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A Sourcing Strategy for Active Pharmaceutical Ingredients (APIs)

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Abstract. We describe the development over the past decade of a sourcing strategy within the *Roche* group for active pharmaceutical ingredients and the intermediates used in their manufacture. The roles of certain production sites have been modified in the light of this strategy. Before sourcing decisions are taken, criteria including life-cycle phase of the product, whether the step under review comes early or late in the synthesis, protection of proprietary know-how, quantities needed, speed, available capacity and full production costs are systematically evaluated on a case-by-case basis. For each sourcing decision, different scenarios are compared, in particular that of in-house *vs.* external production. In future, we envisage intensified competition both among Contract Manufacturing Organisations (CMOs) for business from large pharma concerns and among the large pharma concerns themselves for the capacity available from the CMOs. In consequence, the large pharma concerns will have to continually adapt their sourcing strategies to the changing environment and will have to have available flexible production plants and organisations if they wish to maintain a viable in-house alternative to contract manufacture.

1. Historical Development of API Sourcing at *Roche* (up to 1990)

In common with most similar organisations, *Roche* had for many years a sourcing policy based on the in-house discovery of new chemical entities, the in-house development of the process to be used for their manufacture, and the construction of in-house facilities for their commercial production. We built large chemical production facilities at company headquarters in Basel and in the major countries, where we formulated and sold our products (USA, Germany, France, UK). The period 1950–80 saw a proliferation of chemical production sites, some large, some small, erected for a variety of reasons, including: an increasing demand for our products; inability to expand existing sites in built-up areas; financial incentives from governments to build in development regions; the insistence from the governments of some countries in which we were selling, or planning to launch, drug products that at least part of the manufacture of the API be carried out locally. At one point, we were producing benzodiazepines at sites in Switzerland, USA, Puerto Rico, Brazil, Argentina, Turkey, Spain, South Africa, India and Indonesia, and had plans to set up facilities in Mexico and Pakistan.

During this period, we began, somewhat reluctantly, to evaluate outsourcing in cases where in-house production of certain steps posed technical problems, difficult to manage on sites usually located in built-up areas, *e.g.*:

- transfer of so-called 'blast reactions' (high-temperature *Friedel-Crafts* reactions used to make substituted benzophenones required for the manufacture of benzodiazepines) to manufacturers with more appropriate installations and the necessary special know-how;
- transfer of the manufacture of 2-ethoxy-5-fluorouracil, an intermediate in the manufacture of 5-fluorouracil requiring the highly toxic ethyl fluoroacetate, to a supplier who could make ethyl fluoroacetate *in situ* and thereby avoid having to transport it.

In the case of L-DOPA, we did not have the most efficient synthesis at our disposal, and terminated in-house production in favour of external purchase in the 1970s.

In 1982, *Roche* launched the cephalosporin antibiotic ceftriaxone (ROCEPHIN) and, because we did not have a lot of previous experience of the manufacture of cephalosporin intermediates, we contracted out a large part of the manufacture of key building blocks soon after the product had been launched. The variability in quality of critical raw materials, such as 7-aminocephalosporanic acid (7-ACA), and the extreme sensitivity of the quality of ceftriaxone to trace amounts of impurities in the building blocks resulted in a lot of work and many ups and downs on the way towards the establishment of external sources for these intermediates. The experience gained, both positive and negative, was, however, extremely valuable in showing us how to manage this type of project, and by the end of the 1980s, *Roche* had developed quite an appetite for 'outsourcing'.

At this stage, outsourcing was still carried out on an *ad hoc* basis, and one could hardly speak of a defined sourcing policy. Major organisational changes within the company at the beginning of the 1990s and the ensuing establishment of a chemical production strategy for the Pharmaceuticals Division led to the development of a more clearly defined sourcing strategy.

2. Development of a Chemical Production Strategy (1991–1997)

During 1991–1992, we developed a chemical production strategy based on a life-cycle model. The life cycle of a typical API was split into four stages *(Table 1)*. For a research-based organisation such as *Roche*, where time-to-market is of paramount importance, it is essential to have a strategy for the development and launch phases which ensures that API manufacture does not become rate-limiting, either by failure to supply on time or by not being ready for preapproval inspections by regulatory agencies such as the US Food and Drug Administration. Consequently, a cornerstone of the chemical production strategy was the designation of two 'launch sites' equipped to carry out the key activities in the development and launch stages (clinical supply, process development, launch production). The designated launch sites were: Basel in Switzerland, already the major manufacturing site in the group, and Florence in South Carolina (USA), where construction on a green-field site started in 1993. The other chemical production sites were designated as 'manufacturing sites'.

The chemical production strategy is summarised, in an extremely condensed form, in *Table 2*. This strategy is based on the assumption of a steady flow of new chemical entities, coming from either in-house research or in-licensing, into the development and launch stages; the almost inevitable attrition of projects in the development stage implies a lower rate of entry into the launch stage.

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The emphasis on time-to-market and the difficulty in knowing in advance either the nature of the new chemical entities or the chemical processes needed to make them means that the main characteristic of the launch sites must be *flexibility*, and this, in turn, implies that they be equipped with multipurpose units capable of switching from one product to another at fairly short notice without major refitting. The cost of such units is correspondingly high, and, consequently, once the launch stage is complete, products must be transferred to manufacturing sites or CMOs (Contract Manufacturing Organisations) to release launch-site capacity for the next generation of products.

We evaluated the question of single or double (backup) sourcing at some length and came to the conclusion that, at least in the cases where manufacture is kept in-house, only one site would be used and that the insurance against unplanned interruption of supply of strategically important or particularly vulnerable products should take the form of increased safety stocks rather than double sourcing.

There is a major difference between formulating a sourcing strategy and carrying it out. At the time the above strategy was formulated, construction of the Florence launch site had not begun, and the Basel site *a*) was using a lot of capacity for the production of established and post-patent products and *b*) had a lot of equipment in need of upgrading if it was to provide the flexibility called for on a launch site. The acquisition of *Syntex* in 1994 brought six additional chemical production sites and a significant amount of process-development capacity into the *Roche* group and provoked a reassessment of the chemical production strategy: this did not result in any major changes in direction, but had an significant impact on tactical implementation.

We outline the stage reached, some six years after the first formulation of the chemical production strategy, in the following section.

3. Current Status (1998)

In the aftermath of the formulation of the chemical production strategy, we had to evaluated the production location for a large number of APIs and intermediates. These potential 'product transfers', as they came to be called, could be roughly categorised as either:

- *obligatory transfers*, where the only alternative to finding a new source would be to discontinue making and selling the substance concerned, or
- *optional transfers*, where continued production at the current site would be possible, but where there is a strong business case for developing a new source.

Typical obligatory transfers would be: where it has been decided to terminate chemical production at the site where the substance is made, or where a development product moves into the launch stage, and there is insufficient free capacity on the current site to cope with the quantum leap in demand. Potential optional transfers arise, for instance: when, after the expiry of patents, new suppliers of APIs emerge, often in low-cost countries; or where an external supplier of an intermediate could take the intermediate through subsequent steps of the synthesis; or where the transfer of an older product would release capacity on a launch site.

Obligatory transfers are usually subject to externally imposed time constraints; for optional transfers, on the other hand, there is greater flexibility with respect to timing and the opportunity for a more thorough evaluation of possible courses of action, of which there are three:

1) purchase the product from a supplier who already makes and sells it;
2) make the product at another in-house site;
3) transfer the manufacturing know-how to a CMO.

We discuss various aspects of these three options below.

Table 1. *Stages of API Life Cycle*

Stage	Characteristics
Development	The stage between formal entry of the project into the project management portfolio and completion of the manufacture of the registration batches required for the NDA (New Drug Application). Included in this stage are process development and production of material required for clinical development (Clinical Supply).
Launch	The stage between completion of the manufacture of the registration batches required for the NDA and completed launch in the 8–10 most important markets.
Established	The stage between completed launch in the 8–10 most important markets and expiry of relevant patents.
Post-patent	The stage after expiry of relevant patents.

Table 2. *Chemical Production Strategy*

Stage	API Source
Development	In-house launch site (whenever possible). In case of insufficient in-house capacity, outsourcing of intermediate, not final and finishing steps.
Launch	As for development stage.
Established	In-house manufacturing site or contract manufacturing organisation (CMO).
Post-patent	Purchase from lower-cost producers.

3.1. *Purchase from External Supplier*

This is usually the easiest option to evaluate, because it is normally only relevant for post-patent products, which have been around for some time and for which: *a*) we have a clear picture of our in-house costs for comparing with prices offered by potential suppliers; *b*) we have a clear picture of the quality requirements, based on years of experience in making galenical dosage forms with the API. Despite this, the switch to purchased material is not trivial: at *Roche*, the main use of APIs is for the in-house manufacture of a range of dosage forms at several sites throughout the world (sale of APIs to third parties plays a much less significant role), and the use testing of the material from the new source along with the associated stability trials for all dosage forms at all sites is time-consuming.

3.2. *Transfer to In-House Site*

In-house transfers fall into one of two categories: sourcing from another site already making the product concerned, and transfer from a launch site to a manufacturing site where the product has not been made before. The first is by far the simpler, since the manufacturing process and the specifications of the product are usually the same at both sites, and the re-registration is relatively straightforward. The second is usually complicated by the additional need to install or modify capital equipment, influencing both the timing and the cost of the transfer.

3.3. *Transfer to a CMO*

In one respect, transfers to a CMO may be simpler than those to an in-house site: on

the basis of the technical information supplied and an estimate of the forecast requirement, the CMO offers an all-in price, including the amortisation of any investments, his profit *etc.* In most other respects, they are significantly more complicated.

More and more 'large pharma concerns' are beginning to evaluate outsourcing as an alternative to in-house production, so the competition for the services of good CMOs is increasing, and these, in their turn, can be more selective in choosing who they want to work with. For products late in the product life cycle, the prospect is one of, at best, constant and, at worst, declining volumes for the CMO, with the likelihood of an abrupt drop once patents begin to run out. For products early in their life cycle, both the revenue potential and the risks are higher, for both parties. An intelligent and mutually acceptable system for risk sharing must be developed. The simple long-term 'take-or-pay' supply agreement still sought by some CMOs is not usually a realistic option in the current climate. A more practicable alternative is to place a number of projects with one CMO on the 'win some, lose some' principle. This modality takes its extreme form in the strategic alliance concept currently favoured by large pharma concerns such as *SmithKline Beecham* and CMOs such as *Lonza* and *Gist Brocades*. We have not gone so far at *Roche*, but do have a pool of CMOs, with whom we have built up a working relationship over a number of years, and whom we usually include in the first round of screening of potential transfers. The ability of the CMO to work on more than one project at a time and the importance of not becoming over dependent on one large pharma concern implies a certain critical mass, below which it may be difficult for the CMO to operate efficiently.

3.4. *The Make-or-Buy Dilemma*

As indicated above in *Chapt. 2*, chemical manufacture is considered part of the core business of the *Roche* concern. But we do not have sufficient in-house capacity to produce all the APIs and intermediates we require, and will always need to procure some of them externally. Deciding what, when and where to outsource is a cause of much soul searching, especially when time pressure means that a choice often has to be made on the basis of incomplete data, and recourse has to be made to a qualitative or even subjective evaluation. Typical areas of uncertainty include:

An incomplete picture of the 'true' cost of in-house manufacture. Despite the ever-increasing improvement in accounting systems and the rapid on-line access to the data, the allocation of fixed costs to a number of products in a multiproduct environment is often based on rather arbitrary keys. In particular, if the manufacture of a product is stopped, but the assets used in its manufacture are not eliminated simultaneously, the fixed costs remain and are reallocated to the remaining products. Even if these assets are eliminated concurrently with the transfer, there is often an associated once-off cost to be included in the data on which the business case for the transfer is based.

The opportunity cost of not having capacity free on a launch site for the next development product coming through. This is particularly difficult to quantify, when it is not known what the next development product will be, how long its synthesis is, how much will be required and by when it will be needed.

Sudden losses of development products. The termination of a development project, for whatever reason, is often very abrupt, and if a lot of resources (personnel and equipment) are being used for the manufacture, the short- and medium-term redeployment of these resources can be a major problem in chemical production, both in-house and when the manufacture has been transferred to a CMO.

4. Outlook

In future, we expect both increasing competition between in-house production groups and CMOs for available work and increasing competition between large pharma concerns for capacity available at CMOs. Sourcing will be much more globalised and real costs will drive sourcing decisions.

4.1. *Capacity*

Today, as more and more large pharma concerns turn to outsourcing, available free capacity at traditional CMOs is decreasing, because it is increasingly difficult and risky to pre-invest in production plants without binding commitments for future production. Furthermore, with the constantly increasing complexity of the molecules to be synthesised, capacity demands for new APIs are steadily increasing. This diminishes two of the important advantages of turning to CMOs: fast production start-up and avoidance of long-term blocking of funds.

4.2. *Competition*

On the one hand, there will be increasing competition for available capacity on the market. CMOs will be able to choose partners with a clear sourcing strategy, a willingness to explain this strategy, and a preparedness to enter into closer partnerships. Only companies with a sizeable volume and a reasonable portfolio to be awarded will be able to find competent partners for their outsourcing projects.

On the other hand, there will be fewer companies outsourcing just because it is fashionable. In-house production groups will be allowed to compete with CMOs, and, with more informative accounting systems, comparison of in-house costs with outside offers will be more accurate (fewer miscounted overheads). In this situation, only the most competitive CMOs (inexpensive, flexible, guaranteeing high quality, willing to enter into close partnership) will be attractive to outsourcing organisations.

4.3. *Globalisation*

In the past, most sourcing was 'local' (*e.g.*, European pharmaceutical companies with European CMOs). With growing globalisation, it is easier to find and work with companies from all over the world, and, in consequence, typical 'low-cost-country' manufacturers become more and more attractive, both in terms of their usually lower costs and their increasing willingness to ensure that their facilities and procedures satisfy the demands of highly regulated countries. Traditional CMOs will have to remain on their toes in order to be able to compensate for the low salaries in these countries and to compete successfully with the newcomers.

4.4. *Outsourcing Strategy*

Most large pharma concerns now have defined outsourcing strategies, developed with a long-term strategic view. At the same time, there is an increasing tendency towards being measured against short-term results. In this situation, it is more difficult to convince internal decision makers to adhere to agreed strategies for a specific outsourcing project, especially where the benefits are likely to be longer-term and not 100% quantifiable in advance. Those companies flexible enough to adapt their sourcing strategy swiftly to the changing business environment, but committed enough to their strategy to take full advantage from appropriate outsourcing opportunities, will be most successful in this area.

There is no universally 'correct' and immutable sourcing strategy; the premises underlying such a strategy need to be regularly challenged in the light of the constantly changing internal and external environment, and the strategy itself must be modified accordingly, in order to deliver the maximum benefit.

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