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Custom Synthesis as a Full-Service Program

Franziska Gnehm*

Abstract. In recent years, the requirements of the pharmaceutical industry with respect to their outsourcing partners increased and changed quite drastically. While in the seventies of this century, mainly the production and purchasing of well-known products (chemicals or pharmaceutical dosage forms) were required in order to free up internal capacities for new products, today an outsourcing partner is increasingly considered a service provider that offers development and manufacturing capabilities as well as all the services necessary for the successful submission of a pharmaceutical product. Preferably such a contract partner can offer all of these services, which then makes him a full-service provider. In order to meet the needs of clients, certain requirements must be fulfilled by the service provider. These requirements are described in detail in the following article. Furthermore, the advantages of cooperating with a full-service provider vs. in-house development are described and substantiated. Finally, an example of one full-service provider is given, its history is described, and, of course, the services it offers its clients today.

1. Introduction

In the past, the 'classical' pharmaceutical company would make use of its internal resources and capabilities to develop, manufacture, and market a pharmaceutical product.

In the seventies of this century, the pharmaceutical industry followed the example of the motor industry and slowly began to outsource certain aspects of its competencies. Outsourcing at that time was mainly concentrated on the purchase of chemical actives and intermediates to be used for finished products that were typically in the middle or terminal stage of their life cycle (see Fig. 1). This was done in order to free up internal capacities for newer, higher value-added products. The typical contract manufacturer, at that time, took over the manufacturing process of the originator company. His main goal was to manufacture according to the specifications and the on-time delivery of the product. However, no additional services were required or, therefore, offered.

*Correspondence: F. Gnehm
 Siegfried CMS AG/Ltd.
 Untere Bruehlstrasse 4
 CH-4800 Zofingen
 Tel.: +41 62 746 15 30
 Fax: +41 62 746 12 04

Nowadays, even multinationals are discovering the benefits of cooperating with service companies. Enhancement of internal flexibility and shifting the investment risk onto their outsourcing partner are only two examples of advantages to this industry.

Although research, marketing, and sales will probably always remain the pharmaceutical industry's core competences, the requirements of the pharmaceutical industry shift more and more towards companies that provide solutions and services instead of pure 'white powder'. The following processes could be observed to be outsourced since 1992:

- clinical trials
- process research
- process development
- product formulation
- manufacturing:
 - intermediates, bulk actives
 - dosage form
 - packaging.

2. Concept of a Full-Service Provider

A full-service custom manufacturer is dedicated to supporting its clients in any kind of work with the aim to bring their products to market and to assist them during the whole product life cycle (Fig. 1). In other words, the resources of a subcontractor represent the entire process of drug development and manufacturing from postdiscovery to the commercial marketplace.

Unlike the typical contract laboratory or manufacturing company, which provides only a portion of the development and manufacturing process, clients make

Over the recent years, especially smaller and middle-sized pharmaceutical companies began to outsource larger units of development and production processes. This was mainly due to the lack of internal capacity and equipment of these companies that considered research to be their main core competence. In addition, such companies very often do not have any technology for specialized reactions (e.g., low-temperature reactions) or do not want to make high investments for environmental security of dangerous steps in synthesis (e.g., phosgenation).

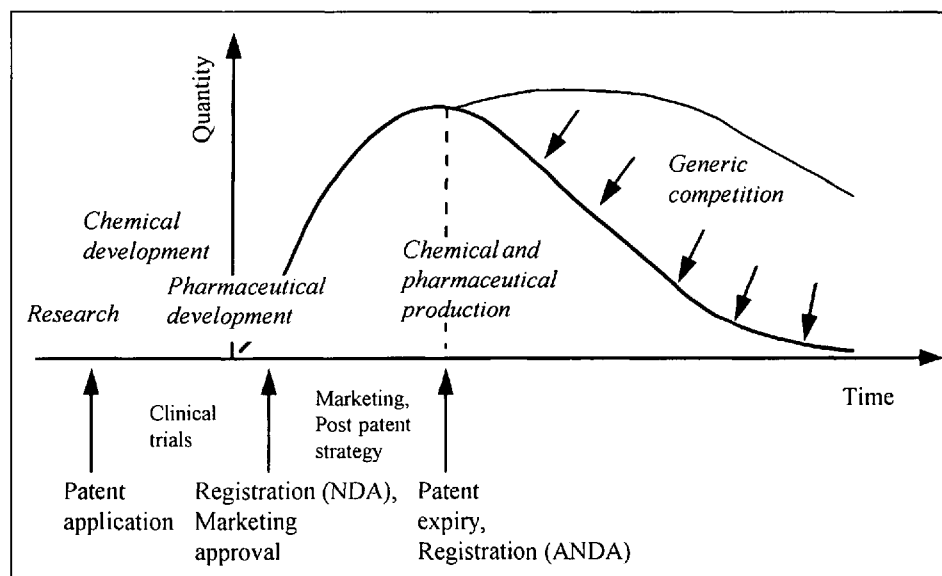


Fig. 1. Product life cycle

use of the entire process, eliminating the need for multiple sourcing and allowing them to accelerate time-to-market.

In addition, the client is cooperating with one partner only. By building stable and long-lasting relationships, the partners get to know each other's philosophies and ways of working, misunderstandings can be avoided, and special requirements of the client are known and considered already in advance. Thus, the partners grow together, which results in a more focused and therefore more successful co-operation.

Of course, a full-service provider cannot always offer all kinds of technical skills or products (e.g., chemical reactions or dosage forms). Some may concentrate on biotechnological actives or sterile dosage forms only. However, it has to be stressed that within his capacities, he can offer the whole range of services needed for the complete care of a product during its life cycle. Instead of a horizontal range of products or services, a full-service provider vertically integrates the internal processes and resources of the customer's business process (Fig. 2).

A contract company mirrors the structures and technical processes of their partner's internal processes in order to fully integrate their procedures. By providing similar internal R&D and manufacturing structures, a contract partner is able to offer the same economies and efficiencies of parallel development and production.

3. Requirements to a Full-Service Provider

Accompaniment of a product during its whole product life cycle (Fig. 1) includes chemical and pharmaceutical development as well as manufacture and all the related services required for submission and successful approval of the speciality by the authorities. Consequently, a full-service provider must have various internal resources such as chemical and formulation development, infrastructure for scaling-up, clinical trial support, chemical and pharmaceutical manufacturing plants, and all services for regulatory support of the pharmaceutical industry. Preferably, all these departments are integrated in a centrally managed organization.

In contrast to traditional outsourcing partners, where only one portion of development is outsourced and the overall coordination remains at the sponsoring company, an individual project management at the contractor's end is essential when outsourcing the whole or larger parts of

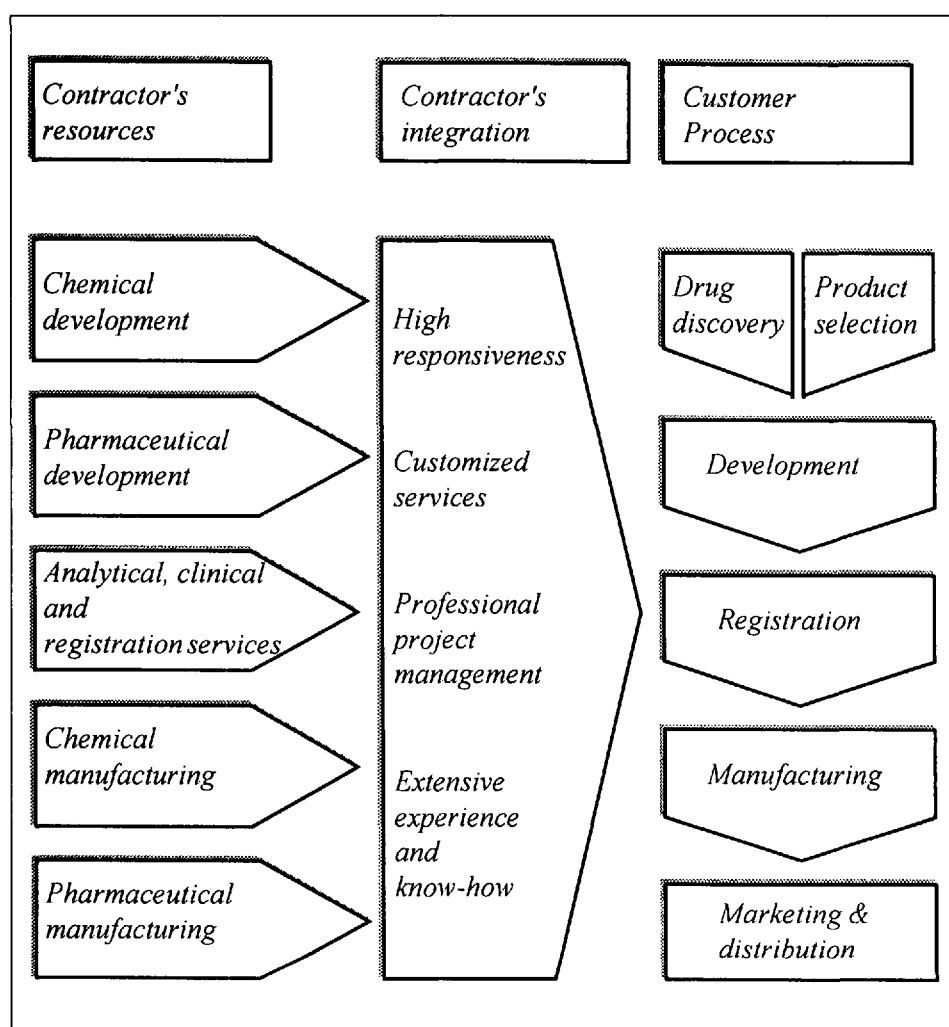


Fig. 2. Integration process

development in order to improve coordination between the different steps of development.

Therefore, a full-service contractor must not only provide technical resources, but also professional project management. This can bring the following advantages:

- Critical steps can be identified in advance and even be avoided.
- Synergies between different project teams can be shown and taken advantage of.
- Bottlenecks within different departments can be avoided.
- Transparency of project status is always assured.
- Internal and external communication can be performed more efficiently.
- The project can be speeded up and thus development costs reduced.

Furthermore, geographical closeness to the customer may be very helpful for various reasons. Communication is much easier if face-to-face meetings can be organized without any large investments in time- and money-consuming business trips. Facilities nearby the customers' mar-

ketplace are also an advantage with respect to any logistic matters. Furthermore, the custom manufacturer who maintains facilities spread all over the world is able to react in a more flexible way to short-term requirements of the local market.

For a full-service provider, independence is considered to be another essential factor. By working for third parties only and not having any own products on the market, a company confirms its position as a dedicated custom manufacturer and removes any conflict of interest with its customers. Since such kind of business can grow only through a strong base of trust and reliability, all customers must be guaranteed total confidentiality.

It goes without saying that all standards (quality control aspects, cGMP, FDA compliance, etc.) must be fulfilled. However, if working with multinational pharmaceutical companies, it has to be emphasized that individual regional requirements have to be taken into consideration. This requires a high level of flexibility and the willingness of the contractor to adapt and use the standards of the customer.

4. Advantages for Both, the Client and the Full-Service Contractor

Compared to internal resources of the client, a cooperation with an experienced contract organization may bring various advantages.

A contract organization usually works together with many different clients. All of these clients have their own history, experience, and requirements. Therefore, almost every client considers another topic to be especially important to him and sets the highest standards there. In the best case, this results in a cummulation of highest standards which the contract organization has to fulfill in every single segment. In other words, the customer also profits from the common know-how and experience which the contract organization gained in cooperation with other companies.

When outsourcing mature products, besides quality, price often plays an important role. By providing proficiency in process optimization of existing procedures, a full-service provider may be able to develop less time-consuming and less expensive chemical or pharmaceutical production processes. It may be easier for the full-service provider to look for alternative processes, because he is not familiar with the traditional production process used by the originator and, therefore, can think of alternatives more independently and from a different point of view than the originator.

Of course, the greatest advantage of a partnership with a full-service provider occurs when clients choose to develop entire compounds with the contractor. This gives the contractor the opportunity to show and prove a wide range of its core competencies dedicated to serve the customer best.

By perfectly integrating his resources into the customer's business process, the full-service contractor is able to support the customers' efforts to be:

- faster
 - by reducing development lead time
 - by enabling the client to concentrate on its own core competency
- safer
 - by cooperating with a partner that respects requirements of the authorities
 - by securing the client's supplies on time
- more cost-effective
 - by optimizing the customer's internal resources
 - by eliminating capital expenditure and manpower costs.

Of course, the customer may also pick only segments of the whole service package. This allows the contractor to prove flexibility and proficiency. Furthermore, he might fill up free capacity occurring during long-lasting projects (e.g., when the results of studies have to be waited for). The client, on the other hand, might not want to outsource very time-consuming projects if he is not yet familiar with the contractor. By outsourcing only parts of a project he will obtain information on the working standard of the contractor without risking much.

After patent expiry, the sales of the originator's product usually decrease because of generic competition. As one possibility of post-patent strategy, some originators decide to develop a generic product of their own. Of course, profits will decrease anyway because of the cheaper price of the generic product. However, it is better to keep a smaller piece of the market instead of leaving the whole profit to generic companies. On the other hand, manufacture or packaging of a generic product binds internal capacities that could be used in a more profitable way. This is just one typical example of outsourcing opportunities for the pharmaceutical industry.

Further advantages to the client are listed below:

- shared investments in risky projects
- ameliorating the product mix.

Since a full-service contractor provides the client with integrated solutions and does not only sell single services or 'white powders', the value chain for both partners increases. Thus, the contract manufacturer becomes an equivalent partner that improves the client's overall performance.

5. Siegfried CMS as an Example of a Full-Service Provider

In 1873, *Siegfried* was founded as a pharmaceutical company producing and distributing chemical specialities and pharmaceutical dosage forms and trading with medicinal herbs. At that time, twelve employees were working for the company. During the past 125 years, the company grew constantly and diversified into different fields.

In the seventies of this century, the *Siegfried Group* consisted of five different divisions: *Siegfried Chemie*, *Siegfried Pharma*, *Sidroga* (natural products), *Siegfried Handel* (trading), *Siegfried Agro* (agrochemicals), and *Siegfried Dienste* (human resources and support in the area of finances). While the pharmaceutical

division was developing and manufacturing a number of its own pharmaceutical products for the domestic market, the chemical division was already active in custom chemical manufacturing on an exclusive basis, primarily for the international pharmaceutical industry, producing key intermediates and bulk actives.

A few years ago, *Siegfried Pharma* decided to withdraw from its traditional market as a pharmaceutical company and began a period of divestiture. It was around that time that *Siegfried Pharma* concentrated more and more of its resources on providing services for the pharmaceutical industry. This concerned mainly the development and manufacture of formulations including services such as analytical support, stability testing, registration or monitoring of clinical trials, and compilation of the documentation required for the submission to the authorities. At the same time, *Siegfried Pharma* stopped all research activities on products of their own to remove any conflict of interest with its customers.

The last step to become a full-service provider to the pharmaceutical industry was concluded in 1997 by merging the pharmaceutical, chemical, and the trading divisions into one division, namely *Siegfried CMS* (CMS stands for Custom Manufacturing and Services). Nowadays, *Siegfried CMS* has five different facilities in operation: Two chemical plants in Pennsylvania and Carlstadt/NJ (USA), a chemical and a pharmaceutical plant in Zofingen/Switzerland as well as a chemical plant in Taiwan which is mainly dedicated to the production of intermediates.

The company has been active in the custom business on a worldwide basis for more than 15 years. By integrating both chemical and pharmaceutical services, it is the aim of the company to serve its customers from first to last. Thanks to long-lasting and successful relationships with various pharmaceutical companies, *Siegfried CMS* gained profound expertise and accumulated know-how which it is proud to utilize for the benefit of its existing and future customers.

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