Christian Gausepohl, Frank Böttcher

GMP Focus

Managing Contract Manufacturers and Testing Labs

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Karlstrasse 2
79650 Schopfheim
Germany
Phone: +49 7622 66686-70
Fax: +49 7622 66686-77
service@gmp-publishing.com
http://www.gmp-publishing.com

Managing Contract Manufacturers and Testing Labs

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Introduction

Outsourcing is "in," and the pharmaceutical industry, a long-time beneficiary of a world based on the division of labor, is no exception. Vast latent economic potential can be tapped through outsourcing. Today, many drugmakers simply cannot escape the external assignment of manufacturing and testing activities, despite the problems doing so may entail.

One of the problems they face lies in knowing when and to whom to "shop out" jobs. Unfortunately, in such an increasingly complex and diverse industry, no single entity can do it all. And even when drugmakers find a partner, how can they control those activities that will now occur beyond their gates, much less ensure a contractor will abide by the same standards they have set?

Regulatory bodies in both the U.S. and the European Union acknowledge the growing use of contractors. EU regulations set forth a clear description of the various activities that may be contracted to another facility. Meanwhile, the FDA provides less specific contracting guidance for drugmakers. Even so, FDA regulations make it clear that, no matter what the contracting arrangement, the manufacturer that contracts out work still retains responsibility for the final product. So careful selection and monitoring of contractors is necessary.

This report by two international regulatory experts lays out the factors to consider and procedures to follow when working with contract manufacturers, including:

- Duties of the contract giver and the contractor;
- Developing a contract manufacturer agreement;
- Auditing contract manufacturers;
- SOPs for assigning manufacturing contracts; and
- Principles of contracting with testing laboratories.

About the Authors

Christian Gausepohl, PhD, *is head of quality assurance and a Qualified Person at Rottendorf Pharma GmbH. His expertise includes coordinating technology transfers, process optimization and validation plans and conducting audits for regulatory authorities, drugmakers and suppliers.*

Frank Boettcher, PhD, *is CEO of Labor L+S AG and a consultant and author on quality assurance and pharmaceutical analysis topics. He is an authorized expert in accordance with the German Drugs Act (AMG §65.4) and is involved in a number of working groups that focus on the testing of medicinal products and medical devices.*

Selecting a Contract Manufacturer

There can be different reasons for outsourcing manufacturing steps. The selection of a contract manufacturer depends on what the contract giver wants to achieve through outsourcing. The risk potential of outsourcing manufacturing tasks should be identified by the contract giver in advance to ensure that the risks posed by the individual contract manufacturers can be determined during the selection process. When selecting a contract manufacturer, the technological requirements and restrictions are of particular importance.

Here are some questions to ask yourself and potential contractors during the selection process:

- How long has the company been conducting contract manufacturing?
- Has the company carried out comparable projects successfully in the past?
- Does the company have experience in carrying out technology transfers, scale-ups and manufacturing for several different customers?
- Is the company big enough to manufacture the planned quantities?
- Is the geographical location of the company suitable in terms of taxes, import/export problems, political stability, etc.?
- Has the company worked with local regulatory authorities on a previous occasion and does it have relevant contacts, especially in the countries to which the goods will be exported?
- Does the company have properly trained scientists, engineers and project managers?

Scope of Activities

There are a number of different activities that can be outsourced to a contract manufacturer, including:

- Manufacture of bulk products;
- Carrying out of individual process steps;
- Primary packaging;
- Secondary packaging;
- Storage and transport;
- Distribution;
- Accompanying analytical testing of processes;
- Pre-release inspections and stability tests;
- Batch certification;
- Manufacture of clinical samples and stability samples; and

- Manufacture of small batches during development and scale-up.

The scope is initially defined based on the current requirements of the contract giver. Additions or changes to services can occur during the working relationship because of:

- Changes at the contract giver, e.g., changes to the strategy and reasons for outsourcing;
- Outsourcing of additional areas of competence as a result of positive experience with the contract manufacturer; and
- Changes in the product life-cycle, e.g., because of a transfer to commercial manufacturing.

Definition of Responsibilities

Chapter 7 of the EU GMP Guidelines Part I, *Outsourced Activities*, clearly specifies the responsibilities of the contract acceptor and the contract giver (see Appendix A). This makes it easier to define the responsibilities in the mandatory contract, and it also helps clarify the expectations of the authorities with regard to the relationship between the contract giver and the contract acceptor.

Contract giver responsibilities specified in Chapter 7 are:

- Risk-based control system for the manufacturing processes and products (section 7.4);
- Qualification of the contract manufacturer before outsourcing (section 7.5);
- Contractual safeguarding of GMP compliance (section 7.5);
- Provision of all information required by the contract manufacturer (section 7.6);
- Monitoring and evaluation of the performance of the contract manufacturer and identification and implementation of necessary improvements (section 7.7);
- Monitoring and evaluation of the protocols and results (section 7.8); and
- Acquiring QP approval for the delivered products (section 7.8).

Contract manufacturers must be qualified before contract manufacturing begins. Their suitability is checked and evaluated during the supplier qualification. A contractual agreement on the responsibilities of both parties is important in order to avoid risks to the quality of the product or compliance with regulations, for example through uncertainties about the evaluation of deviations during manufacture or about the specific requirements in individual countries. The agreement should focus on the transfer of information and knowledge required by the contract manufacturer to reduce the risk to the quality of the product and to ensure operational safety at the contract acceptor. Examples include critical process-related empirical data as well as material safety data sheets or other safety-relevant information about materials, especially about new active ingredients.

A risk-based monitoring system for the outsourced manufacturing steps and products received must be in place at the beginning of contract manufacturing. The processes that are carried out and the quality of the product must be monitored, and the performance of the contract manufacturer must be evaluated regularly.