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Outsourcing, Toll Manufacturing, and Custom Synthesis in Chemical Production

August Hochrainer*

Abstract. Outsourcing, for chemical and pharmaceutical companies, means to buy intermediates or active ingredients that are normally produced by the companies themselves. It can also refer to buying new products that the companies have developed. For various reasons, companies want to buy these products from the outside. Some thoughts in connection with this subject will be discussed below.

Outsourcing has become a key word for the 1990s. The producers of active ingredients in the pharmaceutical and agro-chemical industry are increasingly outsourcing their chemical production. These companies used to be self-supporting in every aspect of their business, but this situation has changed over the past few years. They have started to outsource many of their activities and are increasingly fo-

*Correspondence: Dr. A. Hochrainer
EMS-DOTTIKON AG

Postfach
CH-5605 Dottikon
Tel.: +41 56 616 83 00
Fax: +41 56 616 81 20
E-Mail: august.hochrainer@ems-dottikon.ch



Figure. Aerial View EMS-DOTTIKON. Outsourcing as a business is not new at EMS-DOTTIKON. 40 years ago, when the word 'outsourcing' was not known at all, EMS-DOTTIKON in Switzerland had carried out custom synthesis. In the beginning, it was done only for the chemical industry in Basel. Since then the company has constantly increased its technology and worldwide marketing. Today, EMS-DOTTIKON is a well-known, reliable partner in the field of custom synthesis. Nitration, catalytic hydrogenation and oxidation were the first core technologies of the company. Later on, various other basic technologies like Grignard reactions, bromination, cyanidation were added. A state-of-the-art infrastructure, including a high-temperature incinerator, ensures low-risk, low-emission production. EMS-DOTTIKON is certified according ISO 9001, holds various drug master files and is FDA approved for cGMP production of various intermediates and bulk active substances.

cluding their resources purely on R&D and the marketing of final products. This is opening up new opportunities and good growth prospects for fine chemical manufacturers and motivates them to widen their range of activities. Various trade shows with emphasis on chemical outsourcing (*Chemspec, CPhI, Informex, etc.*) have come along in the last ten years and prove the importance of this business. Additionally, conferences are held regularly internationally to discuss the topic of outsourcing.

What is the Benefit of Outsourcing for Buyers and Suppliers?

Outsourcing – The Customer's Position

The customers may have various reasons for looking for an external source for production of their chemicals. From a long-term view, the motivation is an economic one, but they may also get the product to the market faster.

Companies hope to get the product cheaper by outsourcing than they could make it themselves. Under certain circumstances, this hope is legitimate:

- The supplier is provided with better production techniques.
- The supplier already has equipment well-fitting to the production process.
- The supplier produces in a 'low-cost' country.
- The customer doesn't want to invest money.

Sometimes, a company only wants to buy the product temporarily, with the intention to produce it themselves later on. They use the supplier to complement their own production capacity. Often, the time frame is of first importance. The supplier often can quickly free capacity and supply earlier than the customer would be able to do it.

The customer, first, must find possible suppliers for his product and, secondly, evaluate the best of them. This calls for good technical and commercial knowledge, and increasingly, specialists are required for this task. Major chemical and pharmaceutical companies have formed groups of commercial and technical specialists as outsourcing experts. They have to know the market, the trustworthiness of suppliers, their capabilities and capacities. A customer will only lose time and money if he has to deal with suppliers that cannot keep their promises. Often, for both partners, a clear negative decision is better than lengthy, never-ending negotiations. So, a responsible supplier should state a clear position and promise only that

which he can really do. Customers usually work out a list of 'preferred suppliers' based on supplier audits and other experiences. These form a pool of partners for their outsourcing needs to whom they will turn initially.

Outsourcing – The Supplier's Position

For the supplier, outsourcing doesn't mean easy new earnings in most cases. Important investments are needed. Production procedures have to be adjusted. Technical modifications and add-ons for production units must be installed. Analytical procedures have to be revised. Products and processes have to be registered with the authorities, *etc.* All this requires high expenditures, often to be done under severe time pressures. Remaining still is the risk that the early effort in developing the chemical process can be wasted. For a variety of reasons, the final product may not be launched on the market at all. Because of this risk alone, a sound supplier has to be careful and often reluctant in offering his capacity for outsourcing projects. He can only help with projects where the chance of realisation is high and justifies all the effort.

At the same time, the supplier has to ask some self-critical questions. Will he be able to contribute so that the customer will have a real advantage when compared to his own production or to that of a competitor? Is he really the best choice for this project when compared to the competition? Only when a supplier can answer these questions positively does continuing the pursuit really make sense.

Especially with projects fresh out of the customers' R&D, potential suppliers have to be wary of statements of potential customers. One must remember that most research projects have a very low probability of success. This probability has improved recently with better screening techniques in the preclinical state of pharmaceutical development. Still a lot of investment is done in vain, because the project had to be terminated for some reason. Often, regulatory matters (*e.g.*, already registered production methods) may prevent outsourcing, simply because the effort necessary for new registration may be too large.

In all these cases, good customers will inform potential suppliers at the start of negotiations about all the open problems. In a good mutual partnership, the customer must not ask for too much unpaid work to be done by the supplier, especially considering the high risk of early projects. Both customer and supplier should share reasonably in the risk.

Technical Knowledge is Important but not the Only Issue

From the beginning, the basis for successful custom synthesis is the cultivation of technical know-how that the client often doesn't have himself. Technical expertise is often the advantage a supplier has over the competition. A solid technical base in chemistry means mastering special reactions, working with difficult chemicals and, at the same time, controlling management of waste and the environment. Also the commitment to quality regulations (FDA, cGMP, ISO *etc.*) is important. Suppliers who have these fundamentals in place are in the best position to respond competently and quickly.

The supplier's profit margin for a new intermediate is often influenced by technology. Usually, if he already has in place or freshly develops a good route of synthesis, he will have higher profits than a company that simply toll manufactures using the customer's process.

Customers are willing to pay for development and scale-up if they get quality performance. The work of a good sales manager in the custom synthesis field starts here. In the market for fine chemicals, the sales manager not only must identify new opportunities, he has to know the market, the products and the technical background. He has to know the technology of his own company, its strengths and weaknesses, and how it can be used for the benefit of both partners.

Selling custom synthesis is much more than just selling chemicals. In most cases, the products alone are not enough for success. The general background of the supplier, good personal relations and reliability are also important. With high-valued products, the location of the production site may not be as important in this era of global communication. Sometimes customs and trade restrictions can be important for the choice of a particular geographical production site.

The advantage 'low-price countries' may have, is often overcome by their own reliability and productivity. Although countries like India or China are not yet an important factor in custom manufacturing, new capacity coming onstream in this region will be used as a bargaining chip to drive costs down. The impact of developing countries on the fine chemicals market is still rather low, since labour cost advantage is offset by lack of security of supply and other problems.

The attractiveness of the fine chemicals market also draws new players. In addition to the traditional small- and mid-

de-sized companies that offer custom synthesis, the chemical production divisions of the big agrochemical and pharmaceutical companies are entering this arena. They are looking for contract synthesis in their specialised fields, while at the same time, branching into new fields where they may have only minor technological strengths. Overall, this development means lower production costs for all final products. Some commodity chemical producers are also entering the fine chemicals market, but only few have been successful. Many of these companies often have difficulties assimilating the culture of the fine chemicals market.

What is the Outlook for Custom Synthesis in the Future?

The outlook for chemical intermediates in life science is favourable. Worldwide sales for drugs grew in the range of 7% in 1997. More than one third of the industry's growth has come from products less than two years old. Also the world market for agrochemicals has an average growth of 2%. It is believed that this trend will not change in the near future. This means that outsourcing in form of custom synthesis and toll manufacture will see strong sales and profit growth during the next few years.

Key Factors for Successful Custom Synthesis

- Technical know-how
- Professional competence for quick response to customers' inquiries
- Quick development in laboratory, pilot plant and production
- Reliability (dead lines, quality, etc.)
- Mutual trust (partnership)

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Intellectual Property Right Issues in Custom Manufacture

Markus Gemünd*

Abstract. In recent years, intellectual property rights have become more and more a key issue in negotiations with pharmaceutical and agrochemical companies relating to *Lonza's* development and manufacturing of active ingredients or advanced intermediates. Whilst *Lonza's* customers are interested in ownership and use rights to such intellectual property rights developed by *Lonza* in order to obtain maximum protection for their end product, *Lonza* is interested in being able to use such intellectual property rights for other projects in order to broaden its technology offering to its customers. This article outlines how *Lonza* has been approaching this issue with its customers in order to find a solution covering both parties' interests.

1. *Lonza's* Customer Synthesis Business

Over the last 25 years *Lonza*, developed considerable research and development capabilities and is continuing to heavily invest into these capabilities. *Lonza* has thus been successful in developing new manufacturing technologies, and cus-

tomers approaching *Lonza* with a project or only a project idea have today access to an ever growing technology and know-how pool.

Lonza's investments into research and development are ultimately geared to manufacturing intermediates and active ingredients for its customers under long-term supply agreements. *Lonza* is bearing, however, a high risk that a customer project is being stopped at any time, in particular with *Lonza* being asked more and more to participate in early development efforts. Therefore, it is of vital importance that *Lonza* remains in a position to add intellectual property rights developed in one customer project to its technology and know-how pool and to prevent that the

technology developed by *Lonza* is making its way to other fine chemicals manufacturers without adequate compensation for the value created by *Lonza*. Where *Lonza* is finally manufacturing an intermediate or active ingredient for a customer under a long-term supply agreement, exclusive rights are offered to the customers, as will be further described below.

2. Customer Project Sequence

After receiving a technical package from a customer, *Lonza* starts a first desk evaluation of the project. As no laboratory work is carried out during this phase, intellectual property rights will not be developed by *Lonza* and need not to be addressed in the secrecy agreement under which *Lonza* received such technical package. If the customer is interested to pursue the project according to *Lonza's* project proposal submitted following receipt of the technical package, a research and development agreement is proposed, with intellectual property rights being addressed. Such agreement defines the work program with description of objectives, activities to be carried out by *Lonza*, timing and price.

If upon conclusion of the research and development phase a long-term supply agreement is concluded, the terms regarding intellectual property rights from the research and development agreement will be incorporated into the supply agreement. Additional specific development work (e.g., second-generation process development) could be carried out under amendments to the research and development services agreement, whilst the long-term supply agreement is in effect.

*Correspondence: M. Gemünd
Lonza AG
Legal Services
Münchensteinerstrasse 38
CH-4002 Basel
Tel.: +41 61 316 85 69
Fax: +41 61 316 83 14
E-Mail: markus.gemuend@lonza.ch