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Pharmaceutical Quality Assurance, Contract Development, Manufacturing, and Packaging of Pharmaceutical Products

Swiss Federal Institute of Technology (ETH), Zürich/University of Basel

Winter Semester 1993/94

6-S/1994

Swiss Review for the Pharmaceutical Industry
Revue suisse pour l'industrie pharmaceutique
Rivista svizzera per l'industria farmaceutica
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SWISS PHARMA 6-S/94

INHALT

SWISS PHARMA

ISSN 0251-1673

Swiss Review for the Pharmaceutical Industry
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Rivista svizzera per l'industria farmaceutica
Revista suiza para la industria farmacéutica
Schweizerische Zeitschrift für die pharmazeutische Industrie

Publishers, Editor's Office, Advertisement Administration
VERLAG DR. FELIX WÜST AG
Seestrasse 5
P. O. Box
CH-8700 Küsnacht ZH
Telephone 01/911 00 55
Telefax 01/910 95 95 *Publisher/Editor*
01/910 60 80 *Advertisements/Subscriptions*

Advertising Rates
At present the advertising rates of October 1, 1992 are valid.
Special rates for English editions.

Editor
Dr. rer. publ. Felix Wüst

Subscriptions
The annual subscription fee for all titles listed below is sFr. 100.– per title (for Switzerland). Extra charge for postage and packaging for subscribers abroad:
– sFr. 20.– Abroad/Europe (surface mail)
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Single numbers
– Regular publications: sFr. 20.– plus postage and packaging
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Druck: Lang Druck AG, Sägemattstrasse 11, CH-3097 Liebefeld BE

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Results of the four project groups of the third postgraduate seminar for Pharmaceutical Quality Assurance, winter semester 1993/94, Department of Pharmacy, Swiss Federal Institute of Technology (ETH), Zurich and the University of Basel, Pharmaceutical Faculty

"Pharmaceutical Quality Assurance" and "Contract Development, Manufacturing, and Packaging of Pharmaceutical Products"

Postgraduate Seminar "Pharmaceutical Quality Assurance"

During the last two decades, quality assurance has become a main concept of current good manufacturing practices in the pharmaceutical industry. In view of the complexity of comprehensive quality assurance strategies and the ongoing development in this field, the Department of Pharmacy, Swiss Federal Institute of Technology, and the Pharmaceutical Faculty of the University of Basel organized the third postgraduate seminar for Pharmaceutical Quality Assurance during the winter semester 1993/1994. The objective of the seminar was to offer interested representatives from industries, authorities and universities a forum for a postgraduate education in the rapidly moving and evolving field of quality assurance.

Contract Development, Manufacturing, and Packaging of Pharmaceutical Products

Companies may contract out product development, production or packaging for various reasons. A company could contract out the manufacture of pharmaceutical products when its own facilities are working at full capacity. The development of a new formulation may require specialized know-how and equipment. A contract developer, in this case, could provide the company the expertise and technology necessary. In any case, contract developing, manufacturing or packaging is a challenge for both parties, the contract giver as well as the contract acceptor.

The seminar participants worked in project groups on four selected topics within the framework contract acceptor – contract giver. At four full-day working meetings the results of the project groups were discussed and integrated. Experts from industry and authorities contributed substantially to the successful development of the seminar. One of its objectives was to publish the results of the four project groups in a concise form. Now published in SWISS PHARMA 6-S/1994, the papers present a selection of summaries, procedures and approaches which may provide a basis for your contract projects.*

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«Pharmaceutical Quality Assurance» and «Contract Development, Manufacturing, and Packaging of Pharmaceutical Products»
Editorial by Dr Stephan Marrer and PD Dr Hans W. Schmid, Swiss Federal Institute of Technology (ETH), Department of Pharmacy, Zurich

Results of the project groups:
Pharmaceutical Quality Assurance: Pharmaceutical Development under Contract Quality Assurance Aspects
- Sabina M. Compassi, Michel Keller

Pharmaceutical Quality Assurance: Contract Packaging
- Peter Mühlematter, Carlo Planzer, Richard Sommer

Pharmaceutical Quality Assurance: Flow of Materials and Information during Contract Manufacturing of a Pharmaceutical Product
- Roger Laforce, Claudia Stampfli

Pharmaceutical Quality Assurance: Outsourcing in the Pharmaceutical Industry - Evaluation of a Contract Acceptor
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Pharmaceutical Quality Assurance

Pharmaceutical Development under Contract: Quality Assurance Aspects

*S. Compassi, M. Keller**

Successful development under contract implies that:
- ***the company charged with contract developmental work has got a quality assurance system which is up-to-date and in conformity with the current national and supranational regulations. The key objective of the quality assurance system is to implement the principles and philosophy of GLP, GMP, GCP in all activities of development. Further, project management systems must make it possible to properly plan, monitor and control the activities of the development project.***
- ***the client sets up a project team, responsible for the management of the external project.***
- ***a written contract between both partners exists and includes the following main topics:***
  - ***product profile***
  - ***development programme***
  - ***project milestones***
  - ***payments linked to specific milestones***

Based on a checklist (CDC) edited by the contract acceptor (CA) and filed jointly by the client (CG) and the CA, the development programme defines the general course and the objective(s) of the collaboration.

Introduction

Innovative work is the undisputed basis for the future of the pharmaceutical industry. Without innovative products pharmaceutical companies risk losing competitive strength.

The following figures demonstrate the importance of R&D for the pharmaceutical industry: In 1985 European and US companies invested around 15% of their annual sales in R&D activities. The trend is moving towards even higher outlays [1, 2]. In 1993 expenditure on R&D already amounted to 20% of sales. Taking into account unsuccessful projects, the overall costs of reaching the market with a new substance came to around US$ 52 to 91 mill. or Sfr/DM 100 to 160 mill. in the period 1982–1985 [3, 4, 5]. In 1992 more than 200 mill Sfr, in some cases 300 mill. were calculated [6].

While pharmaceutical research and development obviously are becoming more and more expensive, sales are not increasing proportionally. Thus, the profitability of research and development judged by future returns is diminishing continuously [7]. Compared with R&D activities in other industrial sectors like engineering, the developmental risk of pharmaceutical projects is high. Problems encountered can in most cases not be overcome by simple enhancement of resources. The "death rate" of pharmaceutical R&D projects is considerable: Out of 10,000 newly discovered drugs only one will finally reach the market. The success rate varies, depending on indication and drug substance group [8]. Why do pharmaceutical R&D projects fail [5, 10]? Poor project planning and organization may contribute significantly to a failure due to efficacy and toxicological problems. Often limited time and anticipated costs prevent the solution of problems which could otherwise be resolved. So, time is the most important factor with respect to the profitableness of a new prod-

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uct. For every developmental project financial risks are strongly linked to the time expenditure for development: The future success of a new drug on the market cannot be foretold as market development trends are changing. The longer the development time, the higher the risk that a new product will no longer meet the demands of the market and will thus not prove competitive.
Shifts in direction in the course of a research project are quite common. It is obvious that exact figures to quantitate the effective time and efforts spent on the research to discover a new drug are difficult to arrive at. On the other hand, if development steps are clearly defined, it is certainly easier to measure and to allocate the time and efforts required. Different studies describing the duration of pharmaceutical developmental projects report an average of 10 to 12 years [11, 12]:
- preclinical phase: 2–3 years
- clinical phase I: 1–2 years
- clinical phase II: 2 years
- clinical phase III: 3 years
- clinical phase IV: 1 year

Pharmaceutical R&D activities are thus characterized by high risk and capital intensive long term investments. It is evident that the activities required to generate a new product must be as efficient as possible in terms of time expenditure and overall costs, i.e. overall resource management becomes extremely important.
In order to better cope with these unfavourable conditions, companies tend to favour joint ventures or strategic alliances, concentrating financial efforts and resource power to achieve greater efficiency, especially in highly scientific research. The increasing interest in capital intensive biotechnology has led to a concentration of biotechnological research in the US, where powerful European companies are engaged in strategic alliances and joint ventures or have affiliated companies [13].
Another trend applies particularly to the developmental phase of R&D projects. Contracting of developmental work to outside companies is becoming more and more popular, particularly for advanced projects, where a considerable amount of scientific and technical information is already available and where defined steps in a development plan are to be carried out [14, 15]. The commercial and technical risks are lower for this kind of project than in pharmaceutical research. Steps in a development plan are easier to schedule, since government regulations render the basic planning rather straightforward. The strategy for obtaining approval is more or less clearly defined. The following types of projects are typical in contract development:

New products (analytical, galenical, clinical development)
- innovative galenical formulations for new drug entities
- line extension projects
- generic products

Known products (analytical, galenical, clinical development)
- improvement of known products
- indication extension
- registration documentation

Co-development offers a wide range of advantages: Specialized companies with experience in particular technologies (sometimes patented) and methods can help to shorten development times while simultaneously applying innovative technologies. Often companies specialized in contract development are medium-sized, highly flexible companies. They are able to carry out project developmental work much faster than development departments in multinational companies, where organizational structures often complicate decision-making, slowing down project development and lowering staff motivation at the same time. Further, companies specialized in contract development are careful to make development both measurable and controllable, since their own profit depends decisively on their success. This is a prerequisite not only from the economic side of developmental work but also from the quality assurance point of view. The more transparent activities and decisions in development are, the easier it is to control their compliance with national and supranational requirements. This is precisely the aim of the preapproval inspection programme issued by the FDA. Scientific justifications for everything coming out of the R&D department must be provided. A similar pre-approval inspection programme is being prepared in the European Community by a Working Party.
The quality of a product will depend on how well it was conceived and developed [16, 17]. The aim of pre-approval inspections is thus to assure that the approvals are not given to applicants who have not demonstrated their ability to operate with integrity and in compliance with all applicable requirements (like GLP, GMP, GCP...). An NDA file alone is not sufficient to get a product approved [18, 19, 20]. Computerized systems in the manufacturing area help to plan and to control GMP conformity and expenditures related to operational procedures. These systems are supervised by the quality control or, at a higher level, by the quality assurance department. This philosophy could also be applied to the development area, with conventional project management serving as an appropriate tool [21].
Generally successful development implies that the new product is of the highest technological and scientific quality and has been developed in the shortest time possible and at minimal costs. From this point of view, the need to control developmental activities by modern project management is a prerequisite, especially in contract development.
The objective of this paper is to propose the tools necessary to ensure the quality of a product developed under contract. The following structure is of assistance in the successful realization of such projects:
- *Company, specialized in contract development:* provides a quality assurance system up-to-date and in conformity with current national and supranational guidelines and
  a project management system to plan and control the development activities
- *Client:* provides a project team controlling the external project
- *Contract:* brings both partners together and defines the project by a development programme

Quality Assurance System in Contract Development

1. Definition of the QA-System
The QA system for development is an internal system which ensures that the whole product development is performed in compliance with all applicable rules and leads to a product showing the quality standard as determined at the beginning of the development, or as adapted/modified during development. These rules are on the one hand external such as regulations, governmental guidelines, directives, notes for guidance, laws etc., and on the other hand internal (company rules: guidelines, procedures, SOPs, instructions etc.). These internal rules are usually derived from the external regulations and build up the frame of the QA system. The quality standards represent the quality level and philosophy of the CA as well as the quality requirements of a specific customer (see *CDC, Annex*).

2. The Signification of Regulations
Quality Assurance incorporates GMP, GLP, GCP and many other factors (some of them are outlined in *Table 1:* National and International Regulations): it covers all matters that individually or collectively influence the quality of a product. These regulations can be classified in two categories according to their legal status: a small number of them like the GMP and to a lesser degree GLP regulations are legally binding. Others are rather recommendations: to comply with them is not mandatory in a legal sense, but it greatly improves the chances of acceptance of

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Table 1: National and international regulations (Europe and USA)

Regulations	Regulatory authority	Ref.	Field of application/Examples
GLP	OECD (EC) / FDA	22,23	Preclinical studies
GMP	EC/PIC/WHO/DHSS	24, 25, 26, 27	Manufacturing
cGMP	FDA	28	Manufacturing
GCP	EC/WHO	29,30	Clinical studies
cGCP	FDA	—	see Guidelines
Notes for Guidance	EC (CPMP)	31	Investigation of Bioavailability and Bioequivalence; Manufacture of Investigational Medicinal Products; Analytical Validation; Quality of prolonged release oral solid dosage forms
Guidelines	FDA	32,33	«cGCP»: set of regulations for clinical studies; Preparation of Investigational New Drugs; General Principles of Process Validation Guideline for Submitting Samples and Analytical Data for Methods Validation Guideline for Submitting Documentation for the Stability of Human Drugs and Biolgics
IND	FDA	34,35	Submission for clinical testing
ICH Tripartite Guideline	ICH	36	Stability Testing (New Drug Substances and Products)
NDA	FDA	35	Submission for marketing approval
Notice to Applicants	EC	37	Submission for marketing approval

Table 2: Internal Guidelines

Guideline Title	Guideline Fields (examples)
Organization Guideline:	Responsibilities/Information Flow/Decision Making Levels
Personnel Guideline:	Education/Knowledge/Training
Project Mangement Guideline:	Planning/Implementing/Controlling/Checklist
Analytical Development Guideline:	Analytical Methods Validation
Galenical Development Guideline:	Experimental Design/Scale-up
Starting Materials Guideline:	Specifications/Suppliers/Storage/Testing
Laboratory Controls Guideline:	Testing Methods/Stability/Reserve Samples
Process (Technology) Guideline:	Processing Instructions
Equipment Guideline:	Maintenance/Qualification/Calibration/ Cleaning
Facility Guideline:	Maintenance/Cleaning/Site Selection
Process Validation Guideline:	Definition and Control of Process Variables
Technology Transfer Guideline:	Within/Outside the Company
Clinical Supply Guideline:	Processing/Packing/Labelling/Release/ Storage/Dispatch
Stability Guideline:	Policy/Master Programme/Testing Methods/ Collecting, Reviewing and Analysis of Data
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Contract Works Guideline:	Analytical (special tests), Microbiological Testing

studies/results by the regulatory authorities!

Although earlier stages of product development (i.e. before preclinical studies) are not covered by any regulations, each company should issue internal rules (*Tab. 2: Internal Guidelines*) based on government regulations like GMP, GLP, GCP, etc. These internal rules should conform to the principles and philosophy of the regulations, yet be adapted to the company organization, structures, activities and needs as well. The compliance of all development stages (i.e. including the very early stages) with these regulations will help in the preparation of events such as pre-approval inspections performed by the FDA (see *Introduction*).

3. QA System Objective

The objective of the QA system is to assure the management that all studies/ tests/ processes have been conducted according to the relevant rules and that the data / reports are valid and accurate reflections of the operations actually performed. Assessment of conformity with rules will be done by checking the following points regarding the different systems, e.g. processes, equipment, facilities, starting materials, analytical methods, etc.:

- What systems are required?
- Are the required systems in place?
- Are the systems validated? (see below)
- Are there procedures describing the systems?
- Are the procedures adequate?
- Are the procedures up to date and authorized?
- Are the procedures available to the persons involved and adhered to?

As soon as products are tested in clinical studies in humans, the validation of systems is a legal requirement for two reasons. Validation data should demonstrate that

- volunteers and/or patients treated with a drug in development are not exposed

to unacceptable risks due to the pharmaceutical properties of the product and
- the product tested during clinical phases I, II and III has the same quality characteristics as the one approved and distributed commercially (data reproducibility).

The QA system must ensure that the developed product will have the strength, purity, safety and efficacy shown by the clinical batches and documented in the registration file. Therefore it should cover all activities performed in units such as Analytical Development, Galenical Development, Clinical Development, Scale up, Production, and Quality Control, as well as the global system, i.e. Project Management and Company Organization. Moreover, a carefully planned and correctly implemented QA system for the development of a product investigates failures and helps to prevent all kinds of problems in the course of development and manufacturing of the finished and approved drug product. Within the organization of the company quality assurance serves as a management tool. In contractual situations, it is also a means to generate confidence in the supplier. The QA system thus has a twofold objective: it should control as well as improve the quality of product development by identifying weak links, suggesting changes and following up their implementation.

4. Instruments of the QA System

The QA staff has at its disposal three main instruments to accomplish its job. It will *audit* (first instrument) the operations to be performed according to *procedures* (third instrument). These procedures are written on the basis of *internal guidelines* (second instrument).

a) Audits

An audit can be defined as an independent review to determine the extent to which an operation conforms to quality standards specified for it. Audits of activities will confirm that systems are in place, effectively control quality, and comply with current regulations and internal guidelines.

The main responsibility of the QA is to follow the development of a product by means of periodic audits/inspections of the different steps. Basically the audits should cover all areas necessary in order to ensure that all rules are properly adhered to. They therefore cover the steps performed (studies, tests), facilities, equipment, materials and personnel. The main characteristics of audits can be summarized as follows:

1. Audits are performed according to written procedures
2. Auditors are not responsible for any areas being audited
3. Auditors are trained individuals (experience as auditor and knowledge of the audited field)
4. Audit reports are written and reviewed by management
5. Corrective actions are taken where necessary
6. Effectiveness of corrective actions taken is monitored (follow-up including re-audit)

Depending on the stage at which the audit is performed, the following documents and operations have to be checked:
- Before operations start: Clearly defined specific responsibilities (to preclude duplication of operations or their non-performance or only partial completion) protocol/ plan/ master batch records/ instructions/...
- During operations: Availability of and adherence to procedures (SOPs)
- After completion of operations: Records / reports /...

Example of a Product Stability Programme Audit:

The following example lists the audit steps specific to a stability programme. Points 1 to 3 will be checked before testing operations start. The implementation of work instructions (point 4) will be checked during the operations, and the interpretation (point 6) of data will be reviewed after completion of the testing operations. Point 5 (recording of data) can be checked either during or after completion of the analysis.

1. Are there written procedures for policy / systems descriptions / work instructions?
2. Is there a master stability programme including parameters / specifications / test methods / packing materials / test locations / time programme / sample requirements / storage conditions?
3. Are stability test methods adequate?
4. Are the work instructions correctly implemented?
5. Are the stability data adequately recorded?
6. Are the test data correctly interpreted?

b) Internal Guidelines

These guidelines establish general processes, instructions and general quality standards (e.g. starting materials of USP or/and EP quality) and provide general indications for the accomplishment of all operations involved in the product development. Each department establishes its own guidelines by taking into account the actual structure and resources of the company as well as the applicable legal rules and requirements (see also *1. Definition of the QA system*). All of them are checked and approved by the QA. These guidelines represent a direct interpretation of government regulations such as GMP, GLP, GCP, etc. for stages to which these rules clearly apply. In the case of earlier stages of development, they are a more or less free interpretation of the same regulations, respectively of their philosophy. Examples of such guidelines are given in *Table 2.*

One very important guideline concerns the management of projects for clients. This Project Management Guideline describes a.o. a Contract Development Checklist (CDC), which is a standard questionnaire to be filled out together with the client as the first concrete step of the developmental work. This document defines the general framework of the project and the quality standards applicable. It lists the main work steps to be taken as well as how, in general, to perform them. As good communication is indispensable for mutual understanding, and as the two partners have a more or less different culture (approach to quality concept, terminology, strategy of development, etc.), the CA should ensure that the language adopted in the CDC is well understood by both. The meaning of some terms included in this checklist may therefore vary from customer to customer, while the structure itself will always remain identical. Terms like e.g. analytical method validation should be defined or described in order to avoid misunderstandings on the extent of or the time needed for the performance of a partial or full validation. This question of definitions will be dealt with specifically for each customer in the corresponding point of the CDC and not in the form of a general glossary. Based on this CDC, the Development Programme (DP) will be prepared by the CA, approved by the client and incorporated in the contract. An example of a suitable CDC is included in the *Annex.*

c) Procedures (SOPs)

The SOPs are written on the basis of the principles and standards set forth in the internal guidelines. They describe in detail both the general (what, who, when) and the specific (what, who, when, how) operations.

Project Management in Contract Development

Planning and innovation are often seen as being at cross-purposes. Yet it is quite obvious that both are the crucial and key parameters in any development project [38]. Care must be taken that innovative ideas are not suffocated by rigid planning systems. Any kind of progress is based on human intellectual faculties, human organizing abilities, human executive potential and human technical skills. Psychological aspects of work are extremely important.

Besides technical, scientific and GMP/GCP training, communication as well as psychological conflict-solving techniques should form part of the education of personnel.

The managerial «trick» thus is to focus the wide array of intellectual and regulatory commitments on a specific project and to control the project without destroying the motivation and innovation of its participants along the way [39]. Management techniques developed in other fields, such as industrial engineering, operations management, computer science and business administration, serve as useful quality assurance tools for planning and controlling the implementation of SOPs into project development. In particular, project planning has to be carried out under the supervision of quality assurance. Project planning includes [40]:

- organization of project team, authorities and responsibilities
- planning of the project:
  defining of project purposes: understanding the problem
  planning of strategies and activities: planning of the solution
- scheduling and definition of decision points; budgeting
- monitoring and controlling of developmental activities; cost monitoring, overall project evaluation

1. Organization of the Project Team

In setting up a project, authority and responsibilities on all project levels have to be clearly defined [41] *(Table 3):*

- deciding units
- coordination units
- executive units
- controlling units
- advisory board

Outlines of the basic area as well as statements of the essential functions of these units should be recorded. An overview of the definition of the spheres of authority and competence could be presented in a table of organization with reporting lines and identification of the personnel required [42]. By the means of flow charts interactions of the different units within the company on one hand, and between the company carrying out the development and its contractor on the other hand, could be visualized. Below an organizational arrangement is proposed. Obviously, the organization of the project team will depend on the size and specialisation of the company. The project team leadership is the crucial and the most difficult position in the project organization. Together with the client, the project team leader has to elaborate the development programme. Together with the representatives of the scientific departments, he has to work out a detailed project plan and control the actions defined in this plan.

Table 3: Organization of the Project Team

Deciding Unit:	*Overall Responsibility: Company Management* Head of Project Management Department Head of Business and Financial Department R & D Department Head Head of Quality Assurance = > Decide on overall project activities = > Decide on project team *Project Team:* Project Team Leader: Project Manager Project Leader Galenical Development Project Leader Clinical Development Project Leader Analytical Development Project Leader Quality Control Department = > decide on specific project activities
Communication & Coordination Unit:	Project Team Leader communication and coordination within the company; coordination with other projects Project Team Leader & Area Manager of Business and Financial Department routine communication with the client
Executive Unit:	Project Leader Galenical Development Project Leader Clinical Development Project Leader Quality Control Department Project Leader Analytical Development
Project Control & Evaluation Unit:	Quality Assurance: Overall control that project is planned and carried out according to applicable rules Project Team Leader: Controls that the project is carried out according to the project plan

2. Project Planning

A contract development checklist (CDC) for project planning (see *Internal Guidelines* and *Annex*) as an instrument of quality assurance ensures a proper definition of the product and the development profile. Subsequently, the development programme (DP: see *Internal Guidelines*) is elaborated, including:

- product profile and overall target date
- important milestones / decision points
- milestones to which payments are linked

This development programme forms part of the contract. It is set up by the project team leader, assisted by quality assurance and business representatives on the one hand and the client on the other. Based on these data, a detailed project plan is worked out together with the representatives of the scientific departments. Strategies, activities and milestones are defined in order to meet the development programme. Further, the project plan allows monitoring of project costs.

The project executive representatives have to flesh out the details of the project plan and assign specific duties to the specialists in their department. The project team leader sees to it that assignments are completed in accordance with the project plan. Supervision by quality assurance ensures operations are carried out in conformity with all applicable rules. Planning and scheduling entail considerable administrative work. Frequent updating and revising will be necessary. Fortunately, existing computer software is quite suitable for these purposes [43].

Despite a tendency to believe that a finalized plan cannot be changed, both planning and development are in fact dynamic processes affected by technology, new discoveries and new problems. Thus, a well-conceived plan can act as a dynamic, flexible vehicle providing contingency measures, if needed, to cope with new technical challenges and budget objectives. Moreover, a plan is a solid source of information which can serve as a means of communicating directions and expectations to personnel at every level.

a) Development Programme

The aim of the development programme is to specify what should be developed and which is the overall target date for the completion of the project.

To define the project objective both partners have to agree on a product and development profile elicited from the answers of the development checklist (CDC: see *Annex*). For example, in the case of a galenical development defining the in vivo product profile is rather a straightforward matter. Difficulties arise in selecting the right in vitro models and in setting the appropriate in vitro criteria which should be met in order to achieve a specific in vivo performance. Therefore, establishing information on a significant in vitro-in vivo correlation for a product generally ought to be part of the project target. The most appropriate information on the in vitro-in vivo correlation is obtained with the final formulation after completion of the development work. The partners have to clearly agree on how to deal with this difficulty at the beginning of the project, and they must also agree on an in vitro method prior to knowing the in vitro results.
The development programme must be realistic and attainable. Objectives have to focus on single key results and specify the target date for their completion.

b) Detailed Project Plan
In the detailed project plan the activities and strategies are organized with a view to accomplishing the development programme. The following means for achieving clear-cut results have to be specified:

- *human resources:* qualified and experienced staff
- *facilities:* analytical and/or pharmaceutical laboratories, facility for scale-up and production
- *technologies*
- *equipment*
- *starting materials* and their quality: active and inactive ingredients, packaging materials, reagents
- *financial resources* (budget) available to accomplish the programme

A resource summary should help to prioritize strategies. Sparse financial and time resources may preclude a broad formulation screening in the case of a galenical development project. An optimization has therefore to take into account all those limits and define a compromise developmental strategy. A programme strategy consists of various tasks, the completion of which will result in the attainment of the stated programme objectives.
It is very important to have staff input in a team to gain the commitment needed to meet schedules and to overcome difficult problems. Identifying the various tasks to be accomplished is crucial in order to establish an activity / task sequence. It is obvious that only persons actually experienced in performing the work concerned are able to precisely define the necessary supplies and equipment and to assess the time requirements.

Scheduling /Monitoring and Controlling:
Of the many problems associated with programme planning, setting the project schedule may be the most difficult. Scheduling of all activities demands efficient cooperation within the project team, with the team leader acting as moderator and coordinator. We propose a very pragmatic way to schedule the project tasks. All activities listed as part of the strategy are ordered in a chronological sequence. This listing should make it possible to determine whether certain activities are to be performed simultaneously or successively. Furthermore, resources can be assigned and tracked.
After the various tasks or steps have been described, a time estimate for each is proposed by the representatives of the departments concerned. Now the final planning with start and completion dates for each step can be worked out. The secret of a successful implementation of such a project scheduling system is to choose the right level at which to do the scheduling. In other words, if the schedule is too detailed, people will lose their flexibility to manage and supervise and will spend all their time updating the schedule. They must be free to change assignments and make adjustments to keep on schedule. Scheduling within the department (or one level lower) is about as detailed as is feasible. We propose to schedule by dividing the specific studies into the significant and important tasks. Starting dates and target deadlines must be agreed on by everyone. Employing computerized systems in scheduling is of great advantage, since frequent rescheduling may be necessary when summarizing tasks, resources or costs of all executive departments is involved. Moreover, this technique can be useful to indicate where additional resources are needed or whether the project activities must be assessed by some other measure than profitability.
Further, the completion of some specific steps represents a check point at which the output of the development can be measured. At these check points one may take a go/not go decision for the continuation of a specific strategy, or – if important enough – even for the whole project. Computerized systems may be helpful in the preparation of such decisions as well. They allow comparison of input and output, they afford an overview of time elapsed and money spent and, if cross-linked with other projects, the status of the availability of resources. In addition, they provide a means for efficiently documenting a project process. It is requisite that schedules should reserve some extra time for unforeseen events. Scheduling, like the whole development plan, cannot be a rigid fixed structure for the entire duration of the project, and experienced pharmaceutical managers are aware that delays may occur, even though it is impossible to predict exactly why or when.
Up from the planning stage, a programme to evaluate the project performance should be set up in order to monitor and control the activities with regard to their compliance with the project plan. A project performance assessment has to be drawn up after completion or when an objective is reached.
Monitoring and controlling will take place on different organizational levels. As already pointed out, the overall control of the project is one of the main duties of the project team leader. At the top level company management carries responsibility (e.g. overall coordination of all ongoing projects).
Monitoring and controlling of the tasks within a department are the duty of the authorized department project leader, who evaluates the efficiency and economy of a specific operation. Regular project team meetings should allow a free exchange of the monitoring and controlling information. The completion of the tasks within the project schedule and appraisal of future project results, as well as the implications of the results of such continuous monitoring for specific strategies, should be on the agenda of these meetings.
Based on such data, decisions should be taken to adjust strategies. Monitoring and controlling should allow an almost continuous evaluation of the project. Evaluation reports to inform the management of the company should be filed regularly or at each stage where important decisions need to be taken which exceed the competence of the project team members.

Contract Between CA and CG
Like any work done under contract, the conditions and responsibilities entailed in a development under contract should be described in a written agreement.
An important aspect of such a contract concerns the legal rights to the results generated by the work under contract. The agreement should state clearly who will be the owner of the results. On this basis two main types of work under contract can be defined:

a) In the first type of contract, all results generated are owned exclusively by the CG.
   1) The agreement between CG and CA defines the pure work performance under contract. Payments to the CA are on the basis of receiving fees.
   2) Another variant of the same type of contract provides for fees as under 1) and, in addition, for a profit-sharing of the CA in the success of the product in

the form e.g. of royalties on future sales of the developed product during a fixed period of time.

b) The second kind of contract is characterized by collaboration between the CG and CA, as e.g. in a joint venture. In this case, both partners agree to share the use of the rights to the results and the know-how generated by the collaboration. Such an agreement needs to be checked with a regard to the EC competition rules and other cartel laws.

The contract fixes the framework of collaboration between the CA and the CG and should include (but not be limited to) the following specific points:

1. Recitals / Definitions

The framework of collaboration is briefly outlined by presenting the product to be developed: its initial state and the desired profile to be attained. Based on his technology (in some case patented), know-how and expertise, the CA agrees to develop a product showing a certain profile, described under point *Product Profile specifications* (see below).

For purposes of the contract important terms, e.g. Product, Drug, Stage, Development Programme (DP), Patent Rights, Territory, etc. are defined.

The duties (who does what) and the allotment of the costs (who pays what) are briefly fixed in general terms (see also *CG and CA Duties.*)

2. Product Profile / Specifications

The objective of the Development Programme (DP: see *below*) is presented through detailed information describing the rationale and the physico-chemical, galenical, toxicological and/or clinical profile of the product to be developed.

3. Development Programme (DP)

Like the product profile, the DP is drawn up on the basis of the Contract Development Checklist (CDC: see *Internal Guidelines*). It defines the general way in which the target of the collaboration between the CG and the CA should be worked towards. The DP spells out the following points:

- Personnel and Responsibilities: project team including both partners with defined area of expertise and responsibilities for each position.
- Operations: if e.g. the CA is to perform a partial development, operations to be carried out by him or by the CG are defined in a Table of Responsibilities.
- Development stages: detailed description of the objective(s); definition of the different stages of the development.
- Schedule: a development schedule defining the duration of each main stage. The completion date of each stage represents a checkpoint: at this time the progress of the development work will be assessed and the amounts due as set out in point 4.9 will be paid.
- Quality and extent of data to be supplied by the CG to the CA technical specifications, stability data, testing instructions, etc.
- Quality and availability of data generated by the DP: data are supposed to be used for future regulatory submissions, so they have to show a defined quality standard.
- Audit: of systems and of data, before and during the development.
- Reporting: a written report summarizing all raw data (including tables, figures, graphs) and presenting the progress of the DP will be regularly provided to the CG.

4. CG and CA Duties

CG supports CA by:

- disclosing all relevant and necessary know-how and information; this information may be used by the CA only in the frame of this specific development programme
- supplying him against payment or free of charge with all the necessary starting materials.

CA supports CG by:

- informing him on a regular basis on the progress of the programme or immediately in case of important and urgent problems.
- disclosing basic documents generated by the development work (e.g. galenical preformulations/formulations), depending on the type respectively the stage of the collaboration.

5. Confidentiality

The partners define which information is confidential: e.g. all confidential documents to be exchanged are marked CONFIDENTIAL. They commit themselves to keep strictly secret all confidential information (verbal and written) obtained from the other partner. The identity of the product being developed should be kept inaccessible to external parties by identifying it with a code number. The duration of this mutual obligation of confidentiality is defined.

6. License Option

License (exclusive or not, right to sub-license) for the CG to manufacture the developed product in a defined territory is agreed on.

7. Technology Transfer

The transfer technology point defines what kind of information/documentation will be given to the CG at which stage of the development.

8. Use by CG resp. CA of know-how generated by the DP

The owner of the know-how (e.g. trade secret and/or patent rights) that will be generated by the DP is defined. The use of this know-how by the other partner is fixed: free of charge / against payment. Topics related to the developmental work which could be published (with approval of the CG) are listed: e.g. clinical reports.

9. Costs and Timing Estimates

Cost and timing estimates are prepared for each stage (analytical, galenical development, production of clinical samples, stability programmes, etc.). These values will be incorporated in the detailed project plan (see *Project Planning*).

10. Payments to the CA

Assuming proper implementation of the DP by the CA, the milestones for payments (amounts and time) are defined.

11. Third party

In some cases the CA may need the services of an external laboratory for some special analysis (e.g. microbiological testing). Arrangements made with a third party should ensure that the information necessary for, respectively produced by, the third party will be transmitted with the same efficiency and quality as between the CA and the CG. Such sub-contract jobs are contracted and monitored according to an internal guideline, and should be approved by the CG as well.

12. Duration and Termination of the Contract

Start and end of the development program are fixed, as well as the end of validity of the contract and the rights and obligations of both partners after termination of the agreement. Reasons for cancelling the contract are listed.

It is the responsibility of each party to assure that the agreement is a workable, practical document acknowledged by both.

Conclusions

It is well known that the quality of a product does not derive from how accurately it has been tested, but simply from how well it was designed/developed and manufactured [44].

Guiding a medicinal product from the laboratory to the market, whether in a company's own facilities or in those of a contract acceptor, while ensuring appropriate quality can only be achieved by using a made-to-measure quality management system [45].

Today Quality Assurance systems applied

to the production area – in the pharmaceutical as well as other industries – are well established. The trend is now moving towards the implementation of such systems to the development area as well (see e.g. the ISO 9000–9004 standards).

Quality Assurance systems for development should be designed to its specific needs. They should ensure that a repetition of mistakes is avoided, and not, as is the case in production, the absolute absence of mistakes (zero defects): they should help to make development activities as rational as possible, but without stifling the creativity of the people involved by inappropriate rules. Most of the regulatory rules and specific guidelines apply to routine industrial production. However, their philosophy and principles should also be integrated in the planning and execution of development projects.

In the field of contract development QA systems offer to both partners a means to optimize cooperation in order to ensure successful development, regulatory compliance and product quality in a complex environment (two different company cultures): this is true

- for the CA: a well functioning Quality Assurance system could offer an advantage over the competition. This could influence the CG's choice of a CA. Further, this system gives the company the assurance that projects will be conducted in an efficacious and optimal way as regards quality, costs and time.
- and for the CG the adequately designed and implemented Quality Assurance system of the CA makes the CG confident that his development project will be carried out by the CA in a efficacious and transparent way.

For both partners it simply makes good business sense.

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Annex: Contract Development Checklist (CDC)

This example considers the planning and discussion of a generic product.

0. Applicable development quality standards and regulations

0.1 Applicable Pharmacopoeia

0.2 Applicable Regulations / Guidelines for:
- animal (preclinical) studies
- clinical studies
- manufacturing
- other

1. Starting materials (actives and inactives): documentation and quality control

1.1 Material source:
- Known / preferred sources?

1.2 Materials:
- described in a pharmacopoeia (which one?)
- with DMF: active(s): necessary / inactives: if available
- other (additional) specifications

1.3 Release tests:
- Testing methods: Pharmacopoeia / DMF / Other methods

- Extent and frequency of testing
  Extent: partial (specify) / full analysis
  Frequency: each . .× batch

1.4 Testing methods validation:
- which methods / at which stage

1.5 Stability data:
- available (for one or more sources / complete / partial)
- to be generated / completed
- conditions (T, r. H., …)

1.6 Requirements 1.3 – 1.5 to be fulfilled for which stages:
- whole development
- from clinical development
- other (specify)

2. Packaging materials: documentation and quality control

2.1 Finished product packaging materials:
- specifications (type of material, construction)
- routine tests (quality control test procedures)
- safety to be certified

2.2 Bulk packaging materials:
- same as 2.1

3. Galenical (Formulation) development: Lab scale

3.1 Compatibility studies:
- Qualitative formulations submitted to accelerated stability tests: Batch size / conditions / duration
- With actives / inactives
  - of different qualities
  - of different sources

3.2 Number of formulations to be tested in vivo:
- Qualitative and quantitative formulations
- Batch size

3.3 In vitro testing model

3.4 In vivo testing model: animal/human

4. Analytical development
Development (new methods or adaptation of existing one) and validation of analytical methods for:

4.1 Active
4.1.1 active ingredient in dosage form:
- assay
- purity related to active
- biopharmaceutical testing method: (dissolution, profile, disintegration, other)
- stability testing method

4.1.2 active ingredient in biological samples
- active ingredient assay
- active metabolite(s) assay

4.2 Finished product quality control testing
- Quality control testing protocol
- release specifications
- shelf life specifications

5. Scale-up: Production scale

5.1 Scale-up batches:
- Number of formulations / Batch size / Number of batches per formulation

5.2 Pre-industrial batches:
- Produced on industrial scale equipment / Investigation of critical production parameters / Number of batches

6. Process validation: Production scale

6.1 Batches:
Validation of industrial process
- Number of batches / Batch size
- Production of stability and clinical trial batches for registration file
- Biobatch(es)

7. Stability studies

7.1 Active:
Number of batches / Packaging
- Accelerated: different sources, conditions, duration
- Real time: (different sources), conditions, duration

7.2 Pre-selected formulations:
Number of batches / Packaging
- accelerated (conditions, duration) and
- real time (conditions, duration) for lab *(see 3.)* and production scale batches *(see 6.)*

7.3 Selected formulation (for registration file):
Number of batches / Packaging
- Accelerated: conditions, duration
- Real time: conditions, duration for production scale batches *(see 6)*

8. Bioequivalence studies

8.1 Pilot bioequivalence:
Study with different formulations, produced on
- lab scale
- production scale

8.2 In vitro / in vivo correlation:
Establishing correlation between in vitro testing method and in vivo absorption profile (→ IVIVC = In vitro / in vivo correlation)

8.3 Final bioequivalence:
Study with final formulation produced on production scale (biobatch), *see 6.*

9. Registration
Preparation of the registration file
- according to EU (Notice to Applicants) / US (NDA) / other requirements
- partial file (e.g. chemical, biological and pharmaceutical part / CMC section)
- complete file

■

Results of the four project groups of the third postgraduate seminar for Pharmaceutical Quality Assurance, winter semester, 1993/94, Department of Pharmacy, Swiss Federal Institute of Technology (ETH), Zurich, and University of Basel, Pharmaceutical Faculty

Pharmaceutical Quality Assurance

Contract Packaging: Contract Orders in the Pharmaceutical Industry

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To meet the high expectations in the manufacture of pharmaceutical specialities, contract giver and contract acceptor must work together as true partners when undertaking packaging under contractual terms. In this context, it is important that requirements and responsibilities are clearly defined, agreed upon, fully met and documented. From the start, all arrangements must be foolproof to ensure that quality is guaranteed at all times and that unnecessary work, loss of time and excessive costs are avoided. The checklists and figures incorporated in this paper contain practice-oriented proposals.

To achieve true partnership, a consistent line of action must be pursued. Here again, examples are shown. The continuous process of improving the collaboration between the partners also represents a common opportunity to expand in the market and gain market share for both contract giver and contract acceptor.

Introduction

At a time when a high degree of supply readiness, flexibility, short run-through times as well as low costs are the norm (and also objectives of the pharmaceutical industry), contract packaging is of considerable importance. Lack of capacity, missing technology or cost advantages are the main reasons why packaging is contracted out to third parties.

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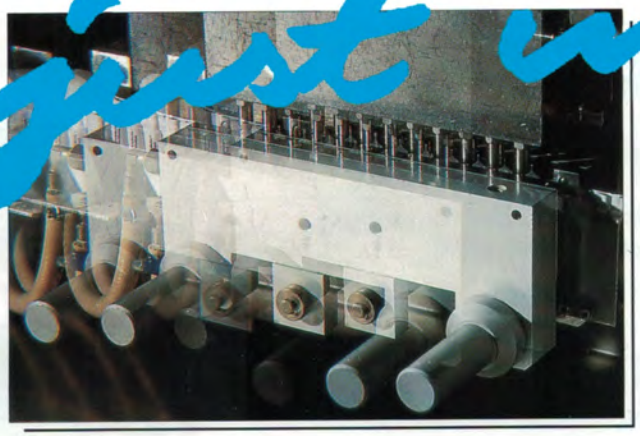
For the contract acceptor, the reaction times shrink continuously. From a GMP point of view, contract orders in principle represent an increased risk. However, the high demands made on the manufacture of pharmaceutical specialities are valid irrespective of whether or not a product is manufactured or packaged by a contract acceptor. It is therefore important that contract giver and contract acceptor together define, and meet, their obligations with respect to both the relevant legal and the GMP requirements. In addition, they must see to it that both sides ensure professional, reproducible processes.

Modern production philosophies such as "Total Quality Management", "Just in Time", "Lean Production", etc. call for increased cooperation between the partners, in accordance with the axiom that "the contract acceptor is part of the contract giver".

For contract acceptors, there are certain limits as far as standardization of processes and information systems are concerned. As a rule, they work for a number of clients, the latter having differing requirements and prerequisites. The opportunity for the contract acceptor lies in the capability of identifying or even creating mutualities and thus enabling processes and systems to be standardized.

Within the frame of our postgraduate seminar, we first determined the output and input functions of a contract packaging process, based on the process model of

...just in time



Auftragsherstellung :

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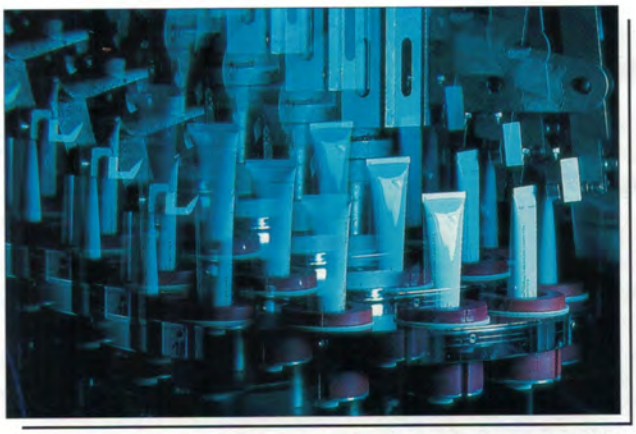
- Liquida
- Salben



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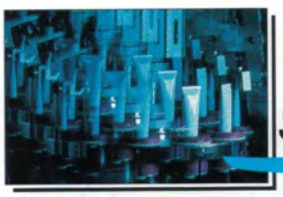

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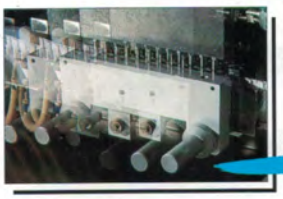

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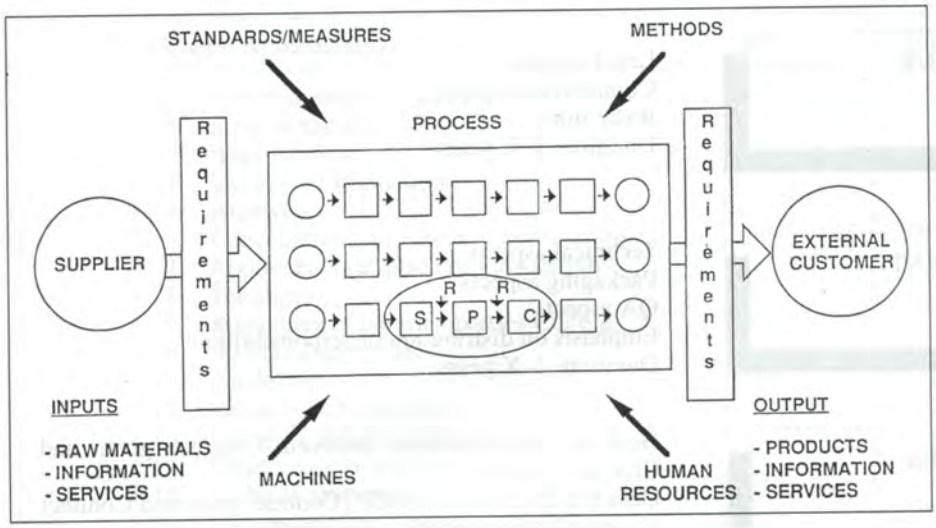

Fig. 1: Process Model

Framework Agreement/ General Conditions (Minimum Content)	OK	Comments
1. *Clear Definition of Contractor's Duties and Responsibilities* Most important point 2. *Quality Assurance* – Agreed Standards – Principal's right to perform audits at Contractor's site 3. *Price/Manufacturing Fee* 4. *Procurement of Raw material* – Material supplied by the Principal – Material supplied by the Contractor – Ownership/Waiver of Right of Retention 5. *Liability for Defects* – Rights and obligations of either party should the products delivered be defective – Loss of material supplied by the Principal 6. *Product Liability* Hold harmless clause? (If Pricipal accepts to hold Contractor harmless from product liability claims, he should make this subject to proof by the Contractor that there is no gross negligence on the part of the Contractor.) 7. *Exclusivities* – Secrecy obligations – Non-competition clause (only to the extent hat Contractor is using Principal's secret know-how) 8. *Use of Subcontractors* Right to use subcontractors should be subject to Principal's prior written approval 9. *Ownership of Work Result* If Contractor's duties include R&D functions Principal should make sure that any inventions/developments made shall belong to him and/or be transferred or assigned to him. Define whether and what additional remuneration Contractor shall receive for such inventions and developments 10. *Reference to Addenda* (Technical Agreement etc.) 11. *Duration* (Term/Termination) 12. *Applicable Law/Jurisdiction*		

Fig. 2: Framework Agreement/General Conditions (Minimum Content)

Crosby [4] *(Fig. 1)*. From the resulting list of functions, we then determined those functions which according to our own experience most frequently create problems in practice or which might be of particular interest for practical purposes. The following subjects were chosen:

Input requirements
- General Agreement (GA)
- Technical Agreement (TA)
- General Guidelines (GG)
- Product- or orders-specific requirements (POR)

Output requirements
- Documentation system CG <–> CA
- Electronic data exchange between CG <–> CA

The chance for a true partnership: a process
- Measuring and eliminating deviations
- Training of staff in the system CG <–> CA

In the following paragraphs these subjects are discussed in detail.

Input Requirements

Once cooperation between a contract giver and a contract acceptor has been agreed, the input requirements must be checked, confirmed and supplemented where necessary. The GMP guidelines of both EC [1] and PIC [2] call for a written agreement stipulating the manufacture or packaging by contract and describing all technical arrangements related to such contract manufacturing or packaging. Both guidelines prescribe in six sections which points should be included in such an agreement. In the course of our work, we studied and compared a number of different agreements. We came to the conclusion that the scope of contractual arrangements will depend on the partners and on the size of the contract order (e.g. value, duration, etc.). In our opinion, the items listed in *Fig. 2* should be considered minimum requirements. The IKS checklist [5] regulating the definition of responsibilities has proved to be a valuable instrument in this context. If it is intended to go beyond the minimum, we suggest referring to the modules shown in *Fig. 3:* these will facilitate the adjustment of individual modules to the actual state of a process. Using examples taken from practice, we examined which information might be included in which module (see *Fig. 4–7*). This led to the finding that some overlapping would be unavoidable: Certain requirements are specified in more than one module. There is a difference between them, however, depending on the degree of detail covered or the emphasis of their contents. It is therefore of advantage if both contract giver and

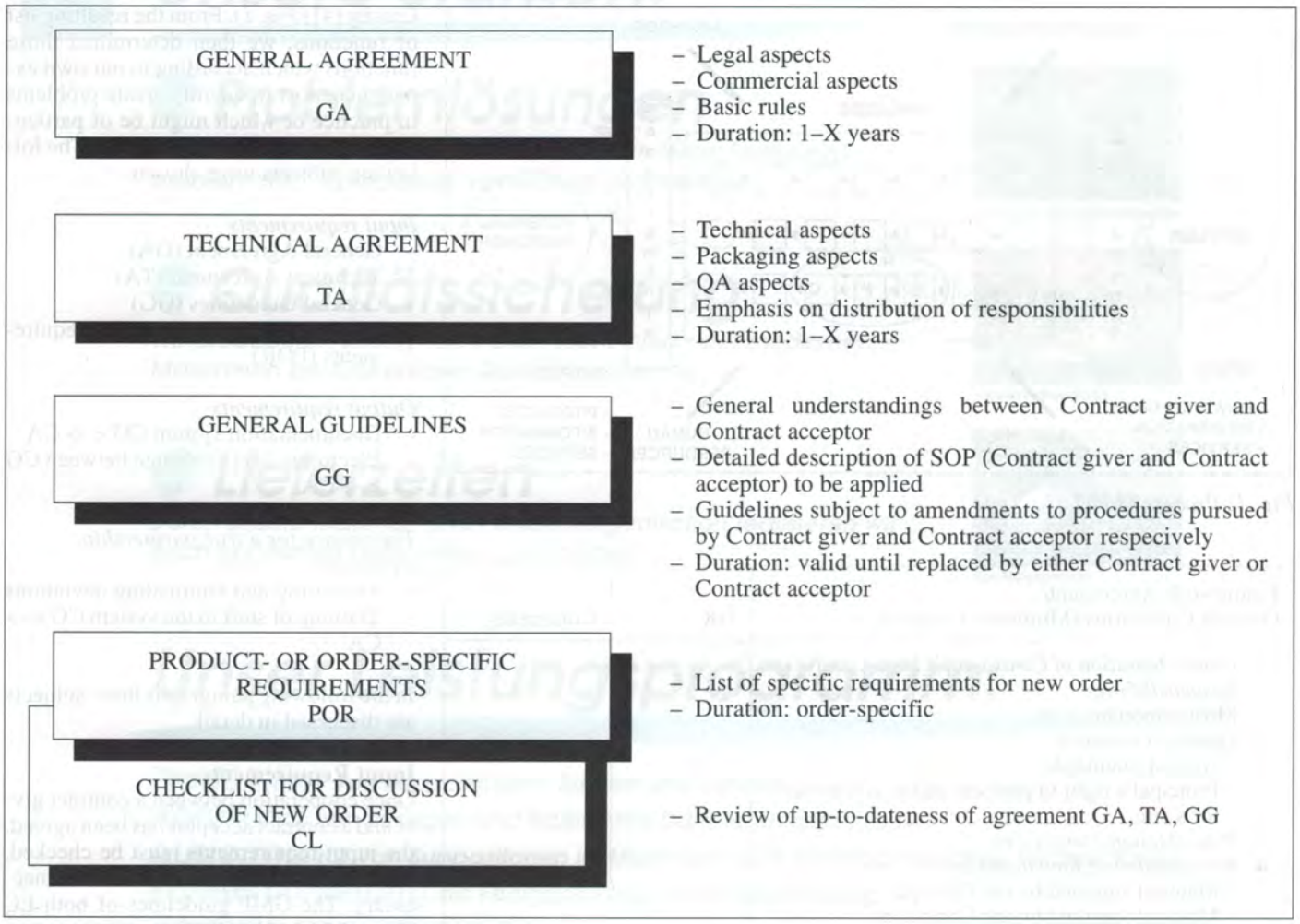

Fig. 3: Input Requirements (Modules)

contrat acceptor have such modules available in comprehensive detail. This will help save valuable time. The modules in their entirety must satisfy all legal as well as the latest GMP requirements. It follows that for the formulation of an agreement, both legal and technical experts should be available, the latter well-versed in pharmaceutical technologies, analytical methods and GMP rule [1] (section 7.10, page 61).

General Agreement (see *Fig. 4*)
When studying those sections of the EC and PIC guidelines dealing with agreement, it becomes apparent that it is useful to draw up separate General and Technical Agreements, whereby the contents of the General Agreement should treat the commercial and legal aspects of the contract.

Technical Agreement (see *Fig. 5*)
This part-agreement regulates, as its name implies, primarily the technical aspects as described in sections 7.10 through 7.15 of the EC guidelines [1]. It clearly stipulates the responsibilities of both partners. To define these responsibilities to advantage, it is recommended to use the matrix form shown in *Fig. 12.*

General Guidelines (see *Fig. 6*)
These guidelines should offer the possibility of regulating important details which, in our opinion, would otherwise overload the contents of the General and/or the Technical Agreement. Such details also comprise activities which are subject to frequent change and can be adapted more easily within the scope of this separate module.

Product- or order-specific Requirements (see *Fig. 7*)
To avoid unpleasant surprises and unnecessary extra work, it is important to specify from the start, mutually and clearly, all product- or order-specific requirements. This can prevent extra costs or supply problems from arising. It is suggested that checklists be used during partner negotiations. In our case, we assumed that contract giver and contract acceptor had already cooperated in the past. The objective of the discussion should therefore be to clarify the product- or order-specific requirements. At the same time, the opportunity should be used to review the other agreement modules as well. The product- or order-specific requirements necessitate distinguishing between a "commercial" and a "technical" part as well.

- *Order/Order confirmation:* In general, the contract giver will submit an order which will be confirmed by the contract acceptor. The order permits the contract acceptor to reserve capacities; both partners are then ready to proceed to the stage of preparing for the work.
- *Packaging instructions:* The scope of the requirements will depend on the length of cooperation already existing between contract giver and contract acceptor. The data are kept by the contract giver in a master file; the relevant guidelines (e.g. GHP Guide EC [1]; section 4.16, page 37) must be taken into due consideration. To ensure that the data are always up-to-date, they should be printed out at the latest possible time (e.g. when goods are prepared for delivery).

General Agreement GA	OK	Comments
1. Contract parties CG/CA		
2. Subject matter		
3. Applicability		
4. Validity of stipulations		
5. Annexes		
6. Cancellation and notice of termination		
7. Applicable law, place of jurisdiction		
8. Duration		
9. Signatures of contract parties CG/CA		
10. Required approvals		
11. Guidelines		
12. Commercial conditions		
13. Delay of delivery dates		
14. Observance of secrecy		
15. Liability insurance		
16. Patents and know-how		
17. Liability for damages CG/CA		
18. Development of packaging/transfer of technology		
19. Packaging (plant, machinery, equipment)		
20. Inspection right of CG		
21. Responsibilities		
22. Subcontracting to third parties		
23. Duty of information relating to special packaging risks		
24. Submission of order to CA		
25. Lending equipment etc. to CA		
26. Obligation to exercise due care		
27. Liability insurance for equipment lent (fire, water, theft)		
28. Required ISO certificates/QA norms		
29. Duty of CA to inform CG about complaints		
30. Responsibility for recalling products		
31. Excluded product groups		
32. Handling of defective lots		
33. Storing guidelines		
34. Theft of material		
35. Loss of material on the premises of CA		
36. Inventory of goods held by CA		
37. Quality assurance		
38. Batch records		
39. Filing of documents by CA		
40. Releasing procedure		
41. Information about special occurrences		

Fig. 4: General Agreement GA

Output Requirements

The product is probably the most obvious output element of a contract order. Its properties have to meet the agreed upon and registered specifications. The quality of the documentation covering the manufacture and packaging of pharmaceutical products is of equal importance. We have chosen the Batch Records as an example.

- *Batch Packaging Records:* It must be emphasized that a contract acceptor cannot be expected to adjust his batch packaging records to the individual requirements of all clients; he must be able to standardize. The contract acceptor's batch packaging records must, together with the contract giver's product- or order-specific requirements, amount to a complete documentation which meets the official requirements (see *e.g. [1], section 4.18, pages 39–41),* and the documentation must clearly state who is responsible for which tasks. *Fig. 8* shows a model example.
- *Data transfer by computerized system:* By adopting the axiom "contract acceptor as part of contract giver", the contract giver will endeavor to rely on as few contract acceptors as possible. With these, he will build up the best professional system of cooperation possible. This can be achieved, for instance, by using Electronic Data Processing networks. The companies of the authors of this postgraduate seminar paper already introduced such a concept serveral years ago. *Fig. 9* shows the diagram of their Electronic Data Processing network. This solution has the advantage of permitting a fast data flow. By avoiding multiple inputs, errors are minimized. The contract acceptor can proceed with the accommodation immediately after having completed an order. He will be able to pinpoint inconsistencies without delay and clarify and correct them on the spot.

Technical Agreement TA	OK	Comments
1. Contract parties CG/CA		
2. Subject matter		
3. Signatures of contract parties CG/CA		
4. Manufacturing (packaging) authorization		
5. Packaging (plant, machinery, equipment)		
6. Packaging instructions		
7. Responsibility for bulk material		
8. Responsibility for primary packaging material		
9. Responsibility for secondary packaging material		
10. Responsibility for text and design		
11. Responsibility for batch records		
12. Responsibility for final check of finished product		
13. Responsibility for release (each individual step)		
14. Responsibility for transport		
15. Responsibility for qualification (equipment etc.)		
16. Responsibility for calibration		
17. Responsibility for training of staff		
18. Responsibility for allocating batch numbers		
19. Control of packaging material		
20. Test documentation from CA to CG		
21. Drawing of reference samples for CG		
22. Drawing of reference samples for CA		
23. Storage of reference samples		
24. Accommodation of packaging material components		
25. Internal guidelines CA		
26. Marking of products		
27. Handling of complaints		
28. Handling of rejected bulk		
29. Handling of rejected packaging material		
30. Retesting of regenerated products		
31. Sampling system		
32. Scope of traceability		
33. Accounting for use of material in excess of plan		
34. Inventory of goods held by CA		
35. Delay of delivery dates		
36. Preventive maintenance/service of equipment lent to CA		
37. Transport guidelines		
38. Guidelines regarding information on dangers and risks		
39. Storage guidelines		
40. Delivery notes		
41. Delivery address		
42. Supply procedure		

Fig. 5: Technical Agreement TA

The Chance for a true Partnership: a Process

Our paper deals at length with the mutual understanding of requirements. It is essential that during the process of cooperation between contract giver and contract acceptor these requirements are actually met. Crosby [4] defines "quality" as "in line with the requirements". Based on a zero-defect strategy, deviations from requirements must be measured and then eliminated together; the conclusions drawn will help to prevent reoccurrences. Experience teaches that the measurement of deviations will result in objectifying and analysing problems, for which it then becomes easier to find solutions. *Fig. 10* shows an example of a possible measurement by contract giver and contract acceptor.

In the final analysis, the process of meeting the requirements and applying the Total Quality Management concept can be realized only if both contract giver and

General Guidelines GG	OK	Comments
1. Contract addresses CG/CA 2. Rules for exchange of documents between contracting parties 3. Submission of analytical and reference samples to CG 4. Delivery notes 5. Delivery address 6. Supply of goods by CG 7. Submission of documents by CG 8. Requirements regarding batch records 9. Minimum batch records required 10. Filing of original documents 11. Disposal of residual material and waste 12. Duration of storing reference samples 13. Printed packaging material: approval of printing details 14. Weight limits (legal requirement) 15. Marking of goods 16. Clearance certificate issued by foil suppliers 17. Guidelines regarding access to plant and control thereof 18. Guidelines regarding quarantine 19. Use of residual material 20. Batch numbering system 21. Regulations regarding health and hygiene 22. Restricted areas reserved for rejected goods 23. Accommodation of packaging material components 24. Handling of waste 25. Handling of goods to be returned 26. Concept of training staff (both contract parties) 27. Procedure for handling complaints 28. Palletizing and marking of finished products 29. Storage of bulk and packaging materials 30. Report on production failures 31. Signatures list of staff		

Fig. 6: General Guidelines GG

Product- or order-specific requirements POR	OK	Comments
1. Product number 2. Product description 3. Order number 4. Quantity 5. Delivery date 6. List of items 7. Specification of outer packaging material 8. Specification for marking outer packaging material 9. Guidelines for palletizing 10. IPC-controls 11. Composition of batch records 12. Weight limits for filling 13. Sampling for CG		

Fig. 7: Product- or order-specific requirements POR

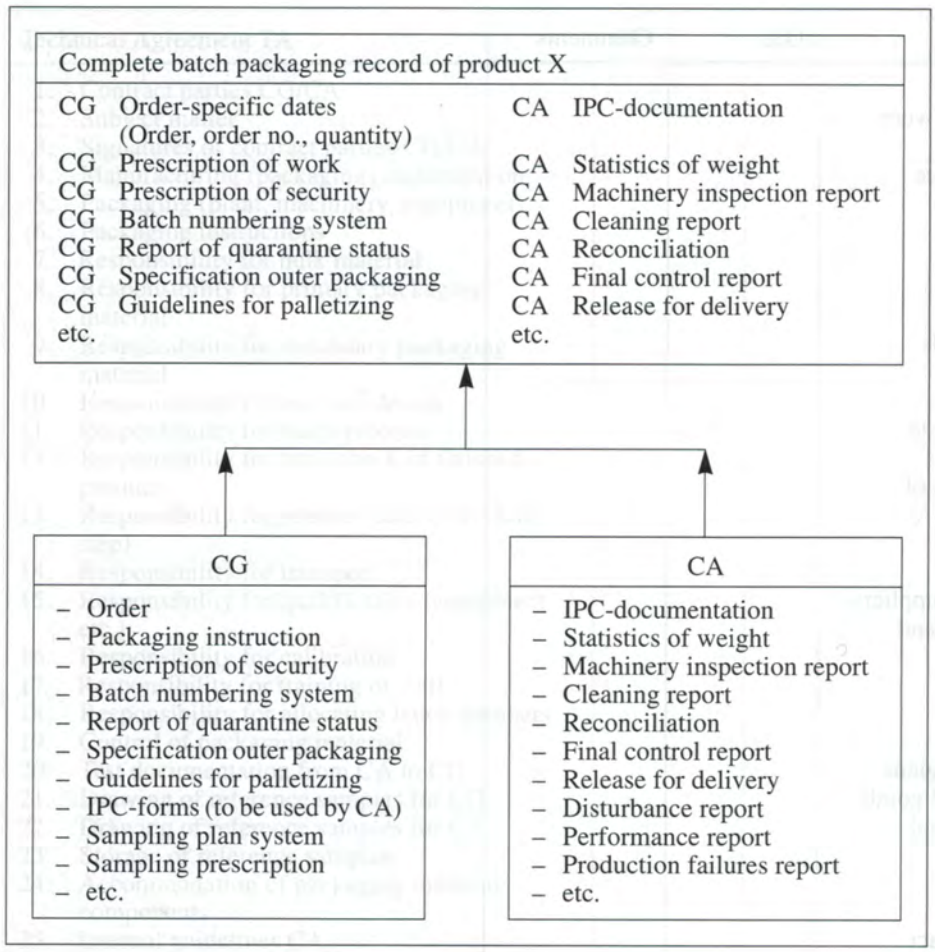

Fig. 8: Batch Packaging Record

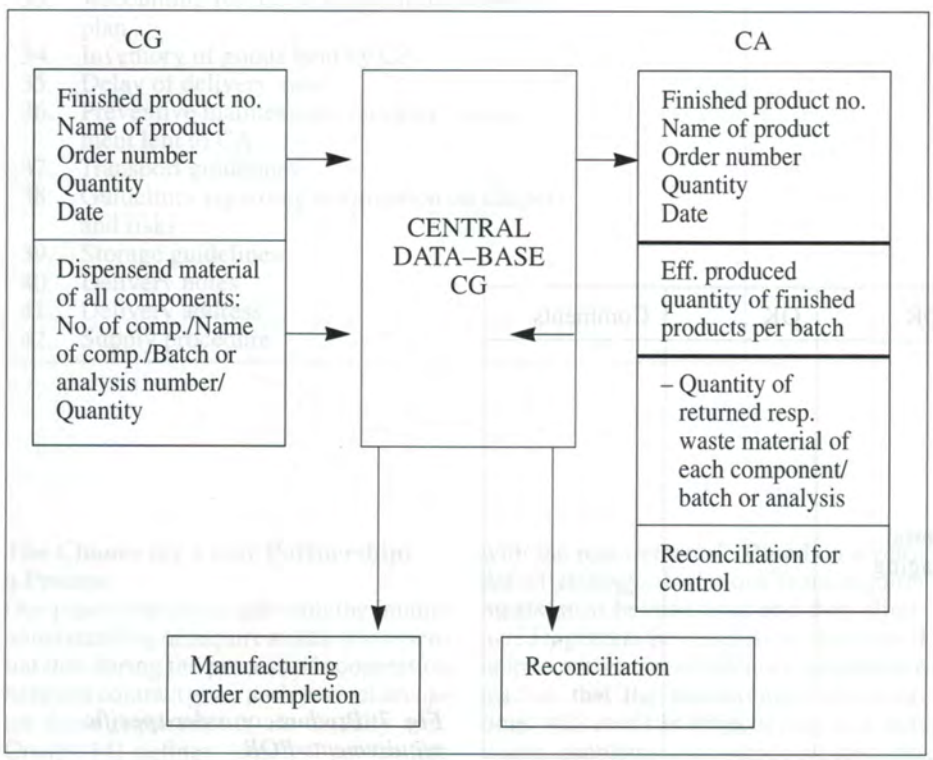

Fig. 9: Data transfer by computerized system

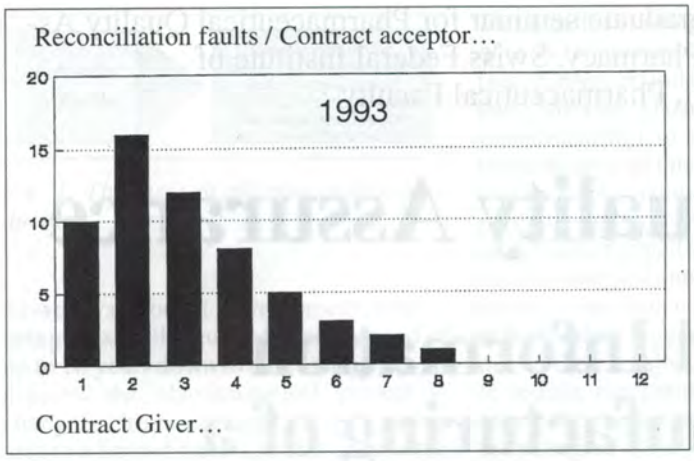

Fig. 10: Measuring deviations

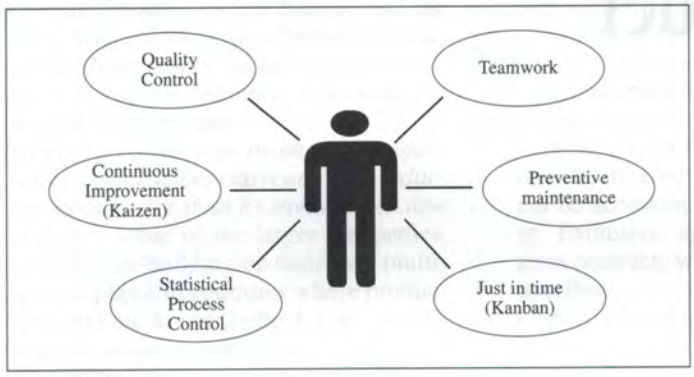

Fig. 11: Modern Production Employee

Subject	Responsibility CG	CA
General GMP training		X
Hygiene training		X
Workstation specific training		X
Training of servicing staff		X
Training of cleaning staff		X
Qualification / Calibration	X	
Batch records	X	
Training EDP System	X	
IPC Methods	X	
QC Methods	X	

Fig. 12: Possible regulation of responsibilities in the field of training

contract acceptor employ qualified staff as per *Fig. 11*. Continuous training is of paramount importance – reason enough to emphasize this aspect in our paper. Training beyond entrepreneurial needs offers an excellent opportunity to cement the partnership between contract giver and contract acceptor. It goes without saying that field staff should be included in such training programs.

The overall responsibility for the quality and professionalism of the personnel used in a process for which such personnel has been specifically trained clearly lies with the contract giver (as per [1], sections 2.8 and 2.9, page 24). During audits, current training standards and the relevant documentation should be reviewed. Depending on the findings or if problems arise, contract giver and contract acceptor must agree on the steps to be taken to close possible gaps and determine the responsibility for respective actions. If longer-term regulations are involved, they can be added to the Technical Agreement in matrix form [5] (see *Fig. 12*).

Literature

[1] The Rules Governing Medicinal Products in the European Community, Volume IV, Guide to Good Manufacturing Practice for Medicinal Products, 1990.

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■

Results of the four project groups of the third postgraduate seminar for Pharmaceutical Quality Assurance, winter semester, 1993/94, Department of Pharmacy, Swiss Federal Institute of Technology (ETH), Zurich, and University of Basel, Pharmaceutical Faculty

Pharmaceutical Quality Assurance

Flow of Materials and Information during Contract Manufacturing of a Pharmaceutical Product

*R. Laforce, C. Stampfli**

This survey study investigates the flow of materials and information between one Contract Giver and two Contract Acceptors for contract manufacturing of pharmaceutical bulk active and a pharmaceutical bulk product. Pros and cons of a "make or buy" decision by the Contract Giver are discussed. A model flow chart was worked out in order to depict and discuss the flow of materials and information. Critical steps for quality assurance during contract manufacturing were identified as: the contract between the Contract Giver and the Contract Acceptor, the know-how transfer phase, the implementation of the production process, process validation, production on industrial scale and In-Process-Control (IPC), process documentation, as well as complaints and product recall. Practical examples were shown in order to illustrate the statements made.

A changing environment in the pharmaceutical markets, brought about by government-imposed price cuts and the resultant need to adapt company structures to new conditions, makes the outsourcing of pharmaceutical production increasingly important.

Introduction

Make or Buy: Outsourcing as an alternative to captive production

Quality Assurance in pharmaceutical production is maybe the most important part within those areas where quality assurance is necessary (like Research & Development [R&D], Evaluation or Packaging). During production the essential steps take place that yield the final product. The molecular structure of the active principle is built, and the active ingredient is brought into an adequate form for the application at the correct dosage. Deviations in quality can severely impair the pharmacological activity of the final product or can harm the health or even the life of the patient.

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Intrinsic quality is affected by essential defects in a product that can cause risks and harm to the patient [1], i.e. the use or the content of an isomer in chemical synthesis for bulk active production or the wrong dosage during galenic production (e.g. a dosage of 82 mg instead of 100 mg per tablet). Slight colour deviations or the wrong carton for product packing, for example, not directly causing harm to the patient, can be regarded as *extrinsic quality* problems. In general, a trace of sucrose in a capsule containing lactose would not cause harm or signify a health risk. (Of course, the product would not be in conformity with the required specifications.)

The tasks of pharmaceutical production can be defined as the implementation of R&D methods (scale-up), manufacturing, and supply to the next steps in product flow [16] *(Fig. 1)*.

The classical European companies such as the well-known multinational pharmaceutical-chemical groups possess enormous in-house production capacities. At the same time there are at least 250 companies that offer contract manufacturing for chemical and pharmaceutical active ingredients and intermediates, providing a wide range of compounds, chemical reactions and special equipment. The total market for this branch was estimated to be US$ 12.5 billion in 1992 [2].

There must exist obvious advantages in outsourcing pharmaceutical production.

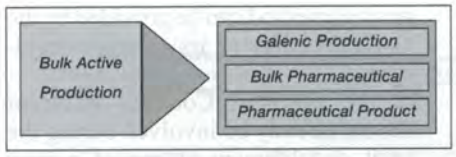

Fig. 1: The tasks of pharmaceutical production

Nowadays product development time is being drastically reduced from a period of up to 10 years down to half as long [3]. At present, the pharmaceutical market is changing from an expanding business area to a limited market, mainly due to the cost-cutting measures imposed by many governments in Western Europe and the USA. *Bigger investments for new production facilities can be avoided* by outsourcing, and captive resources then used for product development.

In existing plants, new products manufactured by contractors can reach the production stage faster than by investing in new facilities. Some of the larger companies, however, are building up their own multipurpose plants in countries where production costs are lower (Ireland, UK), thanks to lower salaries and investment incentives offered by the governments of these countries.

In the case of a slow-growth or shrinking market, collaboration with custom manufacturers gives *materials management* greater flexibility since reducing order sizes or even cancelling orders in case of changed material requirements is easier than jettisoning company owned plants and dismissing employees. Today, many multinational pharmaceutical companies tend to keep free their in-house capacities for products in earlier stages of development and to contract out in phase III and later. On the other hand, if the captive capacities are fully occupied, contract manufacturers can offer *short-term access to adequate production resources.*

Often a company does not want to forgo selling a product with a small market, even if the total production volume is too small for captive manufacturing. In such a case, outsourcing can become an attractive alternative. In general, captive R&D and production capacity can be expanded by collaboration with contract developers or manufacturers, and investments are not necessary. Thus, especially in times of well utilized production capacities, contract manufacturers can be regarded as an extension of captive production, while in periods of overcapacities outsourced production can be transferred back to in-house production plants.

Contract manufacturers offer a wide range of different chemical reactions, intermediates and raw materials as well as services for product development and registration. Through this existing know-how *the range of available technologies can be extended* (e.g. in Switzerland there is only one company offering phosgenation for contract manufacturing), or a product may be synthesized up to an intermediate step by classical organic chemistry, and subsequently particular modifications of the molecule could be performed using enzyme technology. In general, contract manufacturers are faster in the implementation of new technologies than bigger chemical companies due to their smaller size and the pressure to remain competitive. For the Contract Giver this means readier access to new technologies (Butyl-Lithium chemistry, low temperature reactions, new catalysers for bulk active production, or new drug delivery systems in galenic manufacturing). Obstacles to contracting out bulk active and pharmaceutical production should also be mentioned:

- Particular steps of know-how, if developed by the contract manufacturer, will not be accessible to the Contract Giver. Exclusive agreements and long-term contracts will prevent know-how overflow.
- Control over the flow of strategic raw materials and intermediates can be more difficult, although material and information flow between divisons within the same company can also be very complex.
- Because the final responsibility for product quality has to be taken by the company that submits the registration documents for a pharmaceutical product, quality control and quality assurance have to be highly developed within the organisation of the Contract Giver; large companies have more resources to maintain staff trained for the auditing of contract manufacturers.

However, the existence of a considerable number of contract manufacturers in bulk active production and galenic manufacturing – and most of these companies are well established in this market – shows that contract manufacturing is still an attractive business proposition.

Scope of the study

The present study aims to explain crucial steps in pharmaceutical contract manufacturing of bulk active and galenic products for human use with respect to quality assurance and to ask questions as well as to propose answers concerning where improvements were found to be necessary (for the particular situation of contract manufacturers in Switzerland). It was not our ambition to do an exhaustive study but to cover certain aspects of this highly important and interesting sector of pharmaceutical manufacturing. The scope of this study is to investigate the flow of materials and information between the Contract Giver and the Contract Acceptors in chemical manufacturing and galenic production and to point out still unresolved problems. Different aspects of Quality Assurance in Contract Production are identified and discussed under the headings of *Bulk Active Contract Manufacturing and Quality*

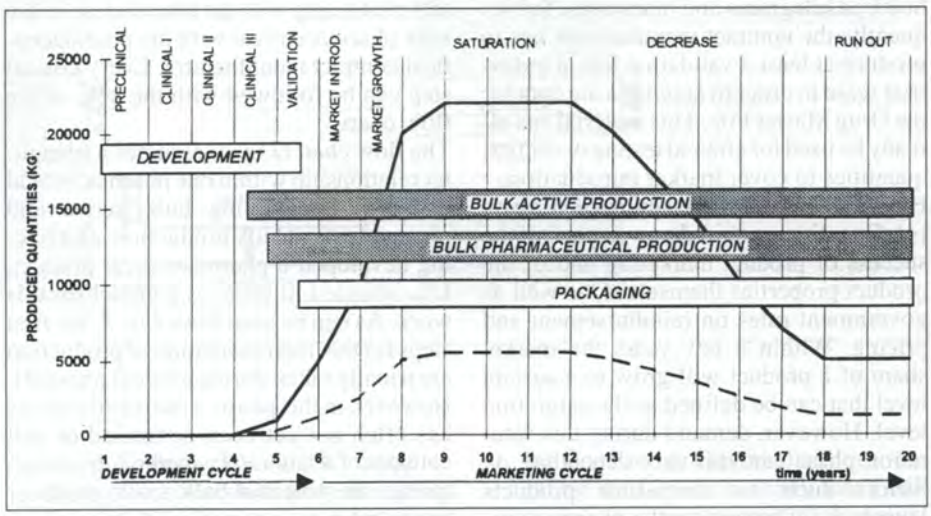

Fig. 2: Schematic representation of the life cycle of a pharmaceutical product with growth and decrease curves for bulk active (broken line) and bulk pharmaceutical production volumes (full line). The highlighted activities are the subject of this publication. The time from the pre-clinical stage up to the production of trial and validation lots is defined as Development Cycle (quantities controlled by the Contract Giver), while the remaining time is defined as Marketing Cycle (quantities according to market demand). The total product lifetime depends highly on the particular product and cannot be generalized [4]. The share of the active ingredient was assumed to be 1/4 of the total quantities of formulated product.

Assurance and *Bulk Pharmaceutical Contract Manufacturing and Quality Assurance.* Solutions for selected problems are proposed. As fas as possible practical examples are shown.

Product Life and Production

Every product goes through its particular life cycle. Although there is no typical lifetime for a pharmaceutical product, it is possible to define different stages in its life. In general, a pharmaceutical product shows a controlled growth (with respect to production volumes) during the development phases, as shown in *Fig. 2.* The development phase includes pre-clinical and clinical stages I–III and the validation phase. During these stages, the amounts of product required are prescribed by the Contract Giver. The quantities required in earlier clinical phases today are larger than a few years ago. As a result, a contract manufacturing project can already become commercially interesting in clinical phase III.

In early or late phase III, sometimes already in phase II, a contract manufacturer is contacted by the Contract Giver. Up to this stage, lasting 3 to 5 years, he may have collaborated with a R&D contractor. In phase III potential contract producer and at the same time galenic manufacturers start their evaluation of the project to be contracted in. After the synthesis of laboratory quantities in order to show competence and to test the information and know-how received from the Contract Giver, pilot and trial lots are produced. These quantities may vary between a few hundred kilograms and many tons. Subsequently, the contract manufacturer has to produce at least 3 validation lots at industrial scale in order to assemble the data for the Drug Master File. This material can already be used for clinical testing or for first quantities to cover market introduction.

From this stage, the marketing cycle starts [4]. Quantities required now depend of the success of product marketing and of the product properties themselves, as well as government rules on reimbursement and pricing. Within a few years the market share of a product will grow to a certain level that can be defined as the saturation level. However, demand during this saturation phase can still vary depending on factors such as competitor products launched, influences on the pharmaceutical market of government action (cost cutting, reimbursement listings), or the introduction of a new galenic form of the same active principle. As is known to almost everybody familiar with pharmaceutical production, one of the longest life cycles observed so far has been that of Aspirin (first sold in 1899 by Merck [5]). Other products may be on the market for 10–15 years and then disappear. During the run-out phase, after the termination of the product patents, generic products will appear and compete with the original. During the decrease and run-out phase sales tend to fall to a certain level and to hold this level for several years. Such products may be replaced by more advanced pharmaceuticals or taken off the market because they are no longer commercially interesting.

This study deals with the *production phase,* starting during clinical phase III and – at least for a contract manufacturer – ending during the decrease or run-out phase. However, a potential contract manufacturer may already be involved in preparatory work in the pre-clinical stage or in phase II. (Other stages of product development and manufacturing such as contract development and packaging of pharmaceutical products were investigated by the other groups of this Seminar.)

Quality Assurance during pharmaceutical production

1. The overall flow chart

In order to visualise the complex network of materials and information flow between the involved parties, in our case between *one Contract Giver* and *two Contract Acceptors* for *bulk active* and *pharmaceutical bulk production* of gelatine capsules, an overall flow chart was worked out. In the following chapters we describe the critical points and milestones for quality assurance during the production of a pharmaceutical product, beginning with the implementation of bulk active production and continuing with the formulation of the bulk pharmaceutical with the pharmaceutical contract manufacturer. Every critical step can be followed with the help of the flow chart.

The flow chart *(Fig. 3)* assumes a triangular relationship within one pharmaceutical company outsourcing bulk active and pharmaceutical bulk production after having developed a pharmaceutical product. It is intended to serve as a model for this work. As can be seen from *Fig. 2,* the first steps for the implementation of production are usually taken during clinical phase III. However, in this phase, a chemical process has often not yet been optimized or still consists of a laboratory method. In consequence the potential bulk active producer has to take over a method that is not always suitable for industrial production or a pharmaceutical bulk manufacturer has to apply a recipe that will undergo modifications as process implementation progresses. On the other hand, an already registered method cannot be changed. As a first statement it can therefore be said that ideally

- a potential contract manufacturer should only be involved if a reliable industrial method can be provided by the Contract Giver or its contract developer;
- or the potential Contract Acceptor should already be involved during the final development stages of a new product. In this case, it goes without saying that the Contract Giver has to take over the quantifiable risk of such a development and should cover development costs and costs arising from the establishment of registration documentation. Many Contract Givers still expect that a future manufacturer should assume these costs at his own risk. In general, however, a production-oriented manufacturer has only a limited laboratory capacity and should select those projects which hold out the highest probability of commercial realization. Since this is a commercial and a capacity problem, it should be resolvable. As a rule, a potential contract manufacturer should at least provide a laboratory sample in order to prove ability to carry out a desired production.

It can be seen from the flow chart *in Figure 3* that most of the *important activities,* also with respect to Quality Assurance, take place during *process implementation.* The preparatory work required to start up an industrial contract production is therefore cost- and time-intensive, and the Contract Acceptor may risk losing the project during the implementation phase, owing to several factors discussed in the chapter *Implementation of the production process.*

2. Critical steps for Quality Assurance

a) The contract between Contract Giver and Contract Acceptor

Communication problems in contract manufacturing can be a risk for the quality of the product. In order to minimize the risk, a written contract between the Contract Giver and the Contract Acceptor should be the basis for a successful collaboration. The obligations of both sides have to be clearly defined [6]. Such a contract can be drawn up in two parts. In the main, the first part is a basis document (skeleton agreement) outlining general conditions. The second part can be a product-specific agreement. In this section, important aspects that should be considered and that can have an influence on product quality are described and discussed. The *skeleton agreement* covers the following obligations of the Contract Acceptor:

- The Contract Acceptor affirms that he holds a manufacturing authorization for pharmaceutical products.
- The Contract Acceptor commits himself to carrying out the production by

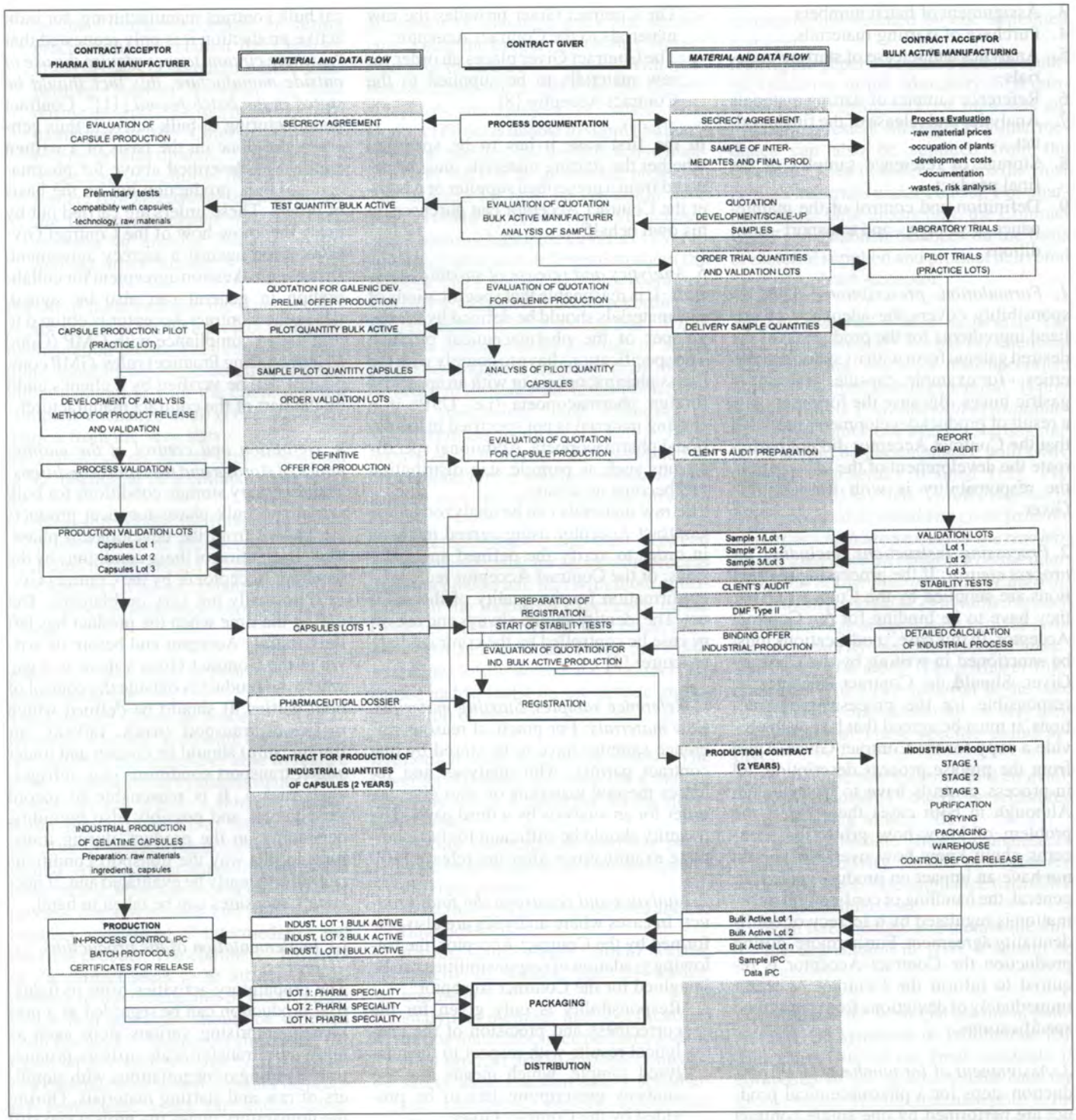

Fig. 3: The flow chart

taking into account and respecting approved pharmaceutical rules and relevant regulations and recommendations of official organizations such as:
Guidelines of the Swiss Drug Regulation authority (IKS, Interkantonale Kontrollstelle für Heilmittel) regarding the manufacturing of pharmaceutical products [7], convention for the mutual recognition of inspection in respect of the manufacture of pharmaceutical products [6], product specific manufacturing formula, processing instructions and testing procedures. The contract manufacturer must not deviate from the agreed product-specific manufacturing formula, processing instructions and testing procedures without written consent of the Contract Giver. Product-specific conditions are, for example, defined by prescriptions and specifications.

- Subcontracting by the Contract Acceptor must be sanctioned by the written agreement of the Contract Giver [6].
- The Contract Giver has to be granted access to the product-relevant areas of the Contract Acceptor's facilities, enabling the former to verify that GMP guidelines are respected. This regulation forms the basis for the Contract Giver's obligation to verify the competence of the Contract Acceptor.

The product-specific part of the agreement defines tasks and responsibilities with regard to the following points:

1. Formulation, prescriptions
2. Processing instructions, In-process control (IPC)

3. Assignment of batch numbers
4. Purchase of starting materials
5. Analytics and release of starting materials
6. Reference samples of starting materials
7. Analytics and release of the final product
8. Storage of reference samples of the final product
9. Definition and control of the maintenance of storage – and transport – conditions

1. Formulation, prescriptions: This responsibility covers the adequacy of utilized ingredients for the production of the desired galenic form with its specific properties – for example, capsules resistant to gastric juices. Because the formulation is a result of product development, provided that the Contract Acceptor did not participate the development of the formulation, the responsibility is with the Contract Giver.

2. Processing instructions, including in-process control: If the processing instructions are supplied by the Contract Giver, they have to be binding for the Contract Acceptor. In this case, modifications must be sanctioned in writing by the Contract Giver. Should the Contract Acceptor be responsible for the processing instructions, it must be agreed that he has to provide a copy for the Contract Giver. Apart from the precise process description, all in-process controls have to be included. Although in both cases there exists the problem of know-how protection, concerns about know-how overflow should not have an impact on product quality. In general, the handling of confidential information is regulated by a secrecy or confidentiality agreement. Furthermore, during production the Contract Acceptor is required to inform the Contract Acceptor immediately of deviations from the agreed specifications.

3. Assignment of lot numbers: If all production steps for a pharmaceutical product are performed by one single contract manufacturer, it may be reasonable for practical reasons for the contract manufacturer to provide lot numbers as well. However, measures should be taken not to assign the same lot number twice to different production lots. This risk mainly exists when the Contract Giver is producing the same product in-house and at the same time it is produced by a contract manufacturer.

4. Purchase of starting materials: There are three ways of starting material sourcing:
- The contract manufacturer buys directly from the market.
- The Contract Giver provides the raw materials to the Contract Acceptor.
- The Contract Giver places an order for raw materials to be supplied to the Contract Acceptor [8].

In the first case it has to be specified whether the starting materials must be ordered from a prescribed supplier or whether the Contract Acceptor can purchase on his own behalf.

5. Analytics and release of starting materials: It is reasonable that specifications of raw materials should be defined by the developer of the pharmaceutical product. The specifications have to comply with the Swiss pharmacopoeia or with an approved foreign pharmacopoeia (i.e. USP) if a starting material is not specified in the national pharmacopoeia. Additional specifications such as particle size distribution can become necessary.
The raw materials can be analyzed by the Contract Acceptor using agreed methods in order to verify the defined specifications; or the Contract Acceptor receives a confirmation for the quality of the product. The identity should always and in every case be controlled by the contract manufacturer [9].

6. Reference samples, Starting materials, Raw materials: For practical reasons reference samples have to be stored by that contract partner, who analyses and releases the raw materials or who gives an order for an analysis by a third party. The quantity should be sufficient for two complete examinations after the release [10].

7. Analytics and release of the final product: In cases where analytics are also performed by the Contract Acceptor, the following gradation of responsibilities can be imagined for the Contract Acceptor:
- Responsibility is only given for the correctness and precision of the analytical results with respect to the analysed sample, which means that the analysis prescription has to be provided by the Contract Giver;
- additionally for the suitability of the analytical prescription, if he himself is elaborating the prescription;
- additional responsibility for sampling;
- the release of the product [9].

8. Storage of reference samples of the final product: Even if the production is completely executed by the Contract Acceptor, the reference sample should be stored by both parties for cases of post-production requests or for the elaboration of stability data.
While PIC (Pharmaceutical Inspection Convention) recommendations [6] prescribe a written contract for pharmaceutical bulk contract manufacturing, for bulk active production it is only requested that "*...where circumstances require the use of outside manufacture, this fact should be stated in the batch record* [11]". Contract manufacturing of bulk active is thus generally not done on the basis of a written contract as described above for pharmaceutical bulk production but on the basis of orders. These orders are carried out by using the know-how of the Contract Giver received against a secrecy agreement. However, a skeleton agreement for collaboration in general can also be signed, where the Contract Acceptor is obliged to produce in compliance with GMP (Good Manufacturing Practice) rules. GMP compliance can be verified by a client's audit on the part of the contract manufacturer.

9. Definition and control of the maintenance of storage and transport conditions: The necessary storage conditions for bulk active and bulk pharmaceutical products are known from the development phase. The observation of these conditions by the Contract Acceptor or by the Contract Giver is normally not very problematic. But during the time when the product has left the Contract Acceptor and before its arrival at the Contract Giver's there is a gap where the product is outside the control of both parties. It should be defined which means of transport (truck, railway, air freight, ship) should be chosen and under which transport conditions (e.g. refrigerated trucks). It is reasonable to record temperature and possibly also humidity, depending on the product, during transport. In this way the transport conditions can subsequently be evaluated and, if necessary, measures can be taken in hand.

b) Implementation of the production process

The preparatory activities prior to industrial production can be regarded as a prephase comprising various steps such as know-how transfer, scale-up tests, production planning or negotiations with suppliers of raw and starting materials. During the preparatory phase the project can still fail due to factors that can only partly be influenced by the Contract Acceptor:
- Alteration or shutdown of the client's project, e.g.: A new chemical route has been chosen that cannot be performed by the actual Contract Acceptor (such as very hazardous reaction types offered by only few competitors).
- *There are registration problems.*
- Market projections drop due to unexpected governmental restrictions.
- *The marketing of the Contract Giver decides to switch to another formulation (change of pharmaceutical manufacturer).*
- Yields or qualities cannot be achieved

by the Contract Acceptor, or during process implementation the Contract Giver decides in favour of a more competitive Contract Acceptor. At least during the initial phases of process implementation the Contract Giver is testing several options.
- *A detailed calculation shows that the project is of no commercial interest for the Contract Acceptor (low margins, increase of starting material costs, non-repetitive business).*

For all of these reasons, the Contract Acceptor may risk losing a project in the implementation phase. The internal evaluation should therefore be based on a trusting collaboration with the client and the complete exchange of all necessary information from the very start.
Several questions should already be asked at the beginning of a collaboration, such as:
- Who will assume the financial risk if a project has to be abandoned?
- From which project stage should the Contract Giver participate in the costs of process implementation and scale-up?

Example: Case Study of Process Implementation
The Contract Giver, an academic-minded research company, is looking for a bulk active contract manufacturer able to realize a four-step chemical synthesis under GMP conditions and selects a suitable partner. Know-how is given to the Contract Acceptor after a secrecy agreement has been signed. After a paper feasibility study the Bulk Active Manufacturer decides to start process implementation and produces laboratory samples of all intermediates and the final product. The commercial aspects of the project seem to be attractive. According to the scheduling of the Contract Giver, first quantities should be supplied soon for market testing. At this point, the Contract Acceptor realizes from laboratory experiments that step 3 cannot be properly reproduced, yields vary and by-products are formed. The Contract Acceptor insists that he should first clarify step 3 of the synthesis. A study of the data available with the Contract Giver reveals that the same problem had already occurred during their pilot but had not been regarded as serious.
For proper process implementation the Contract Acceptor hedges his decision to pursue the project to the successful development of step 3. The Contract Giver comes under pressure from his client, since the trial quantities are required for market studies. Negotiations between Contract Giver and Acceptor become strained. The Contract Acceptor insists on the reproducibility of step 3. After several months of intensive work and studies concerning the proper risk of the Contract Acceptor the project is stopped. With frustration increasing on the Contract Giver's side, too, the project is halted. The Contract Giver is unable to supply bulk active to his partner, and the bulk active manufacturer has lost an interesting project.
The damage for both parties could have been avoided by following GMP recommendations obliging the Contract Giver to supply all necessary information about the process. The Contract Acceptor is obliged to apply a validated process according to PIC guidelines (5.22) stating that *"When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing;"* and according to WHO recommendations (18.1) *".... Haphazard operations cannot be permitted in the manufacture of substances that may be used to save life or to restore or promote health."*
The example shows that trust between partners is essential for successful process implementation and that with more confidence in the industrial experience of the Contract Acceptor the project could have been realized in time. From the GMP guidelines it follows that the Contract Acceptor had to insist on the proper implementation of step 3.

Evaluation and Feasibility Study: The Contract Acceptor can help the Contract Giver by using a checklist asking questions about
- starting materials and auxiliary products, intermediates and by-products
- the final product
- the stability of all intermediates and the final product
- wastes: solid wastes, liquid wastes, toxicity of wastes, gaseous wastes, treatment
- analytical methods and specifications of raw materials, intermediates and the final product and in-process control
- safety data: reaction safety (exothermic reactions), toxicity, safety data sheets, literature

As can be seen from the *case study*, the Contract Giver should also inform the potential manufacturer about what can go wrong. However, the Contract Acceptor should take the active role and the responsibility for obtaining all the information necessary for proper process implementation.
The checklist should include internal information such as economic points, priority within the contract acceptor's project management, risks etc. This information should ideally be collected and compiled in the form of a short *project data sheet*, regularly discussed by the responsible managers and updated by one appointed manager.
During the paper evaluation and the method validation in the laboratory, first quotations for starting and raw materials are usually requested. Strategic key intermediates can also be supplied from the Contract Giver in order to keep the flow of such materials under control. For pharmaceutical bulk production, the Contract Giver can establish balances on the basis of material supplied and product delivered by the Contract Acceptor.

Starting material – Raw materials: The term "raw material" is used for chemical manufacturing, while for pharmaceutical bulk production "starting material" is preferred. In *Bulk Pharmaceutical Manufacturing* the point from which a starting material should be in compliance with GMP cannot be generally defined [12]. PIC guidelines [6] say that *"...full evidence of GMP compliance should be given from the step from which the process or the raw materials used have an influence on the quality of the active pharmaceutical ingredient. This step should be determined in each individual case in agreement with the competent authority and the manufacturer."*
The criteria for DMF (Drug Master File) compliance of a raw material in the case of bulk active manufacturing are very generally defined. These specific points apply:
- A strategic raw material (not an available commodity) should be registered in the Drug Master File.
- An intermediate showing pharmacological activity should be registered and produced in compliance with GMP recommendations.
- If an intermediate is a metabolite during degradation in vivo, it should be registered.

Fig. 4 shows the principal chemical pathway for the synthesis of Indobufene [5]. The active site of the final molecule is composed of the acidic residue and the propyl group. The intermediate prior to Indobufene does not show pharmacological activity; however after the condensation of α-ethyl-phenyl acetic acid with phthalic anhydride the molecule possesses the principal structure of the final product. Furthermore, while the starting material and phthalic anhydride are available on the free market, the third intermediate is not, so it should be included in the DMF. In addition whether to include an intermediate or a starting material in the registration documentation can depend decisively on commercial considerations [12].
If an intermediate or a raw material has to be in compliance with GMP, quality problems can occur (purity, cross-contamination) if this material is purchased via trad-

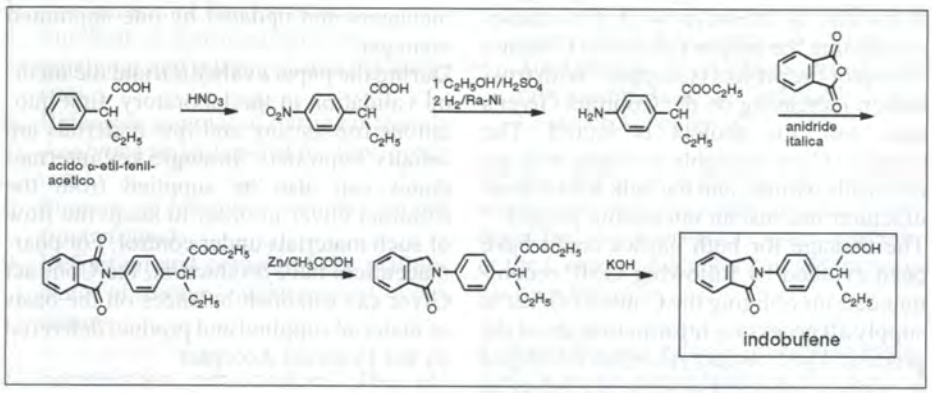

Fig. 4: Chemical pathway for the synthesis of Indobufene [5]. The pharmacological activity of the molecule is given by the functional groups of the acidic remnant and the propyl group. The starting materials are available on the market and do not have to be produced in compliance with GMP rules. The third intermediate, however, would be synthesized by the Contract Acceptor and should therefore be produced in compliance with GMP recommendations. This compound should already be included in a pharmaceutical documentation.

ers or brokers and the origin of the goods cannot or will not be properly declared by specifications and certificates of origin. A bulk active manufacturer should therefore preferably purchase directly from the company producing the compound or from the official representative in the territory.

The quality of raw materials in *pharmaceutical bulk manufacturing* should be well specified according to pharmacopoeia or internal specifications of the Contract Giver, or worked out by the Contract Acceptor (e.g. particle size distribution) and consequently serve as a binding specification. The starting conditions for starting materials of a process implementation in pharmaceutical bulk manufacturing are exactly defined. Entry controls and releases of all materials have to be performed according to GMP recommendations [6]. In pharmaceutical bulk manufacturing no transformation steps have to be performed as in bulk active production. Since the molecular structure of raw materials and ingredients remains unchanged, definitions of product quality are determined mainly by parameters which characterize quality and purity:

- crystal morphology
- particle size distribution
- chemical and biological purity

Modification of the specifications for pharmaceutical bulk active materials and ingredients has to be approved by the written consent of the Contract Giver. The different modes of raw material supply to the pharmaceutical bulk contract manufacturer have already been discussed in the chapter *The Contract between Contract Giver and Contract Acceptor.*

Cross-Contamination: In contract manufacturing and in all plants where different products are handled with the same equipment, cross-contamination is a most important risk factor. Cross-contamination by active ingredients has therefore to be thoroughly avoided. In particular, this is very critical for highly active substances such as *hormones* and *cytostatics,* where a potent effect at low dosage or a long-term pharmacological effect has to be expected, or antibiotics, where sensitization and allergic reactions caused by the contaminated product can occur. The risk of cross-contamination is equal for bulk active and pharmaceutical bulk production, since it arises mainly through residues from equipment (e.g. dust layers on horizontal piping) and personnel and the formation of dust during bulk manufacturing. Cross contamination should be avoided by different prescribed measures [1, 13]:

- *Production in segregated areas:* In chemical manufacturing the approval for a production plant should exclude the above-mentioned classes or vice versa. At the least, a special case-by-case permit should be required. Production in segregated areas is mandatory for penicillin, live vaccines, live bacterial preparations and some other biologicals.
- *Production in campaigns* (segregation by time): The campaign strategy is permissible for hormones and cytostatics, provided the general authorization has been granted.

Cross-contamination has to be avoided by strict cleaning procedures, which must be set out in writing. Rinse water or solvents from cleaning should be analyzed in order to detect threshold levels of the compound that has to be removed. Walls, installations and equipment have to be cleaned after every change of product. Cleanliness in bulk active and bulk pharmaceutical manufacturing plants must be strictly observed.

Validation and validation transfer: If an already validated production method has to be transferred to a Contract Acceptor, this procedure must also be validated for the production in the new facilities. The validation transfer is defined as the *transfer of results, conclusions and experience from validation activities in order to make use of existing experience and in order to avoid duplicated effort.* Validation transfer is thus an analysis of the know-how that is transmissible and of the implementation that remains to be done [14].

Product characteristics (such as light sensibility), specifications of the starting material and of the final product should not change during the transfer of production know-how to the Contract Acceptor. However, modifications of the process parameters may become necessary, because the Contract Acceptor's equipment often differs from that of the Contract Giver.

Since in principle every modification of the production process implies new validation it has to be decided in each particular case and depending on the modification, whether the whole process must be revalidated or whether it would be sufficient to validate particular steps ("critical steps" such as the mixing time for a homogeneous powder mixture).

Process validation requires the production of at least three industrial-scale lots in the same equipment where the product will be manufactured and handled during the industrial phase. Process parameters and key values must be maintained or achieved within the defined ranges. Should a significant deviation from product yields occur, the process cannot be regarded as validated. Process validation shows the Contract Giver that the chosen Contract Acceptor is able to start with the production at industrial scale. In general, during or after the validation lots, quality audits by the client and subsequently by official agencies (FDA, Food and Drug Administration, IKS or other registration authorities) can take place.

Personnel: The recommendations given by PIC and in the EU guidelines [6, 17] of staff containing clear assignments responsibilites and the requirements for personnel hygiene, are valid for each manufacturer in captive as well as contract manufacturing and preclude any communication problem arising between Contract Giver and Contract Acceptor. It is, however, advisable to assign one responsible person in the collaborating companies to handle technical problems and questions related to the particular contract manufacturing project. This measure facilitates the flow of information and requests between

the partners and helps to avoid misunderstandings.
If already existing processes and prescriptions have to be transferred to the Contract Acceptor, staff training with the Contract Giver can be an efficient tool to smoothing the necessary know-how transfer.

c) Production on industrial scale
Sampling: Effective and representative sampling is indispensable for In-Process Control (IPC) and the control of raw and starting materials, intermediates, bulk and final products as well. Non-representative sampling can render useless all data resulting from the analysis performed. Sampling procedures have to optimally represent the overall quantity, i.e. the data must assure the highest possible probability for the whole lot. The following three main points have to be respected:

- *How and where do samples have to be taken (modality)?*
  Sampling depends on the physical state of the product (liquid, solid). Contrary to a solution, for example, for a powder mixture the samples should be taken not only at the surface but also from the core part of the package (drum, bags).
- *How large does the sample number have to be (quantity)?*
  The sterility test can serve as an example: The probability of detecting a contaminated vial decreases when the lot size increases and the number to tested vials remains unchanged.
- *How often and when do samples have to be taken (frequency)?*
  Particularly for this point there are differences between galenic in-house production and contract manufacturing. An additional sampling can become necessary after the delivery of a tabletting mixture produced by the contract acceptor in order to detect possible back mixing during the process step "transport".

In-process control (IPC): IPCs are performed to track the course of the production of a pharmaceutical product or the synthesis of a bulk active and in order to eventually control the process steps, ensuring that the specifications of the final product correspond to the required characteristics.
In both bulk active production and galenic production IPC affords an overview of the process. In the former case it is necessary in order to control the proper course of a synthesis and to carry out the final step at the required quality. In galenic production the goal is to achieve homogeneity for the whole lot (i.e. constant pressure and resulting tablet consistency).
It is therefore necessary to ask which parameters have to be checked in which way, when and how frequently (i.e. continuously or according to a schedule), and which tolerances are admitted until the production process has to be corrected. A provisional definition of the necessary tests is made during the development phase. In general, more tests are defined than those that need to be used during the industrial stage. The final definition of In-process-controls can only be established when several production-scale batches have been completed and when the relevance of the IPCs is confirmed or they have to be changed [15].
During the know-how transfer IPCs have to be taken over by the contract acceptor, and execution and results have to be documented accordingly.

d) Process Documentation
A complete and detailed process documentation represents an essential part of quality assurance in pharmaceutical contract manufacturing. In order to avoid errors originating from verbal communication and quick notes during processing, clearly and correctly written protocols, instructions, lists and other kinds of documentation will help to trace back the history of a lot [6]. A product documentation should include:

- General and product specific prescriptions for production, analysis, sampling, storage, cleaning and maintenance, product specifications, waste treatment, instructions pertaining to organization or responsibilities.
- Protocols of production, analysis, controls or delivery.
- Reference samples.

Special case: Old process documentation
One problem in bulk active contract manufacturing is that old production documentation from the Contract Giver often does not include important details about the process such as safety data sheets or information about waste treatment because these data were not necessary at the time. However, if the Contract Manufacturer should reproduce the process in his facilities, such details can become crucial (e.g. quality of materials for crystallisation), especially if a product does not behave as indicated when tested in the laboratory of the Contract Acceptor. It is obvious that old process documentation cannot be updated. However, for every new product a potential Contract Giver should try to fulfil the requested quality of the documentation. Additional development work will probably have to be invested in order to achieve the new quality standard for an up-do-date process.
The Contract Giver bears the final product responsibility if he is the holder of the Drug Master File; he should therefore be able to control the overall processing [5].
The storage of production and sampling protocols (batch records) and reference samples has to be defined in the contract. If the documentation is not kept by the Contract Giver, he should at least have access to these data during the prescribed storage duration. He may use this information for product complaints or – in the case of the detailed batch protocols – for the final release of the pharmaceutical speciality product, if the responsibility is on his side.
According to PIC- or EU-GMP guidelines the following points have to be included in a batch protocol:

- Name and number of the batch being manufactured;
- dates and times of commencement, of significant intermediate stages, and of completion of production;
- name of the person responsible for each stage of production;
- initials of the operator of different significant production steps and, where appropriate, of the person who checked each of these operations (e.g. weighing);
- the batch number and/or analytical control number as well as the quantities of each starting material actually weighed;
- any relevant processing operation or event and major equipment used;
- a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
- the amount of product obtained at different and pertinent stages of manufacture (yield);
- notes on special problems including details with signed authorization, for any deviation from the Master Formula and Processing Instructions.

After completion, the record should be dated and signed in agreement by the person responsible for the processing operation. However, more important than assignment of responsibility is that the documents are stored and that they are accessible at any time.
Different indications can be found concerning the times for the storage of the process documentation. According to IKS production guidelines [7] the documentation has to be stored for at least 5 years, whereas EU-GMP and PIC guidelines indicate a period of at least 1 year from the expiry date of the final product. EU-GMP and PIC recommendations prescribe a storage time for reference samples of every production lot of 1 year from the date of expiry, while for starting materials 2 years are indicated. IKS indicates a minimum of 5 years or at least 1 year from the expiry date given by the producer. Escher [16] asks whether the storage time for documentation and samples should even re-

spect the absolute legal limitation of actions of 10 years (according to the Swiss Civil Code).
In view of these differing indications Contract Giver and Contract Acceptor should agree on a commonly established storage period for documents that remain with the Contract Acceptor. At minimum IKS guidelines should be adhered to. The *modalities for change* of documentation are described in PIC- and EU-GMP guidelines [6, 17]. It has to be ensured that erroneous use of the old version be avoided by appropriate measures. In particular, this can become critical for contract manufacturing, if a document (e.g. a specification for a final product), was drawn up and renewed by the Contract Giver. In order to verify implementation by the Contract Acceptor, a responsible person of the Contract Acceptor could send a signed version of the document to the Contract Giver.

e) Complaints and Product Recall
For in-house production complaints about pharmaceutical products can occur on the part of users (doctors, hospitals, patients) or of traders (grocers, distributors) as well as official institutions.
In the case of contract manufacturing the complaints reach the Contract Giver first. With respect to the quality of bulk active and pharmaceutical bulk, complaints may also come from the Contract Giver to the Contract Acceptors after receipt of the ordered quantities.
Incomplete batch records or specific know-how on the side of the Contract Giver can prove obstacles to a precise investigation of complaints. In general, the client depends on the Contract Acceptor for details of production. For this reason close and trustful collaboration is indispensable.
Whether a complaint comes to the Contract Giver from "outside" or whether he himself has to complain about the quality to the Contract Acceptor, the latter has to designate a responsible person who can initiate corrective measures. A product recall has to be carried out quickly and efficiently. Contract manufactured final products should always be supplied from the Contract Acceptor to the Contract Giver; they should never be sold directly by the Contract Acceptor to a client of the Contract Giver. All documentation relating to buyers and clients must therefore be available from the Contract Giver.

Conclusions
The scope of this paper is the study of the flow of information and materials before and during contract manufacturing of bulk active and bulk pharmaceuticals in order to identify the critical factors that have an impact on product quality. The systematic approach was carried out by developing a flow-chart using a model relationship between one Contract Giver and two Contract Acceptors for chemical bulk respectively pharmaceutical bulk production. Comparing the steps described in this model relationship with the rules and laws that regulate pharmaceutical production and the quality of the products on the one hand and the practical experience of the authors on the other, two major questions need to be answered:
1. What are the crucial steps in pharmaceutical contract manufacturing with respect to quality control?
2. Are there ways in which the relationship between Contract Giver and Contract Acceptor can be improved in order to assure the quality of the products even more effectively?

During the sequence of an emerging relationship between a Contract Giver and his Contract Acceptors the following critical points were identified:
- the contract between the partners
- know-how transfer phase
- process implementation phase with the potential supplier
- process validation
- in-process control
- the documentation of the process.

Contracts between potential collaboration partners can be subdivided into the skeleton agreement regulating the framework of the collaboration and the product-specific contract or agreement defining the particular conditions for the production and supply of the bulk active or the bulk pharmaceutical product. It should be mentioned that in bulk active manufacturing, skeleton agreements (at least to the knowledge of the authors) are used only rarely. The points mentioned in the chapter *The Contract between Contract Giver and Contract Acceptor* are in general verified prior to any commitment by the Contract Giver through visits to the production facilities and the documentation of the relevant certificates (such as FDA approvals or Environmental Protection Certifications). Two major points are the terms that process changes can be undertaken only with the written consent of the Contract Giver and that sub-contracting of process steps within the whole production sequence must also be authorised by a written statement of the Contract Giver. The forms of the collaboration agreements and contracts vary from company to company. In the product-specific agreement the major points relating to definition of responsibilities concern the formulation of the defined product, processing instructions including IPC, assignment of lot numbers, purchase of starting material, and release of starting material and the final product.
In addition to the quality-related terms, commercial conditions like price ranges for the product, minimum quantities order or ownership of process know-how generated by the Contract Acceptor have to be agreed.
During the process implementation phase the open exchange of all necessary information is crucial. If all relevant information is not made known to or requested by the Contract Acceptor (the responsibility to exchange is reciprocal) this may lead to delays in production and misunderstandings, often causing additional costs. A professional process implementation will therefore already start during the evaluation phase, where checklists are of great help. Such checklists can contain information about chemical and technical details, risks of the process, working safety and environmental risks, waste treatment, starting and raw materials, analytical methods, pitfalls and, last but not least, commercial aspects of the project. The checklist should be provided by the Contract Acceptor because he knows best the crucial aspects for process implementation in his plant.
It is essential to define where starting and raw materials are sourced. There are mainly three ways of sourcing:
- the Contract Giver supplies the starting/raw materials
- the Contract Acceptor purchases all materials
- the Contract Giver supplies key intermediates

Probably starting/raw materials should also be included in the registration documents (Drug Master File) for the pharmaceutical speciality, in particular:
- if the starting/raw materials or intermediates are of strategic interest for the Contract Giver;
- if starting/raw materials or intermediates possess pharmacological acitivity;
- if starting/raw materials or intermediates are in vivo metabolites.

If starting/raw materials or intermediates are purchased from brokers and traders these suppliers should be able to guarantee the quality of the products sold and be in a position to indicate the producer of the compounds.
Cross-contamination is one of the most important factors in contract manufacturing, because fatal effects of cross-contamination can cause severe harm to patients. In particular, low concentration/high activity compounds are very delicate to handle with respect to cross-contamination (hormones, vaccines, antibiotics). Cross-contamination can be avoided by applying the measures described in the WHO, PIC or EU guidelines. The major way to avoid

cross-contamination is segregation either by location (e.g. different production facilities for penicillin live vaccines and parts) or by time (production campaigns for hormones and cytostatics). In order to avoid cross-contamination, validated decontamination and cleaning procedures must be established in writing and all rinse liquids should be analysed for threshold levels of potential cross-contaminants. Even though the latter measure has not been prescribed so far it should be made part of the standard cleaning procedures of a contract manufacturer.

Process validation and validation transfer are crucial for process implementation with a new supplier. Validation transfer was defined as the "Analysis of transferable know-how and of implementation operations that remain to be done". During validation transfer, product specifications should not change, but technical adaptations should be carried out where necessary. Validation on an industrial scale requires at least 3 production runs in the same equipment that will be used for the routine production.

During production on industrial scale the maintenance of the quality of the products by self-policing and staff training and documented In-Process Control (PIC) are critical. Routine is the enemy of quality and a high working standard. This is by the way also crucial for safe bulk active production in order to avoid dangerous runaway reactions or product losses. For bulk active production the reproducibility of the yields of the single process steps is an important parameter for IPC and process safety.

Process Documentation is a further essential prerequisite for high quality pharmaceutical products, and not only for contract manufacturers. It was found that the final product responsibility is with the holder of the product registration (Drug Master File) – in a classical contract manufacturing relationship the Contract Giver. The most important contents are defined in PIC and EU guidelines. The decisive point is to define the parameters and their form to be documented and to establish whether such parameters have to be documented by the Contract Giver or by the Contract Acceptor. The responsibility to keep available the documents for the storage period agreed must also be defined.

Finally, in case of complaints complete batch records are essential. The Contract Giver, who in most cases receives the first complaint (or lodges a complaint with the Contract Acceptor), and the Contract Acceptor should each appoint a person responsible for initiating measures to deal with the complaint.

Successful collaboration between a Contract Giver and Contract Manufacturers depends on the human factor, because, only the full engagement of the persons responsible for production and quality control, and their resistance to any deviation due to routine, can guarantee a high quality product. Self-responsibility of every single worker and manager can only be achieved by steady training and critical self-inspection.

Quality audits performed by potential Contract Givers will improve the Contract Acceptor's quality assurance know-how and should be regarded as a positive input to the know-how pool of his own quality system.

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Glossary

Bulk active product: Any active ingredient of a pharmaceutical product which has gone through all processing stages.

Bulk pharmaceutical product: Any pharmaceutical product which has gone through all processing stages up to, but not including, final packaging.

Captive production: In-house production, i.e. production within the same company or organisation. The production facilities need not to be located in the same area. They can also be located in different cities or even countries but belong to the same organisation.

Cross-contamination: Contamination of a starting material or of a pharmaceutical product with another material or product.

In-Process Control (IPC): Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specification. (Control of the environment or equipment may also be regarded as a part of inprocess control.)

Raw material: Any substance used in the production of an active ingredient of a pharmaceutical product, but excluding packaging material.

Starting material: Any substance used in the production of a pharmaceutical product, but excluding packaging materials.

Validation: Action of proving in accordance with the principles of Good Manufacturing Practice that any procedure, process, equipment, material, activity or system actually leads to the expected results.

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Results of the four project groups of the third postgraduate seminar for Pharmaceutical Quality Assurance, winter semester, 1993/94, Department of Pharmacy, Swiss Federal Institute of Technology (ETH), Zurich, and University of Basel, Pharmaceutical Faculty

Pharmaceutical Quality Assurance

Outsourcing in the Pharmaceutical Industry – Evaluation of a Contract Acceptor

*Ch. Güetli, R. Holenstein, K. Mathys, K. Perrot-Stettler**

The main aspects that must be considered in the evaluation of a Contract Acceptor in the Pharmaceutical Industry are discussed. After a short introduction, the advantages and difficulties of Contract Manufacture and the basic requirements and guidelines are listed. Further, some practical tips for the search for and the first contact with Contract Partners are given. The section on the evaluation process discusses the necessity of an audit after an initial pre-selection. The most important criteria to be considered at such an audit are listed and a method for rating these criteria and to compare different firms in a utility value analysis is shown. Subsequently the main agreements to be established between the Contract Partners in two written contracts are discussed. For the basic contract, comprising the general rules and aspects, a checklist is presented and the contents of a technical agreement that defines specific work arrangements are discussed. Finally the chronological steps in the evaluation of a Contract Partner are presented in a flow-chart.

Introduction

In the continuously growing Pharmaceutical Products market Contract Manufacture is gaining more and more importance. As the research and development of new drugs, the production of special galenical products and the rising demands for analysis call for very specialized equipment and knowledge, a growing number of manufactures are outsourcing. There are many different reasons for giving an order to a Contract Acceptor, but there is one fact they all have to ensure. The manufacture of pharmaceutical products must generally meet the requirements of Good Manufacturing Practice (GMP) fixed by the World Health Organization (WHO), the European Union (EU) and the Pharmaceutical Inspection Convention (PIC), and it must be in accordance with the instructions of the marketing authorizations.

The special demands placed on Contract Manufacture are also fixed in these international Guides, but there still remain many aspects which must be considered for the rational selection of a Contract Acceptor by a Contract Giver. Very often the selection of a Contract Partner "just happens" on grounds of personal connections or by chance. One reason certainly is the absence of a "Guide for Good Evaluation of a Contract Acceptor".

It is the purpose of this paper to discuss the main aspects pertinent to the evaluation and the well-founded selection of a Contract Acceptor. As the present report should be applicable for Contract Research and Development, Contract Production and Contract Analysis as well as Contract Packaging, only topics of general importance are discussed. The glossary and definitions of the terms used in this paper are defined in the "Convention for the mutual recognition of Inspection in respect to the Manufacture of Pharmaceutical Products", PIC-GMP Guide, Document PH 5/92 [1]. First the requirements of the basic Guides and Rules are listed, followed by a chronological discussion of the most important steps involved in the

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carefully considered selection of a Contract Partner.

Contract Manufacture: General Aspects and Basic Requirements

Possible Reasons for Contract Manufacture

If a manufacturer is not able to carry out all steps of a manufacturing process, he is forced to look for a Contract Acceptor (CA) to perform the necessary work. On the other hand, even if the work could be realized in his own company, there are still a lot of reasons for Contract Manufacture (CM):

- the available equipment is at its limit
- the premises and equipment no longer comply with GMP requirements
- special knowledge is necessary for the development of a new product
- special premises, equipment and know-how are required (e. g. production of sealed gelatine capsules, antibiotics, sterile products etc.)
- timing reasons, financial reasons (e. g. in contract development own human resources are not bound, risk can be shared)
- higher flexibility and faster realization of projects

Very often production might theoretically be possible, but investments would be disproportionately high and therefore CM is a good solution. And last but not least the evaluation of a CA gives the Contract Giver (CG) the possibility of checking whether he is still able to compete!

Difficulties in Contract Manufacture

Besides the above-named reasons in favour of CM as a means to save time and money, there are also a number of difficulties that must be mentioned:

- there are probably more companies with different policies working on a single product
- the possibility of contact between the people concerned is smaller and more difficult; therefore misunderstandings are more likely, responsibilities are split and must be fixed in detail, and the documentation is non-uniform
- transport problems might occur (different climate zones)
- transfer of information is necessary

Table 1: Main requirements of GMP Guidelines on Contract Manufacture [1,7]

General
- all arrangements should be in accordance with the marketing authorization for the product concerned
- there should be a written contract covering all arrangements

The Contract Giver
- is responsible for assessing the competence of the CA
- should provide the CA with all information necessary to carry out work in accordance with marketing authorization and any other legal requirements (to guarantee GMP)
- should ensure that the CA is aware of any risks and problems associated with the work
- should ensure compliance of all products with specifications
- should ensure that the product has been released by the authorized person(s)

The Contract Acceptor
- must have adequate premises and equipment, knowledge and experience, and competent personnel to carry out satisfactorily the work ordered
- must be a holder of a manufacturing authorization
- should not pass any of the work on to a third party without approval by the CG
- should refrain from activity which may adversely affect the quality of the product

The Contract
- should be drawn up by competent persons and specify all respective responsibilities
- should ensure compliance of the product with all requirements of the marketing authorization
- should describe clearly who is responsible for every single operation to be done (e.g. purchasing, testing and releasing materials, sampling and analysis)
- should describe the handling of rejected material and the flow of information
- should ensure that any records relevant to assessing the quality of the product are available to the CG
- should permit the CG to audit the facilities of the CA

The necessity for a know-how transfer obliges the Contract Partners to sign a Secrecy Agreement before the real evaluation can start. In addition the Quality Assurance (QA) of the product is more difficult, as there are different Quality Control Systems involved and the "Overall-Quality-Management" must ensure that the product meets all specifications and all requirements of the marketing authorization [2].

GMP Guides

In 1974 an international seminar on the subject "Manufacture and Quality Control under Contract" was organised by the Intercantonal Office for the Control of Medicines (IOCM) in Switzerland [3]. The PIC Guideline PH 3/76 for Contract Manufacture and Analysis resulted from this seminar. This guideline is also part of the German "Betriebsverordnung für Pharmazeutische Unternehmen (PharmBetrV)" [4]. Although no special guidelines for Contract Manufacture exist in Switzerland, definitions and requirements stated in the directives of the IOCM for the Manufacture of Pharmaceutical Products [5] are valid for manufacturing in contract as well.

In the PIC GMP Guide [1] (largely identical with the EEC GMP Guide [6]) and in the WHO GMP Guide, 1992 [7], the basic requirements are described. Beside the general demands on GMP defined in these Guides, one chapter deals with Contract Production and Analysis.

In *Table 1* the special demands relating to this subject are summarized. The WHO GMP Guide describes this topic as well [8] in slightly more detail, yet the general requirements are identical: *"Contract production and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a product or work or analysis of unsatisfactory quality"*.

Definition of the possibilities and requirements of the Contract Giver

Before the evaluation of an appropriate CA can start the CG must be clear about his own requirements. Depending on what part of manufacture he wants to give to a CA, the CG must define what exactly he wants and/or is able to do himself and what work he wants the CA to execute. The questions listed in *Table 2* originate from the GMP/ISO-9000 Quality Audit Manual [9] and are applicable for production, analysis and packaging in contract. They should be clarified before the CG undertakes outsourcing. The answers depend on the product (already registered or not) and also on the CG's own facilities. For Contract Research and Development no comparable documents were found, as the

Table 2: Typical questions that need to be answered to define the requirements [9]

- Who will be responsible for the procurement of chemical compounds and packaging components?
- Who will test and release the chemical/packaging components?
- Who will retain samples of chemical components and the finished product?
- Who will perform stability studies?
- Who will perform release testing and who will actually release the product?
- Who will be responsible for validations?
- Who will be responsible for the issuance and maintenance of the following documentation:
  - specifications for chemical and packaging components
  - specifications for in-process control and for the finished product
  - labelling, lot number system
  - batch record formats, bills of materials
  - manufacturing instructions and test methods
  - procedures, sampling plans and sampling methods

requirements in this field are very specific and must be defined from case to case.

Search for Contract Acceptors

Inquiry for Contract Acceptors

The selection of a Contract Partner is very often not the result of a systematic search but comes about through personal connections or verbal recommendations. Even if such connections exist a rational evaluation of several potential companies should be performed.

Contract Packaging is a generally accepted practice [10, 11]. Therefore it is easy to find companies spezialised in Packaging. For example, most pharmaceutical journals publish various advertisements for these firms. For the production of tablets or other solid dosage forms there are many possible manufacturers available as well. If, however, the development of a new galenic product or the production of aseptic or sterile preparations are planned, finding a suitable partner may prove difficult.

There are several possible ways to start an inquiry. You can:

- contact chemical or pharmaceutical societies, e. g. the SSCI (Swiss Society of Chemical Industry, Department Pharmaceuticals, Zürich) or the German BPI (Bundesverband der Pharmazeutischen Industrie, Frankfurt am Main)
- consult special lists of registered medicines such as the Swiss "Arzneimittelkompendium" or the German "Rote Liste" and search for similar products
- consult trade-specific tables and lists which offer information about many companies and the galenic products they manufacture. These tables exist for entire countries and for defined geographical regions. In Switzerland they are available from "Kompass Schweiz Verlag AG, Zürich" and in Germany at the "Hospimed Information AG, Regensburg".

Regardless of the method employed, one cannot expect to find a complete list of all possible companies. This is mainly due to the absence of a "Union of Contract Manufacturers of Pharmaceutical Products".

First contact, feasibility discussion, and first offer

In order to perform an initial pre-selection of the different companies and prior to a first meeting one must be fully informed about the services and capabilities of each company. The first meeting is very important for the future progress of co-operation and should therefore be prepared carefully. Depending on the thoroughness and the agenda of this first discussion, you might sign a Secrecy Agreement in advance. It should definitely be signed before further know-how transfer, as it is the precondition for intensive co-operation and is effective even if no collaboration contract is signed. The Secrecy Agreement must at least cover the following aspects:

- Confidentiality of CA and CG with regard to their know-how and in particular their manufacturing instructions
- Proprietary rights for controlling, manufacturing, packaging procedures and so on
- Exclusion of generally available know-how
- Availability and period of validity
- Validity after co-operation ends

In the PharmBetrV [4] a draft for an Agreement on Manufacture under Contract is given that includes one paragraph on Confidentiality.

For a first meeting the requirements of the CG (and the CA) should be defined. Therefore it is important to involve already at this early stage of the evaluation a team of representatives from different departments. In any case person(s) from the following sections must participate:

- Project Management
- Licencing and Cooperation
- Quality Assurance/Quality Control

It is very important to designate one person as the Project Manager for this special project. The Project Manager is responsible for the coordination of all activities between the two companies and deals with any misunderstandings that may occur. The Manager for Licencing and Cooperation is important, as he is fully informed about the activities, the potentiality, the strategy and the aims of the company. Furthermore he is acquainted with the company's own products and attends to the interests of the management. Depending on the importance and diversity of the project, representatives of Production, Research and Development, Marketing and Production Planning departments may also join the project team.

In an initial meeting both parties try to gain as much information about each other as possible. The question might come up why the CG is outsourcing just with this product: Are any special difficulties expected? Among other matters the CG will investigate the possibilities and the reliablity of the CA. Some main points of discussion during a first meeting are:

- Who is who (persons involved: figures, strategy, ownership)
- Co-operation of CG/CA with other companies
- Efficiency/Schedule of co-operation (e. g. capacity of machines)
- Marketing aspects of collaboration (proprietary rights on final products and active ingredients, prices, royalities, necessary investments, possibilities for further co-operation)
- Quality Assurance Systems
- Responsibilities and duties of CA, CG (an example is given in *Table 2*)

When a future collaboration appears likely after the first discussions, the CA should prepare a first offer which contains detailed information including:

- the work the CA is doing (exact list of activities included or excluded, e. g. *Table 2*)
- prices for the different services
- validity of the offer (time period)
- contact person and persons responsible for this project

Evaluation Process

Audit

After having evaluated several possible CAs, only a few remain who may be seriously considered and with whom conclusion of an agreement is likely. In order to

Table 3: General aspects

- How long has the CA held a manufacturing authorization, when does it expire and when was it extended?
- When was the last official inspection, when is the next?
- Were there instances of non-compliance? If yes, what was objected to?
- Overall impression, image, strategy, policy and philosophy of the company.
- Pending procedures (regulatory affairs, civil court cases)

Table 4: General matters of GMP. (For filling in the evaluation sheet, the overall rating of this group of questions/aspects may be taken as "GMP-standard")

Personnel
- Does an organisation chart exist?
- Is the qualification of the key personnel adequate?
- Are there basic training procedures and refresher training procedures? Do they include GMP aspects?
- Do hygiene programmes exist?

Premises
- Are all the premises adequate to carry out the operations (size, maintenance, possibility of easy and effective cleaning, special storage conditions)?

Equipment
- Is the equipment up-to-date?
- Are acceptable techniques used and do SOPs exist?

Documentation
- Are batch processing records and batch packaging records (including distribution) kept according to regulations?

Production
- Do written, clearly defined procedures / instructions for the handling of materials and products exist (e.g. for receipt, quarantine, sampling, storage, testing, a.s.o.)?
- Are the processes and procedures validated?
- Are finished products held in quarantine until their final release?

Quality control
- Is the Quality Control Department independent from Production Department?
- Is the sample taking done in accordance with approved written procedures?
- Are reference samples of each batch retained?
- Are the analytical methods validated?
- Are the performed tests recorded?

Quality assurance
- Are self-inspections conducted and recorded?

Complaints and Product recall
- Is an adequate product complain/failure handling system in effect?
- Is there an adequate recall procedure?

Table 5: Matters specific to the order to be placed. (For the evaluation sheet, the overall rating of this group of questions/aspects may be taken as the "know-how" for the planned operation).

- Are the personnel sufficiently qualified and experienced for the planned tasks?
- Is the equipment up-to-date und suitable for the operation to be carried out?
- Is the quality system sufficient?
- Can regulatory requirements be fulfilled?
- Can the documents required for a regulatory submission be supplied even if it concerns the manufacture of special pharmaceutical products such as sterile products or radio pharmaceuticals?

evaluate the status and to assure the quality of the planned function (manufacture/analysis/research and development) a contractor audit should be performed before the contract is signed. Instructions and checklists for a detailed contract manufacturer audit can be found in the GMP/ISO-9000 Quality Audit Manual [9] and also in the PharmBetrV [4]. In order to minimize the expenditure of time and costs of both CG and CA, a short audit covering only the most important criteria can be justified. In order to obtain as much information as possible the audit must be well prepared and a formal checklist used. This audit must take into consideration:
- General aspects *(Table 3)*
- General matters of GMP *(Table 4)*
- Aspects specific to the order to be placed *(Table 5)*

If it is planned to evaluate the results as a utility value analysis, each single aspect of the audit should be rated. The rating scale is chosen in accordance with the one in the GMP/ISO-9000 Quality Audit Manual [9]. The rating for one group of aspects is obtained by adding all ratings of the group and dividing this sum through the number of observations taken into account.

Rating	Meaning (according to the GMP/ISO-9000 Quality Audit Manual [9])
3	excellent
2	adequate or yes (if a quantification is not possible)
1	poor
0	unsatisfactory or no (if a quantification is not possible)

Selection of CA – utility value analysis
On the basis of the information which has been compiled so far, the partner company may be selected. A utility value analysis [12, 13] may be helpful for reaching a sound, transparent and well-documented decision. For each possible CA, an Evaluation Sheet is completed, like the one shown in *Table 6.* First the criteria are defined. Depending on the work to be done, further criteria may be added or omitted, or may be of varying importance. Then the importance of each criterion in relation to the selection must be considered. The responses to the question of how well the prospective CA meets each criterion must be rated. This rating multiplied with the importance results in part-utilities. The sum of all part-utilities gives the overall rating.

Contracts
The current directives and guides [1, 4–7, 14] to Good Manufacturing Practice (GMP) for pharmaceutical products are

Table 6: Evaluation Sheet (utility value analysis)

Evaluation Sheet (utility value analysis) Company: _____				
Criterion	*Importance of the criterion*	*Rating*	*Importance x Rating*	*Comments*
GMP-standard *(Table 4)*				
Quality management				
Know-how concerning the planned operation *(Table 5)*				
Ability to keep to the term (if co-operation already exists)				
Approximate costs				
Internal policy				
Different climate zones (production, transport)				
Overall rating				

Rating	*Meaning* (GMP/ISO-9000 Quality Audit Manual [9])
3	excellent
2	adequate or yes (if a quantification is not possible)
1	poor
0	unsatisfactory or no (if a quantification is not possible)

Importance	
3	very important
2	important
1	less important

Table 7: Checklist Contract

Subject	*Explanation*
Manufacturing authorization	A valid manufacturing authorization of the CA must be available.
Directives and guides	List of the current pharmaceutical rules and the relevant legal obligations which should be followed by the CA.
Object of the contract	Definition of duties between CG and CA.
Quality Assurance	Definition of all respective responsibilities.
Right of Inspection	Definition of the right of inspection by the competent authority and the CG during manufacture of the product concerned.
Starting materials	Regulation of procurement and the property rights of the raw materials.
Guarantee/ Nonconformity	Definition of the procedure for nonconforming products or events.
Liability/Exemptions	Regulation of liability and of exemptions if possible. (If no special arrangements are fixed, each party bears the legal liability and the corresponding risk.)
Exclusive arrangements	Regulation of: – competitive restraint – further contracting out of CA – exclusion of products – secrecy obligations
Definition of the costs	Regulation of all commercial and financial aspects.
Law/Court of jurisdiction	Listing of the relevant laws and the court of jurisdiction.
Reference to other agreements	Reference to all other agreements and contracts.
Know-how	Regulation of property protection (especially for new developments of significant importance).
Validity/Signature	Limitation of the validity if necessary.

based for Contract Manufacture (CM) on the following principles:

- CM must be correctly defined, agreed to and controlled to avoid misunderstandings which could result in a product or work of unsatisfactory quality
- Between the Contract Giver (CG) and the Contract Acceptor (CA) there must be a written contract, which clearly establishes the duties of each party.

All stipulations in this contract should be drawn up in accordance with the marketing authorization (if the product concerned is already on the market). Furthermore any change in these stipulations that could influence the quality of the product or the work must be passed on to the authorities. The legal requirements for notification or prior approval of such variations of the marketing authorization have to be previously clarified in collaboration with the competent local authorities [15].

In principle, the arrangements for establishing a CM can be classified according to their typical characteristics into two different groups [2]. The first group comprises the general regulations and aspects which define the collaboration between CG and CA. Alterations to this group are made very rarely. Furthermore, these arrangements are valid for every kind of CM (e. g. production, packaging, analysis etc.) They should therefore be listed in a basic document, *the contract* which should be drawn up by competent persons with the necessary knowledge of pharmaceutical technology, GMP and law [19, 20]. The checklist in *Table 7* gives a survey of the important subjects that must be defined by the contract.

The second group, concerning the product or work arrangements in question, comprises various aspects which are dependent on the type of CM. They are preferably listed in an annexe to the contract, *the technical agreement* [2]. The main emphasis of this agreement lies in a detailed regulation of the various responsibilities between CG and CA. Every single step of the CM should be written down and allocated to one or both parties. Preferably, this document should be drawn up in three columns. The first column describes the activity or the work, the second the responsibilties of the CG, and the third those of the CA. It is very important to decide on a common language for the pharmaceutical documentation in order to avoid misunderstandings. In respect to the rules governing medical products for human use in the European Community, English is the most widely accepted language for all types of documents. In addition a general ruling for a correct documentation system should be mutually concluded. It must guarantee that every document relevant to fulfilling the CM is supplied by the CG. On the other hand, the CA is responsible for a correct filling in of all the documents concerned during the manufacturing process. They should be available to the CG and the authorities and also valid for future registration purposes.

Depending on the type of CM, other agreements or contracts may be drawn up. It is absolutely necessary that all these agreements are referred to in the contract.

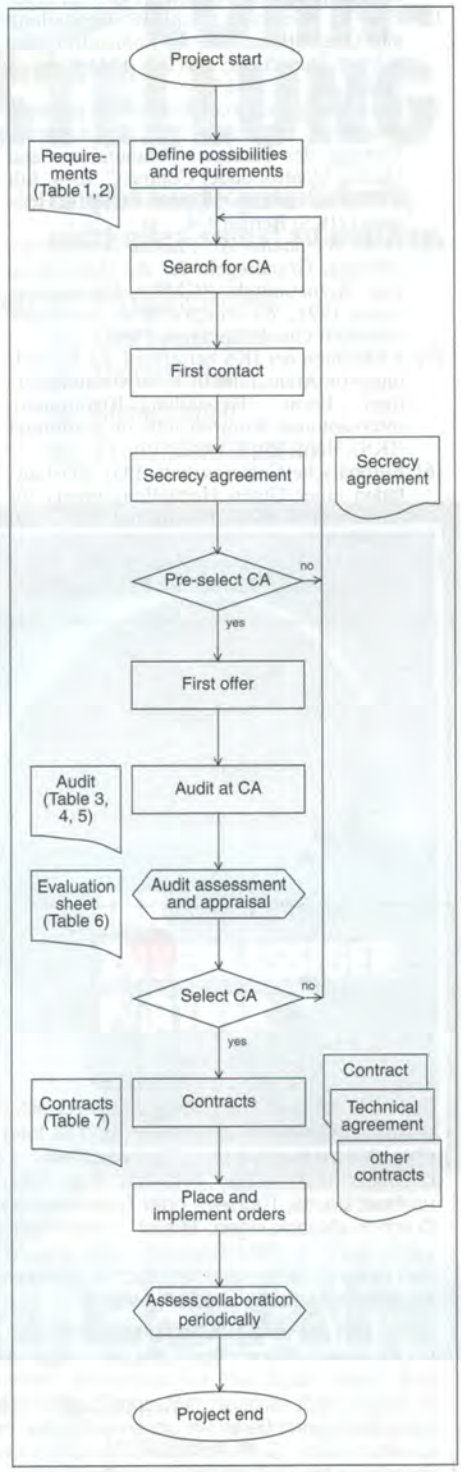
Implementation of the CM

When all contracts have been mutually signed the CM can start with the first orders of the CG. To facilitate this procedure, each order should be transmitted in writing on a joint order form, agreed upon by both parties. Depending on the complexity of the CM and the distance between the companies, it is advisable to arrange regular meetings during the starting period of the collaboration. This helps from the beginning to avoid differences over products or events and may even serve to optimize the CM. When the collaboration is established, a periodical assessment on an annual basis is recommended. The following list sums up the reasons for such meetings:

- Updating of documentation
- Changes within organisation of the CA
- Improvement of communication
- Discussion of new ideas for improvement of the CM
- Implementation of new guidelines or regulatory requirements
- Adaptation to a new situation on the market
- Exchange of know-how
- Keeping of delivery dates

Flow Chart: Contract Manufacture *(Table 8)*

Tab. 8: Flow Chart: Contract Manufacture



Conclusion

This paper is based on the assumption that both Contract Partners are aware of GMP requirements and the legal demands pertaining to the manufacture of pharmaceutical products. It is meant as a guideline to help a CG to evaluate an appropriate CA, taking into consideration all requirements that must be met by the manufactured pharmaceutical product. It might also be useful as a means for a CA to inform himself of what demands a CG may make on him. With the selection of a Contract Partner many important decisions are made that may afterwards be difficult to alter. Therefore if more than one company takes part in the manufacture of a product, the contracting parties must be aware of the potential difficulties, so that they can be taken into account in the evaluation process. For this reason due attention to possible misunderstandings must be included in the written contract drawn up between a CG and a CA. The contract must cover all their respective responsibilities related to the manufacture of the product. The aims of both Contract Partners must be a good collaboration and a product that meets all quality requirements. Good Quality Management with an adequate Quality Assurance System, along with a binding written contract, is an absolute must of CM.

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HOBSCHER & LUTZ

LEBENSQUALITÄT

Ob in der Dermatologie, Gynäkologie, Immunologie oder Nephrologie – unsere Arzneimittel haben weltweit unzähligen Menschen ein gutes Stück ihrer verlorenen Lebensqualität zurückgegeben.

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