, time and resource consuming, critical-path affecting, and in at least 90% of the times a demonstrable waste of time.

Making APIs involves multi-step complex chemistry with the last reactions having to meet rigorous and costly Good Manufacturing Practices that are subject to quality inspections by authorities to verify compliance – a key component of pharma public health supervision. Naturally certain raw-materials are bought in from other upstream industries with less costly operations – so here there is a purchase and sale, an EU member state cross-border transaction or an importation. The White Paper is proposing that every intermediate, whether isolated or not, must be evaluated and registered.

Even if we were to ignore the intermediates that are made inside a same plant (isolated or not), on average any new API will need at least one new starting material, if not also a new reagent, or a new side-chain. Often the synthesis is convergent so the number of new chemicals that might be made by a 3rd party (sold/imported) might double that number¹⁴ - so for every API you will need about 4 registrations. The API itself is exempt because this is the object of infinitely more thorough toxicology and safety studies.

Currently a 10Kg/year quantity triggers a registration; and at the least for every API that is made at a 10Kg scale more than 9 in 10 will never make it to commercial scale. Indeed products often reach clinical demands in excess of 1000kg and still fail to ever be approved for sale in the market. How can anyone defend the cost, the time and the lab animals that are needed for doing toxicology of products that never leave the control and hands of experts? and that have a 90% statistically proven likelihood that they never be more than an R&D exercise. Today there are about 1805 drugs in development and awaiting approval at the FDA¹⁵ - had these been made exclusively in the EU they would trigger surely in excess of 3600 different substance notifications – about double the number of substances object of notification since the scheme started in 1994¹⁶. In fact before the 10Kg threshold is hit Europe’s regulatory environment presents certain competitive advantages that have contributed to business growth in Europe¹⁷.

Considering that the chemical development of a new drug is highly controlled¹⁸ and requires expertise, complete traceability and large budgets, and is already strictly regulated by the Health Authorities (for the final product, industrial licensing as well as for personnel protection during manufacture)– what is the added benefit to public safety to have these registrations on small quantities for R&D purposes that will never reach the public ?

Experience shows that the member state responsible for the authorization process is short-staffed¹⁹. Across Europe there are inconsistencies: one country has a trigger threshold of 100Kg another 10Kg; one country commits to a 30 days delay to reply and 60 in another in 60. The White Paper indicates a commitment to minimise animal experiments²⁰, yet experience shows that at the EU Member State level best use of existing information is not taken into account²¹ - here again we would all benefit from international harmonization on toxicology studies methodology.

The cost of the toxicology work needed for a PORD²² at the <100Kg quantity is in the region of €10.000 per compound – yet, the concerns go beyond cost. The issue is that the legislation causes companies to meet the requirements in every instance without exception, often common sense would recommend in certain cases to delay carrying out such tests only after clinical data provides encouraging results. The legislation also introduces an extra item that needs to be considered and that might interfere with the critical-path of an R&D project, an item that is outside the control of the business and that requires additional resources to address it. For a company with €100m in sales doing about 20 new APIs per year in different phases of development the management of PORDs alone requires a full-time person with a €500.000 budget.

Again the story of roxithromycin sheds interesting light on how the ELINCS is used to create barriers to entry and to create a dominant position in a product.²³

Debate on the wisdom of the White Paper for in the area of Pharmaceutical Fine Chemicals should be analysed in light of the cost/benefit analysis of the EINECS/ELINCS/PORD history.

5. Licensing of Industrial operations

Not unlike any other EU initiative, the IPPC legislation, is yet another layer of red-tape that the Industry and most companies believes is a sound and necessary process – the format and modus operandi is, however, flawed and costly. IPPC has been in force in Portugal since August 2000, the application form has 5 dozen pages and an application fills a truck. In Portugal IPPC is applicable to about 400 factories – by 2007 all must be licensed under IPPC – to date only two have. Again the debate is not whether there ought to be a strict licensing process for our industry but rather whether IPPC is a sound approach for an industry like pharmaceutical fine chemicals that:

- Manufactures in multi-purpose, multi-product plants, where flexibility is the name of the game – and where it is impossible to predict what products the market will demand in two years time,
- New products may require any kind of raw-materials some not even known to man today, or conditions and technologies not yet invented
- Production is batch based and process improvements may offer significant opportunities for cost reduction from changes in synthetic routes, changes in raw-materials or technologies.

IPPC demands us to define all those parameters ahead before the plant is built. At Hovione we hardly know with more than 33% probability what products might be produced in it at a 5 year horizon. IPPC however requires us to state our forecast as written commitments. These are then filed with authorities that would appear not to have the resources to process such a large amount of data. Often also the data is confidential and belongs to our customers, which complicates the matter.

R&D facilities are specifically excluded from the constraints of IPPC, though the their licensing procedure is still labyrinthine, lengthy and frustrating²⁴.

6. European Pollutant Emission Register

This piece of legislation provides another example of the disparate standards that apply across Europe and is symptomatic of the mind-set of the authorities. Portuguese industry was

instructed to file EPER data on a quarterly basis and for every emission. The EU issued guide book stipulated that emissions were to be filed annually and only if the site exceeded defined thresholds. If there are debates on such simple matters what can we expect when local authorities must define what is a “low risk” substance – when little to no guidelines are given...

The EU is keen on transparency, it actively promotes disclosure and EPER would enable every neighbour of a plant to see the list of the emitted pollutants.

7. What should the EU do

As companies have a greater R&D intensity in their business, so their planning is longer term. Additionally the chemical industry is very capital intensive, and long-term investment plans are analysed with considerable care. It should therefore not surprise anyone that the legislative efforts by the EU in the last 10 years have not gone un-noticed. The trends are clear for all to see:

- Europe has not built a new green-field API site plant for 10 years – except possibly the odd Swiss or Japanese API manufacturing facility in Ireland;
- The Pharmaceutical Multinationals have only one common manufacturing strategy: they locate API synthesis in a tax friendly location; this was first Puerto Rico, later Ireland –and, since Europe has killed the chicken of the golden eggs– Singapore, the currently most preferred investment location;
- India and China have in the past 20 years promptly addressed the vacuums caused by the EU patent law situation in terms of generics, and have additionally become the emerging location for the intermediates industry,
- Anyone in Europe that wants to remain in the business is migrating to more favourable locations: Mexico, Canada and USA appear to be the preferred locations.

Pharmaceutical Fine Chemicals merit a treatment of exception – both for their value and for the controls that already surround them. Global guidelines resulting from intense collaboration between Industry and Regulators are much more likely to deliver better results, and at lesser cost, than regulations suited to the Fortress Europe mentality emanating from bureaucrats in Brussels that are disconnected from reality.

¹ In 2000 Cefic reported that the EU trade surplus in pharmaceuticals was €19b.

² Numbers available from 1996 show that for 290 FDA Foreign Inspections 194 related to APIs (66%). Of those 194, 131 (45%) took place in Europe (UK, Ireland, Spain, Germany, Italy, France and Switzerland alone).

³ IMS - World Sales Through retail Pharmacies – 12 months to November 2001: North America \$136.8billion, up 17% and Europe (leading 5) \$53.5billion, up 9%

⁴ Cryogenic reactions are those that occur between -50°C and -100°C. In the mid Nineties the only (non-Large Pharma) companies that had such capabilities were probably Finorga in France, Newport Synthesis in Ireland, Hovione in both Portugal and Macau and maybe also UBE in Japan. Low temperature conditions often support higher yield and purity when strong reaction conditions are required. Computer modelled molecules usually present far greater complexity than traditionally developed compounds. Process chemists have must therefore develop innovative chemistry that very often have led to the use of low-temperatures.

⁵ ICH – the International Conference on Harmonization has issued key documents that affect the preparation of product specifications, the levels of impurities, the form of stability studies, the minimum standards of Good Manufacturing Practices during manufacturing operations, etc..

⁶ ICH Guideline M4 – Notes to the applicant volume IIB: “Presentation and contents of the Common Technical Document (CTD)”, May 2002. The CTD is an internationally agreed upon format for the preparation of a well structured presentation for applications to be submitted to regulatory authorities

in the three ICH regions: Europe, US and Japan. It is intended to save time and resources and to facilitate review and communication

⁷ Jan Leschly, former CEO of SmithKline Beecham in the Ernst & Young 2001 report on European Life Sciences.

⁸ The following companies are just a few examples of companies driven away from Europe because of the uncompetitive generic legislation in Europe:

- Sicor – an Italian leader in cancer drugs now develops its new generic compounds in Sicor de Mexico
- Esteve from Spain has also invested in development and manufacturing facilities in Mexico
- Profarmaco and Nordic Synthesis, now part of the Cambrex group, long-established Italian and Swedish API manufacturers have built pilot plants in the USA.

⁹ The Companies that appear to have dedicated significant R&D budgets to a well-defined and systematic strategy to develop every new generic coming off-patent are not European Companies: they are Teva of Israel, Cambrex of USA, Pliva of Croatia and Apotex of Canada.

¹⁰ Examples of European companies that have been involved in M&A activity of JV collaborations in order to avoid the European block on generic development are as follows: Dipharma of Italy has now bought a plant in Malta; Hexal and Ratiopharm have been known to do their development batches in Iceland; a large amount of generic versions of Glaxo's Zantac® was formulated in Turkey prior to patent expiry in the EU; South Africa is a common location for bio-equivalence studies. Generic firms in New Zealand have become key players in the process of preparing and filing registration dossiers and then selling these files to the various Generic houses – soon to become mere distributors.

¹¹ The Roxithromycin story: Aventis's Rulid went off-patent in Germany in 2001, the first registrations to go onto the market were made by a Jordanian firm using API made by Hovione in Macau. Currently 100% of the generic formulations of Roxithromycin contain API made by Hovione, one of the few European Pharmaceutical Fine Chemicals firms that saw the writing on the wall and in 1986 invested in manufacturing capabilities in Macau – away from EU manufacturing regulations and yet compliant of EU and USA registration requirements enabling it to be a key source of APIs for both the Generic Houses and the Innovator Large and Small pharma.

¹² Examples are: Iceland's Delta acquisition of Omega Pharma in March 2002 and Pharmaco in August 2002.

¹³ Sic – in the Glossary of the White paper. The “burden of the past” are the 30.000 existing chemicals for which little of no information as to safety and eco-toxicity had been grand-fathered in EINECS in 1981 – and the EU has now stated that by 2012 all of them will have to be either eliminated from the market or re-registered.

¹⁴ As example of very new science are the computer modelled HIV compounds – the process for Viracept for instance involved putting together three different building blocks that all required ELINCS registration. Viracept was a fast tracked drug, a clever regulatory strategy together with unique medical benefits got FDA to approve the drug in 42 days – within a year it was being produced at 5-10 tons/month. The ELINCS process was clearly in the critical-path.

¹⁵ 1805 drugs awaiting approval at FDA; 468, 776 and 395 –respectively, in Phases II, II and I; in PharmaBusiness, June 2002. If these were made exclusively in the EU they would trigger around 7200 notifications – about 4 times more than have been registered in ELINCS since it started in 1994.

¹⁶ See <http://ecb.jrc.it/new-chemicals/content1.htm>

¹⁷ Before this bureaucratic hurdle was imposed on cross-border authorizations at the 10 kilo level was imposed, Europe benefited from a significant advantage of the USA on the very early screening of APIs. US law directs that no API be used for clinical development or be exported without an IND being filed. There was therefore a loophole very often used by every Large Pharma company that involved shipping to a pharmaceutical chemical contractor the penultimate intermediate (this is a (new) chemical intermediate and not an API), that could be exported and after formulation could be used in a preliminary screening clinical test - requiring no more than the OK from an ethical committee. The cost and enduring commitments of an IND filing were thereby avoided. This gave Europe a not insignificant amount of business both at the chemistry level as well as at the clinical testing and CRO end.

¹⁸ The companies and people involved in pharma R&D already have tremendous pressures for the best possible control over the products in question. The small amounts of intermediates required for API manufacture are extremely costly (never under \$1000/kg and often more than \$10.000/kg; each batch is monitored and its quality controlled to a greater detail than any product in routine production; it is usually shipped by courier, direct air-cargo if not hand-carried, and its progress monitored in Gantt charts by any number of highly paid project managers. Furthermore our industry accounts for every kilo with a precision that even SAP has difficulty in coping with; our industry when called to manufacture controlled substances (narcotics, psychotropics etc..) will account for any amounts down to the g – and face jail sentences for any failures. The industry already carries out toxicology studies for raw-materials and intermediates in order to prepare safety data sheets and assess maximum exposure levels in connection with HSE. What is the point of introducing a further bureaucratic step in the process ?

¹⁹ The Portuguese office of the Environment Ministry has one senior manager and two assistants to manage this and other functions – as we are led to understand from their letter dated 21 June 2002 asking Hovione not to pressure them to meet deadlines.

²⁰ The ‘3 r approach’ in Section 3.2 of the White paper.

²¹ As recently as July 2002 the Portuguese authorities when faced with a PORD application took no account of a toxicity study carried out in the PRC, and requested the study to be repeated in the EU.

²² Define PORD

²³ Another example of how the industry uses regulations in ways un-thought of by the regulators – take ELINCS and again the example of synthetic derivatives of erythromycin – such a roxythromycin. A common intermediate is called “oxime” – Biochemie is a fermentation company with a leading position in erythromycines, an Austria based API manufacturer that belongs to the Novartis group. Oxime is a key intermediate common to the synthesis of roxithromycin, azithromycin and clarithromycin – with a combined volume of under 1000 tons of API and possibly \$4b in sales at pharmacy prices –oxime sells for \$100-\$200/kg and the total consumption is probably up to and over 1000 tons. Biochemie diligently and pro-actively applied, and got, the ELINCS registration for this product. Since the EU discourages 2nd and further ELINCS registrations for the same compound – Biochemie now has an apparent monopoly on this compound. Naturally the rest of the universe does not sit patiently and pay them a fee, no indeed; at least one competing producer found another salt of oxime and has registered it as another substance. The next effect: a safe substance -known for some time- is the object not once, but twice, of \$350.000 worth of toxicology studies; double the number of animal tests are carried out.

²⁴ Hovione decided in 2000 to build two pilot plants one in Portugal (within an existing site) and one in New Jersey, USA at a green-field site then still to be identified. We filed for the building permit and other licenses in Portugal before we selected the land in New Jersey in December 2000. In September 2002 our New Jersey open for Business and the Portuguese pilot plant is still waiting for permits.