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Supplement to the Treatise

WOLFGANG RUNGE: TECHNOLOGY ENTREPRENEURSHIP

How to access the treatise is given at the end of this document.

Reference to this treatise will be made in the following form:
[Runge:page number(s), chapters (A.1.1) or other chunks, such as tables or figures].

The current case relates to the case of the contract research startup ASCA GmbH Angewandte Synthesechemie Adlershof which addresses essentially pharmaceutical companies as customers and partners. ASCA does not operate as a competitor of ChemCon.

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Introduction

ChemCon GmbH (founded in January 1997 by two chemists) is a private, independent supplier and *service provider* for the global pharmaceutical, biotechnological and fine chemicals industries located in Freiburg i.Br. (im Breisgau, Germany) with a strong orientation towards the US.

> Foundation occurred in a period when the *blockbuster model* (with $5-$10 billion per year for products), on which the pharmaceutical industry has historically been largely based, began to be questioned and the consensus seemed to be that it may not survive.

This model of vertical integration (being active in all the components of the value chain) that dominated the pharmaceutical industry in the past century, characterized by tight control over all factions of the pharmaceutical manufacturing and development process began to break up.

ChemCon is a German service enterprise focusing on *contract research and custom synthesis* of active pharmaceutical ingredients (APIs) and specialty chemicals – new chemicals and generic pharmaceuticals – organic, inorganic and bio-inorganic, bio-inorganic reference substances and research chemicals. A special emphasis is on metal-containing APIs.

The active pharmaceutical ingredient (API) forms the most vital part of every formulated end product, and is an important part of the whole pharmaceutical industry.

According to the World Health Organization (WHO) an "active pharmaceutical ingredient" (API) is

> Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings.

APIs are defined by the US Food and Drug Administration (FDA) as “any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product.”

Operating in the pharmaceutical area means operating in a *highly regulated environment*. Serving the customers requires synthetic developments and productions including analytics to be run in compliance with US FDA *regulations* and related regulations in Europe in *cleanrooms* according to *current Good Manufacturing Practice (cGMP)* which will be subjected to audits.

ChemCon is essentially operating as a “contract research organization” (CRO) and “contract manufacturing organization” (CMO), specifically a Contract Development and Manufacturing Organization (CDMO). That means it will provide *services* in terms of technical processes and products to its customers which *require confidentiality and contractual protections*, for instance, by patents, and clarifications of ownership rights of the supplier and the customer.

Contract research organizations have a natural tendency to bridge gaps in the landscape of pharmaceutical R&D. As laboratories for hire, CROs have emerged as vital agents.

Usually, the customer owns all intellectual property like patents generated under a contract expressed as a *confidentiality agreement*. A highly critical part of such agreements concerns results, insights and developments which are obtained by collaborative efforts. In some cases it is required by the customer that all employees of the CRO/CMO sign the agreement (which is difficult for startups when employees leave the startup during the project). And, specifically for international businesses, there are some additional issues, such as [Vogler 2006a]:

- The partners are from a different country whose legal system forms the basis for resolving disagreements or infringements.
- Confidentiality agreements written in universal terms *versus* project-specific terms.

- Jurisdiction in a foreign country may induce tremendous cost for a startup (sending its representative scientists and lawyers to that country).

Revenue models in the fine chemicals' CRO/CMO areas include, for instance,

- Upfront and milestone payment charge is started by an initially agreed upon sum and further payment is according to milestone agreements
- Earn milestone payments when they complete certain pre-agreed research objectives.
- Royalty payments as to be specified in detail
- For the "full-time equivalent," or FTE, pricing formula CROs quote their customers the cost of employing their scientists on an annual basis.

For CRO/CMO manufacturers developing a non-patent-infringing process is critical.

For the market of *prescribed drugs* the special class of "orphan drugs" [Runge:469; Wikipedia-1] is of particular interest to ChemCon: It is part of its niche!

"Orphan drugs" represent a US Food and Drug Administration (FDA) category that refers to medications used to treat diseases and conditions that occur rarely. In the past orphan drugs for "rare diseases" did not receive proper attention. Big pharmaceutical companies focused usually on diseases "common" for very large populations! And in the 1980s there was little financial incentive for the pharmaceutical industry to develop medications for these diseases or conditions. Orphan drug status, however, will give a manufacturer specific incentives to develop and provide such medications.

The US was the first nation to propose a legal framework to encourage development and availability of orphan drugs; the Orphan Drugs Act (ODA) was approved in the US in 1983. The granting of the orphan drug status was designed *to encourage the development of drugs which are necessary but would be prohibitively expensive/unprofitable to develop under normal circumstances.*

In the US, an orphan drug is any drug developed under the Orphan Drug Act of January 1983 ("ODA"), a federal law concerning rare diseases ("orphan diseases"), defined as diseases affecting fewer than 200,000 people in the US or low prevalence is taken as prevalence of less than 5 per 10,000 in the community. This has been adopted as a subclause of the Food and Drug Administration (FDA) regulations.

As medical research and development of drugs to treat such diseases was financially disadvantageous, companies that do so are rewarded with tax reductions (tax breaks), grants and marketing exclusivity (a "monopoly") on that drug for an extended time (seven years post-approval in the US). In addition, the smaller patient populations for rare diseases made clinical trials relatively easier, cheaper, and hence, more manageable by small firms.

Incentives offered under the ODA, hence, were extremely important for the survival and growth of corresponding startups.

The European Union (EU) has enacted similar legislation. In the EU pharmaceuticals developed to treat rare diseases are referred to as "orphan medicinal products". The EU's definition of an orphan condition is broader than that of the US, in that it also covers some tropical diseases that are primarily found in developing nations.

Orphan drug status granted by the European Commission gives marketing exclusivity in the EU for 10 years after approval. The EU's legislation is administered by the Committee on Orphan Medicinal Products of the European Medicines Agency (EMA, sometimes called EMEA).

Different countries have slightly different definitions. For example, the FDA defines a rare disease as a disease with an incidence of less than 1:5,000 of the general population, while the European Union defines it as a disease with a prevalence of 5:10,000 [Ariyanchira 2008].

It is estimated that 30 million Americans suffer from 7,000 rare diseases. Prior to the Orphan Drug Act of 1983, legislation that financially incentivized the development of orphan drugs, only 38 orphan drugs were approved. Since then, 425 indication designations covering 347 drugs have been approved [Raeside 2013].

> Addressing customers of *prescribed pharmaceuticals*, in particularly orphan drugs, means markets characterized *as policy-driven* and having *mediatorial* characteristics [Runge:139-140,141].

The Technology, Legislation and the Market

ChemCon's operations are based essentially on *classical synthetic (fine) chemistry*. The broad chemical experience and competence of the firm is listed in terms of [ChemCon 2006:21]

- Classes of compounds and
- Types of reactions.

In particular, concerning *metal and metalloid compounds* the following metals are given: B, Mn, Fe, Co, Zn Ga, As Se, Ru, Pd, Ag, In, Te, Pt, Au, Tl, Bi, La, and Ce.

The synthetic and manufacturing processes on a small scale, even if a cleanroom is needed, and subsequent scale-up to volumes of production according to customers' demand requires appropriate, often common and largely standardized *process equipment and facilities*.

Analytical facilities of ChemCon cover the typical equipment found in universities in departments of (organic) chemistry, such as advanced NMR, IR, UV/Vis spectrometers and gas chromatography (GC) and High Performance Liquid Chromatography (HPLC) units [ChemCon 2006:14]. Correspondingly one finds lists of equipment for R&D, the pilot plant and production of ChemCon [2006:8,11,12]. The health/pharmaceutical orientation requires additionally microbiological control approaches and compliance with (EU and US-specific) pharmaceutical legislations. This leads to *quality control* (QC) involving

- Analytics
- Validations and
- Stability Tests.

When medicines have passed the development and production stage before launch to market they must be subjected to clinical testing, essentially to clinical trials [2] of defined Phase I-III (cf. Figure 6). These staged clinical trials are generally considered to be biomedical or health-related research studies in human beings (and animals) that follow a pre-defined protocol. They are associated with sizable cost for a full series of clinical trials. Negative impacts may occur for each of the stages [Runge:596].

- Phase I: Looking at Safety
- Phase II: How Well the New Treatment Works
- Phase III: Comparing a New Treatment to the Standard Treatment
- Pase IV: Continuing Evaluation.

In Phase III trials, participants have an equal chance to be assigned to one of two or more groups (called "arms").

For a study with two groups one group gets the standard treatment (control group). The other group gets the new treatment being tested (investigational group). The process of assigning participants to groups is called randomization. The so-called *verum* (treatment) arm receives the treatment that is to be tested, and the control group receives, for example, an alternative treatment or *placebo*. Both groups are tracked and compared to determine whether the treatment of the *verum* group was better than that of the control group (or not).

Merely giving a treatment can have non-specific effects. These are controlled for by the inclusion of patients who receive only a placebo.

> Approximately 10 percent of new molecular entities (NMCs) make it to the market from Phase II clinical trials and 50 percent from Phase III [Thayer 2012].

Ultimately, public administrative organizations or agencies, such as FDA or EMA, review the drugs to be launched to ensure that they are safe and effective.

Worldwide orphan drug sales when ChemCon was founded and in its early phase is given in Table 1. More data until 2013 and extrapolation till 2020 are available [EvaluatePharma 2014].

Table 1: Worldwide (WW) orphan drug sales exclusive generics ($, billion) [EvaluatePharma 2013; 2014]. *)

Year	1998	1999	2000	2001	2002	2003	2004	2005
Sales	12	14	17	21	25	28	35	40

*) Read from a chart; for the range 2000 till 2005 time period when ChemCon entered the scene provided data in [EvaluatePharma 2013] and [EvaluatePharma 2014] differ slightly.

During the 1998-2005 period the share of global sales of orphan drug sales was 5-7 percent of all prescribed drugs and climbed to almost 10 percent in 2011 [EvaluatePharma 2013]. Barring any significant payer protest, orphan drug sales are assumed to make up 19 percent of the total *share of prescription drug sales* by 2020, totaling $176 billion, predicted in the Orphan Drug Report 2014. Orphan drug sales in 2013 was given as ca. $90 billion [EvaluatePharma 2014].

According to BCC Research [2007; 2010]

- Biologic drugs accounted for a major share (64 percent) of the orphan drug market.
- The size of the biologic orphan drug market was projected to grow at a 6.9 percent CAGR [Runge:639] *versus* 4 percent for non-biologics.
- Orphan drugs for the cancer sector generated the largest amount of revenues, accounting for 36 percent of the market.
- The US accounted for 51 percent of the global market in 2009.

Since around 2004 the pharmaceutical industry suffered from declining performance, in particular, concerning the numbers of launched drugs and the time and cost to develop them.

The year 2007 pharmaceutical market was characterized as another series of unfortunate events forcing the pharmaceutical industry to turn to new ways to adapt to adversity [Ainsworth 2007]:

- Generic competitors had tightened their grip on branded pharma
- Another wave of expirations of patents for drugs, including high-margin blockbusters. Generics growth was expected to continue to accelerate in the coming year, with another $20 billion in combined sales of branded drugs expected to be coming off patent during 2008.
- A declining number of new drugs were approved, more were failing in development.

To adapt also to increased regulatory scrutiny, pharmaceutical companies were beginning to experiment with technologies that can reduce the overall costs and increase the effectiveness of compliance monitoring.

The consensus seemed to be that the blockbuster model (with $5-$10 billion-plus per year products), on which this industry has historically been largely based, will not survive. Additionally many blockbuster drugs will lose their exclusivity in 2015 [Ainsworth 2007].

Hence, pharmaceutical companies entered into an increasing number of joint ventures and third-party relationships and *a trend to be more toward alliances* emerged.

All this shifted the focus of pharmaceutical companies from the essential medicines to a *new business model* focusing, for instance, on orphan drugs. Orphan drugs were seen as "niche busters" that may help pharma companies to reduce the impact of revenue loss caused by patent expiries of blockbuster drugs.

> Pharma companies' *new business model of orphan drugs* could offer an integrated healthcare solution that enables pharma companies to develop newer areas of therapeutics, diagnosis, treatment, monitoring, and patient support. Incentives for drug development provided by governments and support of FDA and EMA are a further boost. [Sharma et al. 2010].

The products can move through approval quickly, bring high prices, and enjoy seven years of market exclusivity by law (in the US). Although there are an estimated 7,000 orphan or rare diseases – each of which affects fewer than 200,000 people – only about 350 therapies to treat them are approved [Thayer 2012]. Still, orphan drugs were an $80 billion market in 2011 according to EvaluatePharma [2014].

For pharmaceutical companies, it has turned out that orphan drugs offer a greater return-on-investment than non-orphan drugs. Orphan drugs that have been filed for regulatory review or are in phase III trials provide a 1.7 times greater return of investment than non-orphan drugs. Moreover, phase III development costs for orphan drugs are half of those of non-orphan drugs, even though orphan drug development time does not appear to be any shorter [EvaluatePharma 2013]. And the smaller patient populations for rare diseases made clinical trials relatively easier and cheaper.

EvaluatePharma [2013] reports, for instance, that

- Of the 43 new drugs approved by the US FDA in 2012, 15 were orphan drugs, representing 35 percent of the industry's new drug output.

In 2006, 13 out of 19 blockbuster orphan drugs were biologics, but the market exclusivity period had already expired for nine of these. These drugs were able to maintain their market position because of the lack of competition from biogenerics [Ariyanchira 2008].

For instance, Ariyanchira [2008] presents a list of biologic blockbusters with expired market exclusivity in the US. Lists of current Worldwide Top Selling Orphan Drugs (and Top Producers) are listed in EvaluatePharma [2013; 2014].

According to EvaluatePharma [2014].

- Median cost per patient differential 19 times higher for orphan drugs compared to non-orphan
- Revenue per patient for the Top 20 USA selling orphan drugs is moderately correlated (R2 = 0.61) to the number of patients treated in 2014. A similar analysis of the Top 10 selling Ultra Rare drugs confirms a closer correlation (R2 = 0.85).
- This analysis confirms industry perceptions that smaller patient groups allow a pricing premium to be achieved *versus* non-orphans.

Historically, rare diseases received little attention from pharmaceutical multinational corporations (MNCs) as the small target audience could not justify the huge investment needed for drug development. Incentives offered under the ODA was more for the survival and growth of startups [Ariyanchira 2008].

On the other hand, the biotech sector realized the benefits of ODA right from the beginning. Many successful biotech companies came into the market with orphan drugs, which provided these companies a space of their own, free of competition from big pharma.

As a general rule, orphan drugs were not expected to create high revenues, which is why ODA was proposed in the first place. But in 2006 50 orphan drugs broke that rule with annual revenues exceeding $200 million. Out of these, 19 were blockbusters. These highly successful orphan drugs have played a crucial role in changing the industry's perception about orphan drugs [Ariyanchira 2008].

> Some of the key growth factors involved in the transition of orphan drugs into blockbusters include *market exclusivity options for multiple orphan indications, off-label usage (for a use other than the one for which it was approved) and expansion to non-orphan indications, and freedom from generic competition*. Although drug companies cannot promote off-label use [1], physicians can legally prescribe drugs this way. They do so at a rate of roughly 20 percent of all prescriptions in the US [Thayer 2012].

Market exclusivity played a crucial role in the success of the orphan drug market (7 years of market exclusivity in the US, 10 years in the EU). Market exclusivity by itself, however, is not a great incentive for investing since orphan indications have a small market size. On the other hand, *opportunity to expand to related orphan indications* offers the potential for a significant collective patient population.

> Focusing on large therapeutic areas such as cancer, and acquiring approvals for multiple related orphan indications, has proven to be a good strategy for many drugs. One classic example is Gleevec from giant firm Novartis, a kinase-targeting drug for chronic myelogenous leukemia (CML).
> One year after receiving FDA approval for CML, the company received another orphan drug approval for gastrointestinal stromal tumors. Further focusing its efforts to gain approvals for multiple orphan indications, Novartis gained five more approvals for Gleevec [Ariyanchira 2008].

Furthermore, *serving many "small" markets around the world* would also provide a significant increase in the overall addressable patient population.

Biotech companies have long championed the development of orphan drugs. And as the biopharmaceutical market is highly attractive to generic companies it was clear that legislation permitting biogenerics (biosimilars) would come sooner rather than later. Such legislation would have a tremendous impact on the orphan drug market. With reduced profitability, attracting investment in areas with low economic return will become a challenge [Ariyanchira 2008].

However, most often, big companies choose to acquire or collaborate with biotech companies rather than start a new drug development program targeting an orphan disease.

Nevertheless, the process to develop a biogeneric drug is more complex than that of developing a generic copy of a chemical-based drug. The fact that achieving similar levels of clinical efficacies by duplication of biologics is not as easy as for conventional drugs and was delaying the competition for orphan biologics from generic drugs. Due to the biological processes involved in making a biologic, it is nearly impossible to exactly duplicate one. The challenge for regulators and companies, then, is to ensure that the small differences between the products do not cause safety or efficacy problems in patients

The future of the orphan drug industry will depend heavily upon the entry of biogenerics ("biosimilars"), since biologics account for over 60 percent of the orphan drug market. It can be expected that the orphan drug market growth will remain positive as more and more governments are taking action to promote this sector [Ariyanchira 2008].

Biosimilars are approved in the highly regulated markets of US, EU, Canada, Australia and Japan via stringently defined regulatory pathways [Cauchi 2015; FDA; EMA; Gaffney 2014].

In the US there is an “abbreviated licensure: Pathway for biological products that are demonstrated to be “biosimilar” to an FDA-licensed biological product or “interchangeable” with it. This pathway is provided in the part of the law known as the Biologics Price Competition and Innovation Act (BPCI Act). Under the BPCI Act, a biological product may be demonstrated to be “biosimilar” if data show that, among other things, the product is “highly similar” to an already-approved biological product.” [FDA]

FDA has defined the notions “biosimilar product” and “interchangeable biological product” and requires licensed biosimilar and interchangeable biological products to meet the Agency’s rigorous standards of safety and efficacy. That means patients and health care professionals will be able to rely upon the safety and effectiveness of the biosimilar or interchangeable product, just as they would on the reference product.

EMA's guideline refer to “Similar Biological Medicinal Products” and explains what it means by a "similar" biological medicine. Four qualities must be taken into account, EMA says: Safety, efficacy, quality and biological activity.

EMA says [EMA; Gaffney 2014] “each biosimilar product will have to be evaluated based on its own merits. For example, regulators say they plan to evaluate the analytical methods, clinical comparability models and manufacturing processes used to create and validate the biosimilar product. Products that can be ‘*thoroughly characterized’* and shown to be similar to the reference product are more likely to benefit from EMA's biosimilar approach.”

Though EMA will require that all reference products should be authorized in the European Economic area the regulator will allow companies to compare a biosimilar "in certain clinical studies and *in vivo* non-clinical studies" with a non-authorized comparator, as is the FDA.

As with other guidelines on the subject, a "stepwise approach" for firms is recommended to build upon rigorous data at every stage of the evaluation process.

Notably, EMA explains [Gaffney 2014]: "*If the biosimilar comparability exercise indicates that there are relevant differences between the intended biosimilar and the reference medicinal product making it unlikely that biosimilarity will eventually be established, a stand-alone development to support a full Marketing Authorization Application (MAA) should be considered instead*."

Looking at the API environment ChemCon is operating in some basic facts shall be outlined. The global API market is highly fragmented – differentiating essentially

Source and purpose of manufacturing:

- Captive API manufacturing (in-house for own use)
- Merchant manufacturing, API contract manufacturing (for customers’ use)

Technical type:

- Synthetic chemical API
- Biological API

Type of drug (and orientations for CROs/CMOs):

- Branded or innovative prescription drugs
- Generic prescription drugs
- Over-the-counter (OTC) drugs.

The *global market for APIs for human use* was valued at $101 billion in 2010. Of the total market value, the *captive market* (APIs produced by pharmaceutical companies themselves for their own needs) accounted for 61.4 percent of the total API market, or $62 billion, in 2010. The *merchant market* for APIs (APIs sold by third parties) accounted for the remaining 38.6 percent, or $39 billion. India, China, and Italy will continue to be major suppliers of APIs to the global

market, with Indian suppliers expected to see strong growth during the next five years. [Van Arnum 2012].

The *global API merchant market* is almost evenly divided between *APIs supplied to the generic-drug market and APIs supplied to the innovator-drug market* (also called branded drugs) [Van Arnum 2012].

The *global API market* (*merchant and captive market*) was valued at $113 billion in 2012, up from *$91 billion in 2008*. The global API market grew at an annual growth rate of 7.2 percent from 2004–*2008 [*Van Arnum 2013*].*

In 2008, the *global captive API market* was valued at $55 billion and rose to $69 billion in 2012. The *global merchant API market* was valued at $36 billion in 2008 and increased to $44 billion in 2012 [Van Arnum 2012; Chao Xiong 2011].

In 2004 the *merchant API market* was worth $28 billion. Drug companies made most of the world's APIs, about $41 billion worth in 2004, for their own use (captive market) [Thayer 2006].

The *global generic API merchant market* was valued at $17 billion in 2008 and rose to $22.5 billion in 2012. In 2012, the *global branded, innovator API merchant market* was valued at $21.5 billion, slightly less than the generic market. The strength of the generic API merchant market is expected to continue [Van Arnum 2012].

In another source [Pollak 2011] in 2008 global sales of merchant APIs for branded, patented drugs was given as $19.0 billion, those of APIs for generics was $17.0 billion totaling $36.0 billion.

For market players pursuing high-tech routes can be a differentiator, especially from competitors in low-cost regions that offer undifferentiated services. But, whether it is technology or service depends on a customer's specific requirements; developing a track record for delivering *whatever it is a customer needs is key*.

It is about the API manufacturer's competitiveness, regulatory history, manufacturing capabilities including quality workforce and what other products it manufactures. And for generic companies it is whether it can provide the API in the specific way the generic company demands.

When a generic company is trying to circumvent a patent, how fast the API manufacturer can develop an alternative non-patent-infringing process is critical to the generic company's success in gaining first approval.

As described above over more than the last decade the pharmaceutical industry was hit by a number of issues, requiring rethinking its main business model and implementing new approaches. Analysts said the crisis is self-evident and change inevitable [Runge 2006:190-198]. The pressure to do that fast was further increased by the recent Great Recession (Dec. 2007 – June 2009, 1 year, 6 months – as defined in the US).

Specifically the rise of generic drug manufacturers are posing stiff competition to pharma multinational corporations (MNCs) in pricing. Furthermore, an increasing number of biotechnology-based drugs entered the market. European countries such as the UK, France, and Germany, but also the US are promoting the use of generics by providing incentives to the doctors for writing prescriptions relating to generic drugs and also to the pharmacists if they offer the generic equivalent of prescribed drugs.

Correspondingly, to become more effective in drug discovery, in recent years the drug industry's discovery paradigm has shifted to *identifying targets, finding compounds to hit them, and then optimizing leads*. [3] Before this, industry relied more on *in vivo* phenotypic screening, intuition, and serendipity. But the industry has not gotten any better at predicting valid targets or developing successful candidates [Thayer 2012].

Some pharma companies look at new compounds from the start as potential treatments for multiple diseases. As biological systems overlap, researchers may share compounds that fail in one disease with researchers working in other areas. Although safety is always a concern, side effects or toxicity in one application may not be an issue when a drug is delivered differently or at a different dose. In fact, "what's a side effect for one disease could be the disease indication for another." [Thayer 2012]

High Potency Active Pharmaceutical Ingredients (HPAPIs)

High Potency Active Pharmaceutical Ingredients (HPAPIs) is a recent key concept to renew the pharmaceutical industry and is regarded as a boon for the pharmaceutical industry. The HPAPI segment is the potential cash cow of the pharma procurement basket but the challenge is understanding the market and fine tuning procurement approaches for this technology.

A majority of the top pharma multi-national corporations (MNCs) like Roche, Novartis, GSK, Pfizer, Merck etc. are currently focusing on building their pipelines with high potent drugs, especially for cancer treatments [Shruthi 2012].

Advances in clinical pharmacology and oncology research have positively impacted the demand for HPAPI worldwide in the last decade. Moreover expansion of the global oncology therapeutics market has also created an environment conducive to the growth of the HPAPI market.

Since mapping the human genome, the war on cancer has seen a major shift, with there being potentially a different drug to be used not only for different cancers, but also for different patients. It will require changes not only in regulatory policy, but also how we think of drug development and production. HPAPIs are able to target and eliminate specific diseases, often taking patient-specific genetic information into account [Patnaik 2011].

> The High Potency Active Pharmaceutical Ingredients (HPAPI) market is driving the active pharmaceutical ingredient (API) market growth globally at a fast rate.

There is an increase in consolidation within the pharma industry both for the innovative pharma firms and the CMOs or CDMOs. This means also via related streamlining pharma companies can transfer the innovation risk to the vendor.

The resource demands and level of specialization needed to manufacture *relatively small volumes of HPAPI* means that often it is economically not viable for pharma companies to keep this in-house. Therefore, there will be growth in demand for manufacturing of HPAPIs destined for use in new, to be patented products.

Pharma MNCs and contract manufacturing organizations (CMOs) are looking to invest in infrastructure and technological capabilities for HPAPI manufacturing.

GBI Research [2010] presented results of inquiry into the HPAPI scene that HPAPIs are the fastest growing segment of the API market worldwide and forecasting the period between 2009 and 2015 with many companies poised for massive expansions of the facilities for producing such compounds. Revenues in the global HPAPI markets were given to be $5.9 billion in 2005 and $7.5 billion in 2009.

During that period the market was dominated by patented HPAPIs by the innovators and the branded sector held the majority share of the market (81 percent; generics 19 percent). However, the generic sector was set to grow as the branded HPAPI drugs will go off patent in years to come [GBI Research 2010].

In 2009 the US was seen as the biggest market for HPAPIs (46 percent), followed by Europe (35 percent) and then Asia (9 percent) with Japan leading and China and India following fast. The highest growth rate was attributed to Asia and Pacific (APAC).

Also a number of contract manufacturers were setting up High Potency API manufacturing capabilities. And GBI Research [2010] revealed an increasing trend of contract manufacturing being used in the HPAPI segment. Heiss [2015] provides a list of recent investments for HPAPI capabilities by CMO companies.

HPAPIs result essentially from *translational science*. [4] In translational research, basic research gives input to the development of a treatment or other forms of interventions, but considerations of practical problems inform what questions basic scientists should look at. Ideally, it goes back and forth.

During the last decade, the demand for HPAPIs has grown rapidly, mainly as a result of advances in clinical pharmacology and oncology research [PharmaBiz Editor 2014].

According to Heiss [2015] HPAPIs may have

- Biological activity at approximately 150 μg/kg of body weight or below in humans (therapeutic daily dose at or below 10 mg)
- An occupational exposure limit (OEL) at or below 10 $\mu g/m^3$ of air as an 8 h time-weighted average (TWA)
- High selectivity and/or with the potential to cause cancer, mutations, developmental defects or reproductive toxicity at low doses.

Cytotoxics are a sub-category of high potency drugs:

- Pharmacological agents that inhibit the proliferation of cells within the body
- Agents that possess destructive action on certain cells that may be genotoxic, oncogenic, mutagenic, teratogenic, or hazardous to cells.

Most commercial anti-cancer drugs are cytotoxic. Cytotoxic drugs are high potency, but not all oncology drugs are cytotoxic.

While one may initially think of HPAPIs as chemically derived products, biological therapeutics – such as monoclonal antibodies – are also HPAPIs by their very nature.

While in the past anti-cancer drugs targeted only cells in the cell-cycle (the sequence of growth and division of a cell) and did not take into account the uniqueness of every type of cancer, advanced clinical research is shedding light on the specific therapeutic targets.

As such, pharmacological research is entering into a new era of targeted molecules with selective cytotoxicity. Related bio-conjugates combine the highly specific delivery of an HPAPI to targeted cells, with significantly reduced side effects to non-targeted cells – a “smart bomb” of drugs known as *antibody drug conjugates*, or ADCs [Patnaik 2011].

Antibody drug conjugation technology uses monoclonal antibodies (made by identical immune cells that are all clones of a unique parent cell) or other biologics to deliver HPAPIs to targeted cells. In conjugated form, the HPAPIs exhibit more selective cytotoxicity, thereby, sparing non-target cells from many of the toxic effects and improving the safety profile. Structurally ADCs include a small-molecule, cytotoxic payload and an antibody connected with a linker. [5]

With three components to manufacture and combine together under containment conditions, the production of ADCs can be a complex process.

Conjugation of highly potent cytotoxic molecules creates an environment significantly more challenging than that needed for handling bio-molecules, as in API manufacturing. For bio-molecules, the key is avoiding contamination from people involved in the production process [Patnaik 2011].

In HPAPI production worker protection takes on a whole new meaning. Complex air-handling requirements are carried out to prevent the material from entering the environment, and workers are required to wear full protective gear [Patnaik 2011].

The number of ADCs in development has grown rapidly in recent years and is also a factor for the growth of the HPAPI market. “The toxin that is conjugated to the antibody in ADCs has been the fastest growing segment of the HPAPI market, with demand quickly increasing in recent years.” [Challener 2014]

Currently, the majority of HPAPIs are anti-cancer products (cytotoxics and cytostatics) (Figure 1). Oncology is the largest therapeutic area by far in terms of revenue generation for pharma [PharmaBiz Editor 2014]. However, other HPAPIs include therapeutics such as hormones, narcotics, retinoids [TotalBioPharma 2014] as well as tyrosine kinase inhibitors and derivatives [Challener 2014]. Heiss [2015] lists also respiratory disorders and glaucoma to be treated by HPAPIs.

Cancer and hormonal replacements are high revenue segments in the industry. In addition, extended application of HPAPI is in cardiovascular, central nervous system and musculoskeletal drugs adds to the attractiveness of the segment [Shruthi 2012].

Around 60 percent of global HPAPI produced is being used for making high potent oncological drugs. Currently there are 288 small molecule targeted therapies at various stages of development for the treatment of cancer [Shruthi 2012].

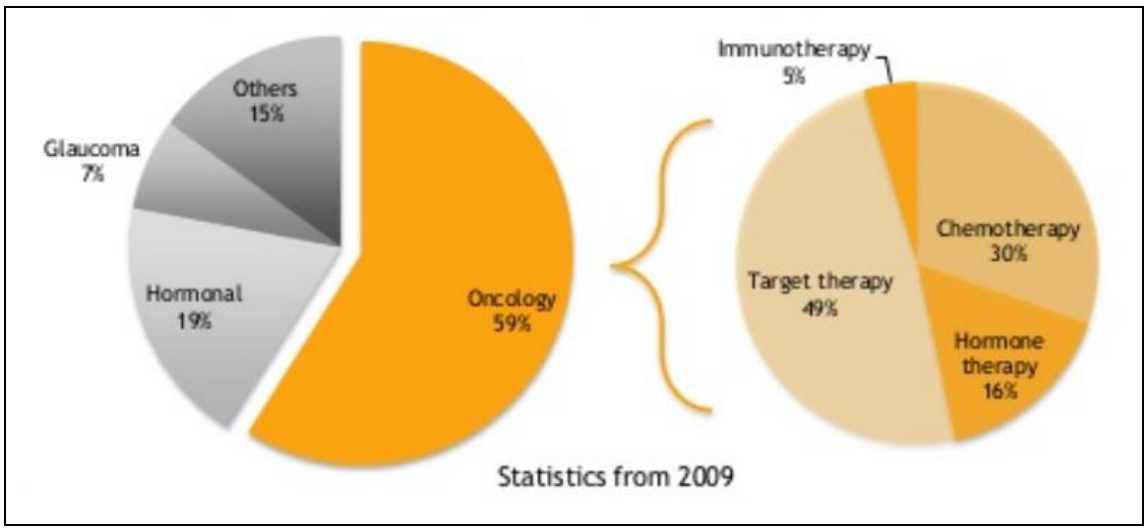


Figure 1: HPAPI market growth drivers – clinical [Heiss 2015:13].

HPAPIs offer the benefit of requiring lower amounts of compounds to be produced. However, these new HPAPI are not only highly potent, but are also potentially harmful when present, even at very low levels, in another product as a cross-contaminant or in the air to harm workers. Multiproduct facilities pose the greatest risk to exposing one API to another high potency API.

HPAPIs must be *produced under special conditions* that not only protect the operators from exposure to the compounds, but also prevent contamination and the inadvertent carryover of a different product that was previously produced or is simultaneously being manufactured. While today’s modern HPAPI facilities are meeting today’s requirements, there is a continual need to improve these technologies going forward.

The focus will be on the development of production and handling methods that will be either single-use systems and/or new technologies which can continue to improve upon today’s product protection of the API from cross-contamination from other HPAPI produced at the facility or site [Transparency Market Research 2015].

The new technologies that can provide increased protection of the API from cross-contamination by “nearby” HPAPIs when reactors are used for both kinds of products must address *cleaning and removal* steps.

> Appropriate *process design* is in fact critical for the entire HPAPI production operation [Challener 2014].

The development of related new technologies is of increasing importance as the number of multiproduct facilities, which post the greatest risk of contamination of HPAPIs, are growing around the world in order to meet the greater demand for these products [Challener 2014].

The advent of HPAPIs has required not only a rethinking of pharmaceutical production operations, but also drives advances in equipment design [Patnaik 2011]. In response to the demands of HPAPI production, equipment manufacturers have stepped up with many adaptations and enhancements in product design with innovations. An overview of corresponding equipment is given by Patnaik [2011].

The major difference between API and HPAPI manufacturing facilities is the *specialized containment* that ensures both the employees and the environment are protected. This requires investment of millions of dollars over and above what a GMP facility may entail.

The use of *analytical methods* that provide very low detection limits is also necessary in order to confirm that the required residue levels have been achieved. And there is certainly an interest in continually achieving lower detection limits when handling HPAPIs [Challener 2014]. HPAPI uses Process Analytical Technology (PAT) tools to a much greater extent than API does [Patnaik 2011].

HPAPI production challenges may broadly be divided into three categories [Patnaik 2011]:

1. *Handling requirements*: Worker protection is key, requiring complex air and material handling systems
2. *Personnel considerations*: Highly skilled and trained personnel are required, with regular training programs and standard operating procedures (SOPs), full personal protective equipment (PPE), etc.
3. *Plant and equipment*: Specialized and multi-functional equipment for both the handling of the HPAPI as well as air-handling, to include fully contained sampling and testing methods with engineering controls as the primary source for containment and isolation.

The requirement of *highly skilled and trained personnel* for HPAPI production seems to provide a competitive advantage for certain European firms over their US counterparts:

> "Thanks to the eroding pharmaceutical chemicals manufacturing base here in the U.S. over recent decades, the kind of expertise and experienced personnel (a key requirement of a HPAPI facility) to draw from and train in order to establish a safe HPAPI production operation, has gotten more difficult to find. For now, the advantage lies in other markets, such as Switzerland and Germany, where the manufacturing base has remained intact and, in fact, has evolved in the direction of greater value addition. However, some U.S. manufacturers have taken strides in this direction. Most notably, Sigma Aldrich (SAFC) has opened a $30+ million state-of-the-art HPAPI facility in Verona, WI." [Patnaik 2011]
>
> But Sigma Aldrich was acquired in September 2014 by the German pharma and specialty chemicals firm Merck KGaA for $17 billion [Heiss 2015].

Appropriate process design at the development scale is also necessary to ensure that the process will fit the equipment and capabilities of the facility upon scale-up. Most very highly potent APIs and ADC payloads require small clinical and commercial quantities, and the production of gram-scale GMP APIs and payloads can be challenging.

Single-use manufacturing technologies for controlling cross-contamination and maximum carry-over limits (MACO) after cleaning when implemented as part of a risk-based approach are on the rise for small-scale highly potent products such as ADCs. "Another important trend is the widespread acceptance of portable dedicated equipment, including both single-use and

permanent systems for small-scale production of very highly potent compounds such as ADC payloads, which often have OELs lower than 0.1 µg/m3·8 h." [Challener 2014]

According to market research firm RNCOS the value of the global HPAPI market will reach $15.3 billion by 2017 [Challener 2014]. Transparency Market Research [2015] attributes the global HPAPI market to grow at 9.9 percent CAGR between 2012 and 2018. According to studies, the HPAPI market, which was valued at $9.1 billion in 2011, is estimated to reach $17.5 billion by the end of 2018. Other sources valued the HPAPI market at $8.9 billion in 2011.

For the worldwide API market for 2011 Heiss [2015:7] gives $107 billion as an estimate. HPAPI is a niche high growth segment and contributes around 10 percent to the global API market [Shruthi 2012] which – with ca. $10 billion – is essentially in line with the above values.

Specifically, as HPAPIs are increasingly used in the form of Antibody Drug Conjugates (ADCs), Monoclonal Antibodies (mAbs) and other biologically active drugs, the increase in the number of approvals for these are expected to drive the growth of the HPAPI market at a rate of eight to nine per cent between 2011 and 2015 [Shruthi 2012].

Compared with the overall growth in the *pharmaceutical market* of about seven percent per year, *HPAPIs are estimated to have an annual growth of 12 percent* [PharmaBiz Editor 2014]. Earlier source reports HPAPIs to grow in the pharmaceutical industry with a rate of 8-10 percent [Shruthi 2012].

The endeavor adopted by *federal government to promote generic drugs* is believed to have bolstered the market opportunities for HPAPIs. In addition, insurance companies are likely to favor generic drugs as compared to patented drugs due to cost effectiveness [Transparency Market Research 2015].

Overall, present market conditions reflect impressive growth opportunities for HPAPI in the near future. However, the same may also attract a large number of new players to the market, which amplifies competition, making the global HPAPI market highly fragmented [Transparency Market Research 2015].

HPAPI production with such annual growth rates represents a second wind to many CMOs, but there is still a learning curve even for long-established API manufacturers.

And, as the cost of technology and processes to establish a plant and comply with the regulations is extremely challenging, there are *high barriers of entry* into the HPAPI market [Shruthi 2012].

Drivers of the HPAPI market, according to RNCOS, include a *rising demand for cancer HPAPIs* (Figure 1), increased private player participation, particularly in developed regions, and technological advances in process manufacturing of these challenging APIs [Challener 2014].

Geography wise, *North America* has been dominating the global HPAPI market, owing to high investments in the development and expansion of healthcare systems in the region. The *European parts* of the HPAPI market have witnessed fluctuating growth over the past few years. However experts believe increasing demand for oncology drugs will ensure rapid growth of the HPAPI market in the region in near future. *Asia Pacific* is also expected to register impressive growth in the HPAPI demand over the next few years owing to significant boost in the production of generics. India and China, are expected to witness highest growth in forthcoming years [Transparency Market Research 2015].

HPAPI has immense potential to be a highly lucrative segment in the near future, and the related current need for HPAPI manufacturers is to elevate their operational and technical efficiency to stay ahead of the market. For instance, Shruthi [2012] describes HPAPI sourcing strategy for pharma companies as well as scaling up the operating model of HPAPI manufacturers.

For instance, manufacturers may look to have an *effective labor force* trained in the *technology* to handle requirements and *safety regulations*, so as to maintain the operating guidelines in keeping toxicity within the acceptable levels: A two pronged approach of achieving operational efficiency and cost optimization, by streamlining plant operations through technical capabilities and skilled labor [Shruthi 2012].

This would require a balance between cost and containment of the toxicity. Any concessions to the operating standards will add to the risk of a potential mishap due to occupational exposure limits going above the acceptable limits [Shruthi 2012].

Although the market at present is led by the patented high potency drug development, the majority of the patents in the branded sector are slated to expire in the next few years. This would translate into a favorable market prospect for HPAPI manufacturers and help them accommodate to the various demands of clients by producing generic versions of the popular compounds in bulk [Transparency Market Research 2015].

The HPAPI market is also driving the active pharmaceutical ingredient (API) market growth globally at a fast rate. This coincides with the API market facing a period of large growth as its dynamics have undergone a major change with the expiration of patents pertaining to global best-seller drugs in the US. This has led to drying up of pipelines for new drugs, and therefore the market for generic drugs is quickly growing. Thus, the patent expiry factor is slated to drive the API market for the coming years. APIs to generic drug manufacturers coupled with increased outsourcing of bulk drugs by MNCs has made the API business lucrative [PharmaBiz Editor 2014].

China remains the largest API supplier with 18 percent of the global market, valued at more than $80 billion. India is one of the leading players in the global market for APIs with a value share of approximately 13 percent. It is estimated that India is the third largest API producer in the world after China and Italy. However, by the end 2015, India is expected to be the second largest producer after China [PharmaBiz Editor 2014].

North America accounts for the highest API market; with a share of 32 percent in 2011 and is expected to decrease to 27 percent by the year 2016. Europe accounts for 31 percent of the total API market and is expected to decrease to 29 percent by the year 2016. Moreover, Asia accounts for 26 percent market share as of the year 2011 and is expected to grow to 34 per cent by the year 2016 [PharmaBiz Editor 2014].

Awards and Publicity

In 2004 ChemCon was awarded the Prize for Young Companies by the L-Bank and the State of Baden-Württemberg (first among 565 participants). ChemCon leaders wanted the prize money of €40,000 to be used for the liquidity of their company [BIOPRO 2004c; Gonser 2005; MBG].

In 2009 ChemCon received the STEP Award in the category “Processes”.

STEP AWARD Spirit to expand	The STEP Award is a competition to reward innovative and high-growth companies in Germany, Austria and Switzerland. The initiators are Infraserv Höchst and Frankfurt BUSINESS MEDIA – The FAZ-Fachverlag. The aim is to give companies in the growth phase important impetus for its successful development [STEP Award].

Main Sponsors	STEP Award 2009: Commerzbank, Hessen Agentur, Merck Serono and Sanofi-Aventis. In addition, a number of other companies and institutions participate as a sponsor.

ChemCon GmbH specializes in the development and production of small quantities of highly active pharmaceutical ingredients, among other applications, for rare diseases focusing on metal-containing substances. The related *innovative concept* is the *adaptation of infrastructure and means of production to the respective manufacturing process*. This allows producing such active substances quickly, in high purity, with great certainty for employees and environmentally friendly [STEP Award 2009].

ChemCon recently participated in ”Service Provider of the Year 2014“, a competition organized by the Baden-Württemberg Ministry of Finance (State of Baden-Württemberg) and appeared within the Top 20 of the competition of over 1 million principally eligible, registered companies in Baden-Württemberg [ChemCon 2014a].

Participants submitted descriptions of their companies' services and could be judged in one of two categories; either exemplary customer satisfaction or innovative services. ChemCon's Dedicated Equipment Strategy, which had already won the Step Award in 2009, is an *innovative way of optimizing its manufacturing facilities to meet the exact requirements of the customers.* Dedicated glassware is used for each project to eliminate the possibility of cross-contamination, while the cleanroom facilities and manufacturing equipment can be adapted on a project by project basis so that one cleanroom can be used to manufacture a range of different APIs.

The Entrepreneurs

Dr. Raphael Vogler (born 1968) and Dr. Peter Gockel (born 1962) founded ChemCon GbR in January 1997 in Freiburg i.Br. (im Breisgau, Germany) which was legally changed to ChemCom GmbH (LLC) in 1999 [Gonser 2005; Zülch et al. 2006:223; Vogler 2006b:97-98; Vogler 2008:7; aiHit Ltd. 2015].

Raphael Vogler served as Head of Business Development and Chief Executive Officer (CEO) of ChemCon GmbH and was responsible for the image and representation of the firm [Zülch et al. 2006:223]. Peter Gockel became Chief Scientific Officer (CSO) and later also CEO of ChemCon America, Inc.

Peter Gockel studied chemistry at the Albert-Ludwigs-Universität Freiburg and received his doctorate degree in 1995 from the Inorganic Chemistry Department of Prof. Dr. H. Vahrenkamp.

He passed his Abitur (final examination of a German Gymnasium, a prerequisite for studying at a university) in 1981 focusing on chemistry and biology. In 1984 he started to study chemistry, married in 1986 and presented in 1991 his diploma thesis dealing with “metals in life processes”. Currently, he has three grown up children [Vogler 2008:3].

According to a LinkedIn entry Dr. Gockel was Project Manager (January 1996 – January 1997) of a project dealing with the “Development of Catalysts for Carbon Dioxide Fixation” funded by the German Federal Ministry of Research and Technology (BMFT).

Generally, there is much more information publicly available for Raphael Vogler than Peter Gockel. It looks as if Vogler is much more extrovert and open to communication and networking than his co-founder, in line with his role of a CEO.

In September 1994 Raphael Vogler began his work on a diploma thesis with the Inorganic Chemistry Department of Prof. Dr. H. Vahrenkamp and received his doctorate degree in 2000.

The PhD student Peter Gockel became his direct colleague and supervisor. Gockel and Vogler were initially workmates; they produced many results and, over time, a *friendship* developed. And finally their business idea emerged and matured! [Vogler 2008:2-3]

Raphael Vogler is a goal-oriented person whose goal naturally varied according to age. For instance, at fifteen his goal was to engage in scientific activities. Correspondingly, when he passed his final examination at the Gymnasium in 1987 (Abitur) his focus was chemistry and mathematics. A following community service ("Zivildienst") with the German Red Cross (DRK) generated his interest in medicine. In 1989 he started to study chemistry at the Freiburg University and at the age of 23 his goal was working with people [Vogler 2008:2].

The cornerstone of the career of Raphael Vogler was placed already at the Otto-Hahn-Gymnasium (OHG) in Tuttlingen (Germany) when he chose mathematics and chemistry as advanced courses. The classes gave him so much that he decided to study chemistry.

Together with his fellow student Peter Gockel he realized in 1994 the first business idea focusing on consulting: They founded the company ChemCon, Chemical Consulting GbR. For an entry into production the necessary capital was lacking [Gonser 2005].

Striving for independence through self-employment was exemplified to Dr. Vogler already during teenage years. The desire to become self-employed was in line with corresponding role models in the family.

His mother had always her own small hair salon in the family's house. And Dr. Vogler said: "I had no inhibitions regarding self-employment; it always attracted me. Ultimately, however, I do not consider self-employment as a success *per se*, but the realization of an idea. If this can only be solved through self-employment, then you should not be deterred." [BMBF 2005] His father was an independent businessman [Kramer 2014].

Founding the company ChemCon as a duo ("entrepreneurial pair" [Runge:191,305,319,338]) was seen by Dr. Vogler as an advantage.

Based on social ties of *friendship*, reasons put forward by Dr. Vogler included the founder colleagues to be very *different personalities, but complementing each other* very well. "We blindly trust and understand each other perfectly despite our diversity." In addition, both may act as a *soul mate* for the other one: "It is sometimes a very good feeling, not to be alone, because in spite of many people around you can often feel very lonely as an entrepreneur," said Dr. Vogler. When both met at the university during practical work in chemistry laboratories "we both had much fun with our work." [BMBF 2005]

Concerning key determinants of entrepreneurship Dr. Vogler explains that most of his *ideas* result from conversations with friends and colleagues, but he is aware that having an idea is only a first step. And he continued, "At the university I have met many people who had good ideas. But the much more critical aspect is that you have the courage and the stamina to implement your idea. One of my life philosophies is the following famous quote: There is nothing good, unless you do it!" [BMBF 2005]

Concerning leadership as a founder and entrepreneur Dr. Vogler emphasizes that you have to be an outspoken "allrounder" (German meaning) and ready to take on a wide variety of tasks, such as long discussions with lenders or suppliers; you must be able to present extensively and should be able early on to deal with guiding and motivating employees [BMBF 2005].

Concerning the importance and relevance of a having a business plan when starting a new venture Dr. Vogler emphasized several aspects, but did little to be explicit what in his view makes up a "good" business plan:

"In the beginning you hold the business plan as a necessary evil, and for a lot of work; the latter is certainly true. I've learned that the business plan is perfectly suited to prepare the concretization of your ideas. A good business plan is worth gold, for oneself as well as for financial backers. What is equally important is the continuous further work on the business plan, since the only known certainty is the change." [BMBF 2005]

Finally, Dr. Vogler seems to believe in the power of networking and team work. He was a founding member and early president of the life science business association "BioValley Deutschland e.V.", Freiburg i.Br. and was also one of the founding fathers of the "Drug Discovery Net" [Zülch et al. 2006:223].

Remarks Concerning Corporate Culture

The following remarks regarding corporate culture focus essentially on the first seven to eight years of ChemCon's existence. During the early period of startups important developments of corporate culture will take place and much of it will be retained at later phases of a successful firm.

Fundamentally, ChemCon's corporate culture is *customer-oriented* which is mandatory for a service organization. Correspondingly, it values the *trust and confidence its clients* attribute to the firm to engineer successful outcomes in a timely and efficient manner. Furthermore, there is a *continuous striving for technical excellence and quality*.

Therefore, *employee development and training* has been implemented as a defined organizational process covering all employees.

While many small and medium-sized German companies do not hire trainees anymore, ChemCon provides training and apprenticeship. Occupations, for instance, include chemical lab technicians ("Chemielaborant/in") and industrial clerks ("Industriekaufmann/-frau").

Already in September 2003 ChemCon became accepted by the Chamber of Industry and Commerce (IHK) as a company authorized to train chemical lab technicians/technical assistants; since 2004 it was also authorized to train industrial clerks [Vogler 2008].

Training is necessary for operation in the highly complex technical and norms and standards- and regulation-driven environment and furthermore it socializes the apprentices into the corporate culture. It ultimately turned out to be a *competitive advantage* specifically for services in the highly sophisticated area of HPAPIs.

Now, every employee receives training in cGMP and standard operating procedures (SOPs). R&D and production staff is trained in laboratory techniques and methods as well. The independent quality assurance (QA) department reviews all data and procedures [ChemCon – Quality].

ChemCon´s APIs are subject to full release by qualified persons. Its quality review process provides assurance of the quality system and the effectiveness of corrective and preventative actions (CAPA). Routine internal and external quality audits for cGMP compliance assure that ChemCon's quality systems are consistent with current industry standards [ChemCon – Quality].

Other notable features of ChemCon's corporate culture are described by Vogler [2006b]. Internal behavior is guided by rules for *communication, information sharing and team formation* for all employees – meaning the rules are transparent, can be put into practice and employees are aware of these.

During the early phase of ChemCon and anticipating the FDA-certification process the emphasis was on developing technical SOPs (standard operational procedures), on regular training and the strict implementation. Additionally, to optimize internal organizational processes, clear

rules for business processes were developed and implemented. To fit the fast growth of the firm a *multi-step plan for development* was set up [Vogler 2006b].

The first step concentrated on customers and generation of transparency for all employees involved in customer relationships based on a Customer Relationship Management system. A commercially available ERP-system was used for this purpose. However, it had to be tailored according to the special needs of ChemCon.

In a second step, via a questionnaire, cooperation capabilities of employees were assessed and the following aspects for improvements were revealed [Vogler 2006b]:

- Assignments of competence and responsibility
- Existence of sufficient rules for leading teams
- Information management.

As a result of utilizing external consulting concerning set up of workgroups highest priority is that the individual employee above all has the *required qualifications* with regard to the tasks at hand and has *excellent team working ability* for a successful integration into the workgroup. Usually management assigns the team leaders, who then are free to select the team members.

Basically no team has more than six members. Teams then work based on a clearly defined task independently and self-responsibly. This is particularly true for the division of (sub-)tasks in the group. Division is based on competencies, knowledge and bents. Apart from professional qualities also social and emotional aspects are considered so that an efficient working atmosphere can be formed which allows constructive criticism. General agreements and clear rules for communication must exist. Mutual trust and acceptance among the team members are basic requirement.

Vogler [2006b:110-111] lists explicitly ChemCon's rules for forming teams and working in teams.

Despite the large possibilities of options for communication provided by I&CT *personal information sharing and face-to-face communication* play important roles whether in small groups looking for problem-solving or in one-on-one talks with employees setting goals and how to achieve them or discussing training needs and planning career ("employee development"). Over time with an increasing number of employees further modes and instruments for communication were established.

Furthermore, management (CXOs) has cultivated *personal contacts* with all employees following a "management-by-walking-around" approach.

Business Idea, Opportunity, Foundation and Product Developments

ChemCon, derived from Chemical Consulting, was founded by Raphael Vogler und Peter Gockel who intended originally to be active as chemical process consultants using the legal status of a GbR (in German Gesellschaft bürgerlichen Rechts) meaning, the owners are generally liable for the debts of the company. Actually it was a PartG – Partnerschaftsgesellschaft – [Vogler 2008:7] which is to a certain degree comparable with a US GP – General Partnership.

PartG is restricted to "professional services" (in German freier Beruf), such as physicians, engineers, scientists, architects, lawyers etc., generally persons with special professional qualifications allowing self-employment.

Peter Gockel and Raphael Vogler started 1997 at the bottom: in the basement of the family home of Peter Gockel [Vogler 2008; MBG 2005] where they also set up a "mini-laboratory" [Gonser 2005; Vogler and Gockel 2005].

Their business idea grew out of joint research including their doctoral theses on peptide synthesis, zinc complexes and stability constant determination using potentiometric titration at the Institute of Inorganic and Analytical Chemistry at the Albert-Ludwigs-Universität Freiburg, led by Prof. Dr. H. Vahrenkamp.

The basic foundation idea [Vogler 2008:5] was specifically the subject and *techniques* of metal-containing biomolecules, *preparation* of related metal complexes and *measuring* properties of metal-containing biomolecules in solution.

- December 1995 – Dissertation Peter Gockel metal-containing biomolecules and *measuring* their properties in solution: "Gleichgewichtsuntersuchungen an Zinkkomplexen cystein- und histidinhaltiger Peptide in Lösung" (Equilibrium studies on zinc complexes of cysteine and histidine containing peptides in solution).
- May 1995 – Diploma thesis of R. Vogler: metal-containing biomolecules, preparation of related metal complexes and dissertation in 2000: "Zink-Peptid-Komplexe als Modellsubstanzen natürlicher Metalloproteine" (Zinc-peptide complexes as model compounds of natural metalloproteins).

ChemCon GbR was founded in January 1997 without customer and order as an idea and based on competencies in synthetic and analytical chemistry. The company got its first order for synthesizing in December 1997. Production began in July 1998 which transformed the consulting firm into a manufacturing company [BIOPRO 2004a].

These two aspects initiated the *innovative founding idea*: Producing active pharmaceutical ingredients (APIs) for *rare diseases* (*orphan drugs*) with the revolutionary main focus on metal-containing active agents (cf. Box 1 for more details).

This means ChemCon is a "competence spin-out" using indispensable special competencies or/and skills, which, at least, one of the founders acquired at a scientific or research institution [Runge:194].

One basis of the business idea "metals in biological processes" was a simple question: How do metals in biological processes? [Vogler and Gockel 2005]

Metal-containing drugs at that time included, for instance [Vogler 2008:5],

- Platinum complexes in cancer therapy
- Gold complexes for arthritis treatment
- Lithium salts in psychotherapy
- Zinc salts in wound healing.

Focusing on *metals for bio-inorganic APIs/drugs* represents a *tremendous scope for things to be discovered* and exhibits *a certain analogy with metal complexes for homogenous catalysis*.

The founders estimated the market potential for their idea to amount to ca. €600 million per year worldwide [Muller and Arzt].

Apart from APIs ChemCon also addresses innovative (fine) chemicals for research purposes.

The two business problems a potential customer will have to which ChemCon will provide the business solutions are [Vogler 2008:19]:

1. He/she does not know how he can *produce gram to kilogram quantities* of the active ingredient.
2. He/she is not even able to produce the active ingredient in the *necessary quality* that it may be used on humans.

ChemCon's fundamental areas of competence are the transfer of a developed process in the laboratory to so-called GMP production (*scale-up*) in *scales from milligram to multi-kilogram* and active pharmaceutical ingredients for *clinical studies* up to commercial grade.

GMP refers to the Good Manufacturing Practice Regulations promulgated by the US Food and Drug Administration (FDA) to ensure that products are consistently produced and controlled according to defined quality standards and the risks involved in any pharmaceutical production are minimized.

There was a structured preparation of the firm's foundation. The first joint official appointment of the later founders showed up in September 1996: Looking for advice for a business startup by the Freiburg IHK Südlicher Oberrhein (Chamber of Industry and Commerce) [Vogler 2008:6]. Such an approach is also observed with the foundation of WITec GmbH [Runge 2014a].

From the first business idea, for which Vogler and Gockel have been declared insane by their fellow students, until the actual foundation two and a half years passed and additionally it took one and a half years until the business went off properly. The first breakthrough was certainly *a first large production order*, an active substance then having been used to treat certain cancers. On this contract the founders had been working for a long time [BMBF 2005].

The *ultimate founding idea* referred to manufacture of active pharmaceuticals for rare diseases with the revolutionary focus on metal-active substances. However, the two to-be founders knew that this would require a lot of money and that as students they would had no chance to get the needed money – and they had no collaterals to get loans [Vogler 2008:5,7].

As a "substitute" Vogler and Gockel generated the idea of establishing a consulting firm for the pharma industry, which would develop chemical processes for the customers and also look after their implementation. However, it soon became clear that without own laboratories and products they would have no chance in this difficult market [Vogler and Gockel 2005; Vogler 2006b:97-98].

Therefore, they focused all their activities on research, and in 1997 the first office was created in the basement of a family home of one of the owners. When the first production order came from the US they moved to the Innovation Park of the Freiburg Industry Area and established in 1998 the first cleanroom for producing APIs [Vogler 2006b:97-98].

Opened in early 1998, the Biotech Park Freiburg was Germany's first business incubator for companies in the biotechnology sector. This facility was an important component of site development in Freiburg: Here entrepreneurs and young companies were offered space and perspective in the dynamically developing field of biotechnology for the successful corporate development. These conditions were then ideal for ChemCon that shortly after BioTech Park's establishment moved into the first available rooms/facilities and over the years continuously expanded its areas.

Two US firms, Chemwerth, Inc. and Strem Chemicals, Inc. played a very important role for ChemCon's start and further development.

Actually, when Raphael Vogler and Peter Gockel were directing ChemCon to be *exclusively* focused on consulting services, they were also involved in a small, third-party-funded experimental lab project at the university [BIOPRO 2008]. And "it became quickly evident that the customer wanted not only advice but our products," said Vogler [MBG 2004]. Consulting remained, after all, an integral part of the company's service.

The American company that financed their small project back in 1994 contacted them and asked them to synthesize a chemotherapeutic drug under GMP conditions. Through this constellation Vogler and Gockel succeeded to catch investment for a cleanroom that was subsequently certified by the American FDA as a GMP laboratory [BIOPRO 2008].

Actually, in Box 1 the foundation environment and process of ChemCon are more complex than described above as outlined by Vogler [2006b].

Getting Strem Chemicals and Chemwerth as very early customers (1999/2000) directed ChemCon inevitably to the US market and to familiarize with the business and legal situation for pharmaceuticals and their educts and to look for establishing an appropriate representation in the US.

With the further development of sales and the US only contributing around 80 percent the company concentrated on the majority of its customers and established a subsidiary in the US. "Our business requires a lot of consultation." [BIOPRO 2004a]

In August 2003 ChemCon America Inc. was founded in Florida, a 100 percent subsidiary of ChemCon GmbH. This well planned step was made to intensify the services for the US customers. Also a local R&D laboratory was planned to follow the sales and service office in the near future.

Chemwerth is a drug development company based in the US that has (now) a department of 16 Regulatory and Compliance employees auditing the factories on a 6/12 month basis utilizing Chemwerth's so-called Six System audit program.

By January 2004 “ChemCon has had a relationship with Chemwerth, Inc. over the last five years as the exclusive US agent for generic products. During that period ChemCon/Chemwerth has had an NDA [6] product approval and a first to market *generic* approval. They were working together on additional *generic products* in the pipeline and expected to be first to market with two additional generics within the next six months.” [ChemCon 2004a; Chemwerth]

The ChemCon/Chemwerth partnership continued to be successful based upon ChemCon’s technical expertise and Chemwerth's strong regulatory compliance program. Relatedly, ChemCon became “visible” in the US at exhibitions and conferences, For instance, “like in the past years, ChemCon decided to exhibit together with ChemWerth at Informex 2004 in Las Vegas organized by SOCMA (Synthetic Organic Chemical Manufacturers Association).” [ChemCon 2004a]

At Informex 2004 “Sharing the booth with ChemWerth was also excellent for intensifying already existing customer relationships.” [ChemCon 2004b].

In March 2004 Prof. Dr. Vahrenkamp from the University of Freiburg and Dr. Michael Strem from Strem Chemicals visited ChemCon’s location in Freiburg. “Strem Chemicals as one of the first customers and Prof. Vahrenkamp … supported ChemCon since its foundation in 1997 with excellent cooperation.” [ChemCon 2004b]

According to Vogler “our first breakthrough was certainly our first large production order, then for an active substance which has been used to treat certain cancers. Only due to this order we have laid the foundation for today's chemical production plant. Towards this contract we have been working long. However, here again, I would emphasize that market, ideas, products and the competition is constantly changing and you have to always be vigilant in order to obtain ever new "breakthroughs" [BMBF 2005].

> Efficient research and development processes which comply with regulatory requirements of the market(s) but simultaneously take care of the commercial interests of the firm may generate important competitive advantages.
>
> Directives and standards do not dictate development processes but provide a framework within which the individual corporate processes must take place. Partners, suppliers, customers and company-internal units have further requirements. Therefore, the created and used processes have to be optimized in a way that they meet simultaneously the regulatory requirements.

The following “timetable” reflects the first years of ChemCon’s essential development steps:

Autumn 1997: The first co-workers entered the company [Vogler 2008:9].

- Thilo Vogler, brother of Raphael Vogler: first business managerial assistant
- Martin Gockel, brother of Peter Gockel: first chemical helper.

November 1997: ChemCon gets its first production order. It is the production of a noble metal-containing medicament for the treatment of lung and prostate cancer.

1998: ChemCon turned to be an API manufacturing company, working under full cGMP compliance. Characteristics of the first contract were [ChemCon 2006]:

- Metal complex of an organic ligand
- Cytostatic substance
- Injectable grade, full microbiological control in a cleanroom environment (injectable APIs are subject to a higher level of microbiological regulation than other APIs)
- Scale: 10 kg per month.

The majority of orphan drugs are cytostatic drugs for the treatment of cancer. The product CC 3 (CC stands for ChemCon 3, for third successful product development), for example, is a substance for the treatment of children suffering from leukaemia [BIOPRO 2008].

December 1997: After a meeting with representatives of the City of Freiburg, the construction of a cleanroom production lab in the new Innovation Park was agreed upon.

June 1998: ChemCon started production in its own cGMP cleanroom laboratory (current Good Manufacturing Practice: highest quality standards in drug production). And in the same year the first employees were hired [BMBF 2005].

November 1998: The first part-time employee, a microbiologist, was hired. Currently he is control manager of the company!

March 1999: After having opened its *first own cleanroom* this was then supplemented by a *research laboratory* and a *microbiological analysis laboratory* [CASID].

March 1999: ChemCon was established as a GmbH (LLC). The very positive growth allowed an extension of the team to 10 employees by the end of the year [BMBF 2005].

May 1999: The first full-time chemist was set. He is now head of research and development.

1999 - 2000: With support of banks ChemCon could build laboratories and production facilities that meet the latest state-of-the-art technology and the highest safety standards.

March 2000: The first trained administration assistant was set.

In 2000 FDA certification was achieved. The two managing directors could also open up the American market. Among other things (like the cleanroom) acquisition of analytical equipment was sponsored by the Bürgschaftsbank (a guarantee bank) and the public MBG Investment Company [MBG 2005; 2004].

In July 2000, ChemCon passed the first FDA audit without shortcomings and thus it was the youngest, independent company in Germany which succeeded in doing this so far [BMBF 2005].

Also in 2000, ChemCon established an *analytical department*, which was expanded continuously until today [CASID].

Concerning intended growth of ChemCon the two scientific founders were aware of their weaknesses! By a skillful personnel policy *business administration* of the company got a firm basis.

By September 2000 a business economist with broad experience in the pharmaceutical industry joined ChemCon as a business angel. By part-time work he took over increasingly the financial planning of ChemCon. Beginning in 2003 he was fully employed as *financial controller* and CFO (Volker Schneid, CFO of ChemCon, formerly Boehringer Mannheim and Roche) [Vogler 2008].

2002: With 25 employees ChemCon was working on ca. 350 projects for more than 30 companies and institutions [Anonymus 2002].

2003: ChemCon could already look back at more than 250 realized syntheses, 25 active pharmaceutical ingredients in different stages of development and four drugs on the market in the US and Europe [BMBF 2005].

The *spatial capacity doubled several times since the founding* of the company and the number of employees increased by the end of 2003 to almost 40. In this year ChemCon provided for the first time also apprenticeships for lab technicians, in 2004 also for industrial clerks [Vogler 2008:17].

August 2003: ChemCon America Inc. was founded in Florida/USA and in the medium term there should be built a development laboratory and a sales department for the US market [BMBF 2005].

January 2004: In the course of the *expansion* of ChemCon´s laboratories all modifications have been done as planned and without interfering with the operational activities. On time on December 1 ChemCon was able to start using two walk-in fume hoods and the additional low bench and regular hoods. Also an *additional cleanroom* on the second floor has been put into operation on schedule." [ChemCon 2004a]

In the course of expanding the production area also laboratory space was doubled in the area of research and development as well as for non-GMP production with additional 60 square meters [BIOPRO 2004b].

In 2004 ChemCon was awarded the Prize for Young Companies by the L-Bank and the State of Baden-Württemberg (first among 565 participants); on November 10, 2004 the award of Baden-Württemberg Sponsorship (€40,000) took place on at the Stuttgart New Palace [MBG 2005]. ChemCon received the BW-L-Bank-Award for its *excellent management and steady economic development* [BIOPRO 2004c].

The market entry was successful with seven placed agents to cure, for example, childhood leukemia or lung cancer [MBG 2004]. And with its almost 40 employees ChemCon GmbH was able to achieve *profitability in 2003*, despite huge investments in high-quality laboratory facilities in the previous year [BIOPRO 2004c] and *from then on it continued to stay in the profit zone*.

> According to a founder's estimates ChemCon owed its turnover and its profitability by the end of 2003 especially its "*production in the niche*" with *tiny dosage amounts* of less than a thousandth of a gram or rare substances that are performed in the pharmaceutical industry as "*orphan drugs*". [BIOPRO 2004a] It usually delivers a few kilograms per year per order [BMBF 2005].

"Such developments are always tricky," said the company's directors. With their production "of the *highest quality in small quantities*" and also scale-up from milligrams to kilograms and more under full GMP conditions in two cleanrooms, ChemCon saw a "real gap" with an attractive offer for all pharmaceutical and biotechnology companies [BIOPRO 2004a].

Small amounts are used when the drug is either still in development, they are used as extremely low doses (HPAPIs) or there are few patients who need them (orphan drugs). The chemical production of small amounts of pharmaceutical agents of maximum available pharmaceutical quality is ChemCon's market niche [BMBF 2005].

"Our profile is unique in the world," said Vogler. Around ten to twenty companies are working worldwide with a most similar profile. "We estimate that we have developed just one percent of the potential market in the first seven years of our existence." [BIOPRO 2004a]

February 2004: ChemCon took over a part of Gödecke´s library [ChemCon 2004b]. Gödecke was a former pharmaceutical company located in Freiburg/Germany – as is ChemCon. It now belongs to the US Pfizer Group. [7] A comprehensive library is useful to solve tricky (synthetic) problems [BIOPRO 2008].

In 2005 ChemCon worked for more than 100 customers already. It acquired 24 new customers in 2005 and was able to double the revenue with European customers compared to 2004 [ChemCon 2006]. Furthermore, five large projects were started with US/Canadian customers.

Most *customers* are medium-sized pharma companies and these often need very efficient APIs for producing drugs to treat rare diseases or for applications for emergency medicine [Vogler and Gockel 2005]. For instance, according to ChemCon, the annual production of an antihypertensive agent is sufficient to reduce the high blood pressure of 20,000 emergency patients [Kramer 2014].

Since October 2005 the European Community applied a cGMP compliance system for APIs.

2005/2006: There were further investments. ChemCon was establishing the third GMP manufacturing area. After two cleanroom facilities dedicated to injectable grade API manufacturing, a third laboratory dedicated for oral/topic grade API manufacturing was necessary. ChemCon already worked on three oral/topic API projects [ChemCon 2006].

By 2006 ChemCon's status regarding its competencies and services is outlined in Figure 2. It is to be noted that its contract research/customer synthesis offerings included already high potency cytostatics (HPAPIs), before the outburst of activities in the related field after 2009.

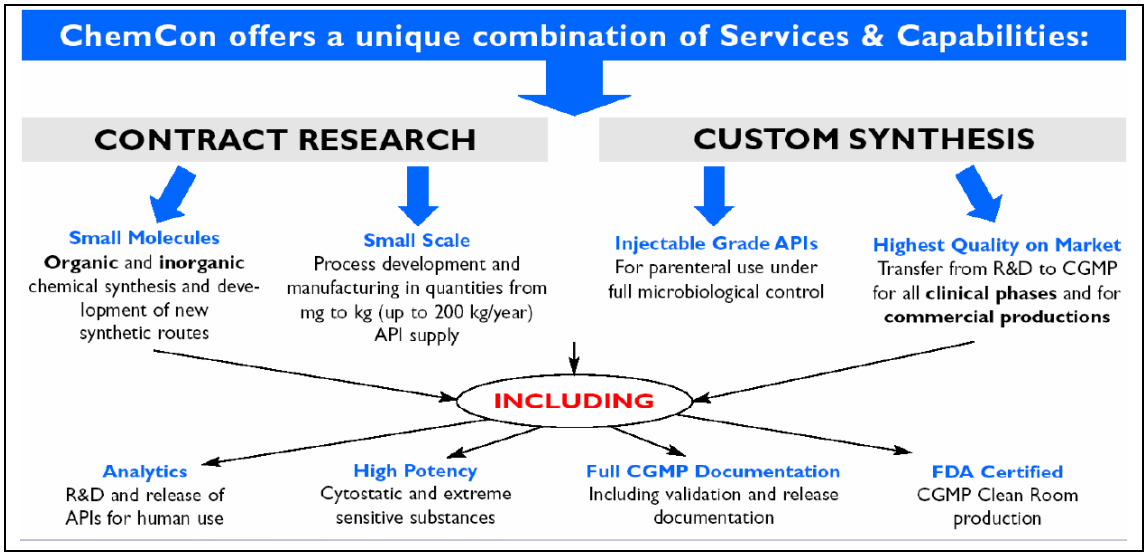


Figure 2: ChemCon´s unique combination of Chemical Services in 2006 [ChemCon 2006].

To increase and keep visibility ChemCon representatives attend trade shows; it is part of its marketing strategy:

"Usually, and depending on the active ingredient required, ChemCon produced about 20 to 150 kilograms per year. "It is not easy to establish a profitable company based on this concept," admitted Raphael Vogler. "However, companies that are able to produce very small quantities of active drug ingredients under GMP conditions are able to occupy a market niche. This is what we have done." [BIOPRO 2008]

In Jannuary 2006 ChemCon received an order for the largest quantity in the company's history. It required the manufacturing of 1,000 kg of a specialty chemical to be delivered in Q1/Q2 in 2006. With this project ChemCon entered *a new dimension of scale*! [ChemCon 2006]

The characteristics of the customers and some examples are shown in Figure 3; exemplary projects with customers and indications are given by Chemcon [2006:20]. Notably, apart from other big pharma firms ChemCon has the Swiss pharma giants Novartis and Roche as customers which are located in the Basel area close to Freiburg.

Figure 3: ChemCon's types of customers and some representatives by the end of 2006 [ChemCon 2006; Vogler 2008].

Specifically, clients who commission ChemCon to produce a pharmaceutical substance *must already have "a specific molecule in mind and should be able to draw it on paper*," said Vogler. The *chemical structure serves as the basis for synthesizing* the desired substance. "Our chemistry laboratories are equipped with all that is needed for process development," said the company director.

Starting from a chemical substance or specific molecule that the customer in the US or in Europe wants to see synthesized for a medically active drug ingredient is the first step of a customer's order (Step 1 in Table 2) which "means a lot of development work," said Vogler. "We must think about how the formula put on paper is implemented into reality." "An enormous amount of time needs to be spent on development processes," said Vogler. "It is our task to find out how the formula on paper can be turned into a real product." [BIOPRO 2004a]

The substance must be characterized exactly according to international guidelines, documented and tested for contaminants. "For a kilo of product for a Phase I trial in the clinic, we provide approximately ten kilos of documentation" estimated the ChemCon boss. "For the implementation there are many possibilities." [BIOPRO 2004a]

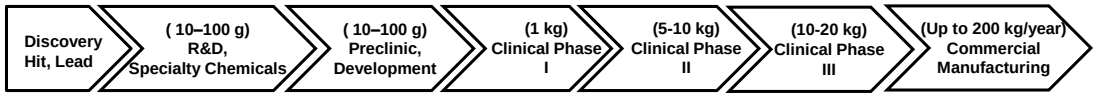
Specifically, for Vogler process development means that ChemCon supports the client all the way up to when the product reaches market maturity and also takes over the production of the drug. “This is the ideal situation. Pure development products are very difficult to calculate,” said Vogler [BIOPRO 2008].

ChemCon’s key processes for CRO or CMO are outlined in Table 2. Its starting is: Intensive communication with the “*customer partners*” until orders received and parallel planning of synthesis. After process development the steps include scale-up and manufacturing (last row of Table 2) to finalize the overall process with analytics to confirm necessary quality and purity of the product before it is released to the customer with a related extensive documentation.

Concerning the missing Step 7, after an audit by German Health Authorities (Regierungspräsidium Tuebingen) without any problems, in 2006 ChemCon received the permission to release final dosage forms for human use [ChemCon 2006] – in clinical phases for testing (Figure 6).

Table 2: ChemCon’s steps of order processing and scaling up [ChemCon 2006; Vogler 2008].

Step 1: Contact ChemCon	Step 1: Draw your molecule, contact us, and we will work at your synthesis! • Elaboration of chemical processes and development of synthetic routes • Implementation of synthetic routes and scale-up of chemical processes
Step 2: Process development	Step 2: Process development at state-of-the-art laboratories • Development and custom synthesis of organic and inorganic chemical specialties and standards • Handling of high potent, toxic, air / moisture / temperature / light sensitive compounds • Reaction performance at temperatures between -100°C and 230°C • Parallel synthesizers for fast process development
Step 3: Pilot scale manufacturing	Step 3: Production of the substance in pilot scale e.g. for later use for preclinical testing • Scale-up of chemical processes • Custom synthesis of organic and inorganic chemical specialties, standards, reference material, etc.
Step 4: API manufacturing	Step 4: Manufacturing of the API in ChemCon´s cleanroom facilities • Process transfer from R&D to cGMP including scale-up from mg to kg and process validation • GMP-development for small molecules in pharmaceutics, generics, diagnostics, applicable for all clinical phases up to commercial material • Commercial API manufacturing in small scale (g to multi kg)

	Step 5: Analysis of the product • Analytic method development including release plan, analytical data sheet, certificate of analysis, analytical reports, analytical validation master plan, method validation plan and report. • Stability and degradation studies
	Step 6: Release of the final API by the regulatory team The manufacturing under cGMP includes a complete set of documentation like type II drug master files (DMFs), master batch / cleaning / labeling records, validation master plans, reports, etc.
Finally the customer holds the product in his/her hand	Organic or inorganic chemical specialty • Reference standard, diagnostics, intermediates • API for preclinical use • API under cGMP for all clinical human testing stages • Commercial API including all validation and documentation
ChemCon's QM-Documentation	Manufacturing Documents QC Documents Part of ChemCon´s Quality Control: All products shipped are provided with an Analytical Data Sheet for non-GMP material and a Certificate of Analysis for GMP material
Missing so far: Step 7	Step 7: Providing the final dosage form ("Darreichungsform") for drugs, such as tablets or solutions/drops (orally), gels or creams, injections, aerosols, etc. (cf. Figure 6) – so far done by other firms, service providers who specialized to do this [Vogler 2008] (This step did not take place at ChemCon in 2008 and before.)
Scale-Up	
	

When ChemCon existed for more than eight years it had just under 40 employees, more than 2,000 square meters for operation, had more than 100 customers from the pharmaceutical and biotech world, several hundred products, and generating profits for three years. And Vogler said: "I am sure that we are only at the beginning. Our launch was well done, now the building phase is ahead. We want our products to play a leading role on the global market and for this we must have a lot of ideas and implement them also in the coming years." [BMBF 2005]

ChemCon offered products of their own manufacturing and also products from business partners (cf. also Table 3):

- APIs for the market
- Specialty chemicals
- Biological extracted compounds
- Catalysts
- Kinases
- RNAs and Nucleotides.

It manufactured also narcotic drugs, psychotropic substances and their precursors, such as ChemCon Remifentanil hydrochloride. In a slight reversal of roles, for instance, ChemCon was representing its early customer Chemwerth and marketing its products to the European market [CHEMWERTH].

By the end of 2008 business activities and results comprised [Muller and Arzt 2008]:

10 APIs and 4 specialty chemicals were on the market

- 12 APIs to be launched
- 5 anti-cancer agents in clinical phase II
- 6 APIs in the preclinical phase.

In 2008 ChemCon worked for more than 200 customers [Vogler 2008:33]. But the weak dollar [Runge:626] forced ChemCon to reconsider its customer base.

In the past, ChemCon used to earn a high proportion of its revenues in the US and Canada (ca. 80 percent). Gockel, co-owner of the company, therefore decided to settle in the USA a few years ago and took care of the client base on that side of the Atlantic [BIOPRO 2008].

However, the company increasingly faced serious problems because of the weak dollar. That is why the company was looking for alternatives to the American market. “In 2007, we gained 55 percent of our revenues in Europe, and we hope to reach about 70 percent in 2008,” said Vogler, who also sees promising markets in emerging Asian countries in addition to Japan where the company is already doing successful business. “We are unable to compete with the cheap prices in India and China,” admitted Vogler frankly, adding that Africa and South America are not areas where they are likely to make money in the near future. However, Vogler was optimistic to find new markets in Australia and New Zealand, where he hopes to find new clients. He also foresaw interesting prospects in Israel.” [BIOPRO 2008]

Financing and Organization

For the establishment of ChemCon GmbH each founder contributed €15,000; share capital (Stammkapital) is €30,000. According to the Firmenwissen Database ChemCon’s *equity ratio* (Eigenkapitalquote) averaged over the period 2011-2013 is ca. 24 percent.

Profitability was achieved in 2003 [MBG 2004; Vogler and Gockel 2005] and since then ChemCon always stayed in the profit zone.

To get the required start-up capital the first product order served as loan collateral [Kramer 2014]. According to Vogler “We have repeatedly spoken for years with donors, the perseverance [Runge:262] has finally paid off. Surely it is one of the most elaborate steps to obtain funds for one’s idea. We must also be prepared as a founder to take risk, in terms of capital.” [BMBF 2005].

The pharmaceutical market has *high entry barriers*. Between research and finished product there are substantial investments in laboratories, expensive analytical equipment, staff and customer contacts [Vogler and Gockel 2005].

> ChemCon always sticks to a fundamental principle of financing from the beginning: *Investment follows demand*. Only when the first order was present, the founders spoke with potential investors and banks concerning financing, and built in 1998 the first cleanroom in Freiburg Biotech Park [Vogler and Gockel 2005]. Development/growth of ChemCon was/is essentially based on own cash flow

The first loan came from the Volksbank Freiburg. Via the L-Bank, the State Bank of Baden-Württemberg, ChemCon got contact to the Bürgschaftsbank Baden-Württemberg (BB, Guarantee Bank), which provided the necessary collateral for loans, and to Mittelständische Beteiligungsgesellschaft (MBG) Baden-Württemberg which holds a silent participation in ChemCon GmbH since 2000 [Vogler and Gockel 2005]. The price: Interest rates up to 20 percent – related to the risk young entrepreneurs represent for the bank [Kramer 2014].

With support of the banks ChemCon could build laboratories and production facilities (that match the latest technology and the highest safety standards in 1999-2000) [Vogler 2008]. The first cleanroom in Freiburg Biotech Park built in 1998 was financed by startup loans secured by the Guarantee Bank (BB) and MBG [MBG 2004; Kramer 2014].

With around one million DeutschMark (DM, €0.5 million) investment capital ChemCon established the cleanroom laboratory [Anonymus 2002].

At this stage there were always contacts with venture capitalists. But in those times (before and during the Dot-Com Recession) ChemCon's business plan was not promising enough for use of venture capital. The loan financing had the advantage that the founders have not remained only managers, but also the company's owners to this day. Nevertheless, the founders did not exclude that in the future there may be cooperation with venture capitalists [Vogler and Gockel 2005].

In 2004 the company was awarded the Prize for Young Companies by the L-Bank and the state of Baden-Württemberg associated with prize money of €40,000 [Vogler and Gockel 2005].

During ChemCon's early phase after 1997 funding flowed also from both the state program "Junge Innovatoren" ("Young Innovators") of the Ministry of Science and Ministry of Economic Affairs [Runge 2014a] as well as a part of the pilot project "Campus-Gründerverbunde" ("Campus Founders' Junction") for high-tech founders. In this way the laboratory, equipment and library of the University could be used for the set-up work [Vogler and Gockel 2005], for instance, for still necessary research and experiments. Vogler and Gockel could utilize that to work on their first product – provided that the laboratories were not used by the scientific community.

Via the Founders Initiative the University of Freiburg (today Campus Technologies Oberrhein – CTO) Gockel received a biennial promotion by Baden-Württemberg's Ministry of Economic Affairs, which was specially designed for entrepreneurs with a university degree [Kramer 2014]. The Steinbeis Stiftung (Steinbeiss Foundation) conveyed business knowledge to the founders [Kramer 2014].

And finally there was the backing by the families: Raphael Vogler's brother Thilo, a business economist, helped with the business plan, Gockel's brother Martin, himself a chemist, helped with the first production [Kramer 2014].

The Mittelständische Beteiligungsgesellschaft Baden-Württemberg (MBG) holds a silent participation in ChemCon GmbH since 2000 [Vogler and Gockel 2005]. In order to secure growth Bürgschaftsbank (BB) and MBG accompanied new financing rounds several times. Guarantee Bank (BB)/equity participation (MBG) occurred in 1998, 2002, 2003 and 2004 [MBG 2004]. Also the public Technologie-Beteiligungsgesellschaft (tbg) of the KfW-Group played a role.

The market entry was successful with seven placed agents to cure, for example, childhood leukemia or lung cancer [Vogler and Gockel 2005].

According to the Firmenwissen Database ChemCon currently is oriented towards two private banks, Commerzbank and the medium-sized Südwestbank AG which operates only in the South West of Germany.

Organizational development:

ChemCon's organizational development can be described in terms of company-internal and external structure. For instance, from its start Prof. Dr. H. Vahrenkamp of Freiburg University acted as a "scientific advisor". And this relationship with Prof. Vahrenkamp was kept even after his retirement, when he became a member of the firm's Advisory Board.

The Advisory Board of ChemCon, founded in 2005, consisted of professionals in the fields of pharmaceutical and chemical industry, the academic environment and in the financial sector [ChemCon 2006:28].

For operations ChemCon focused on three locations [ChemCon 2006; Vogler 2008]:

1. R&D, Development and Manufacturing: Freiburg, Germany (ChemCon GmbH)
2. Financial Headquarters: ChemCon GmbH, Ludwigshafen, RP, Germany
3. US Headquarters, bearing: ChemCon America, Inc., Orlando (FL, USA); sales representation: ChemCon America, Inc. and Detroit (MI, USA).

Based on text in articles about ChemCon, ChemCon's job announcements and employees' profiles (in Xing and LinkedIn) and referring to a typical value chain of technology ventures [Runge:57-60] a *tentative organization* has emerged which is presented in Figure 4.

Basically ChemCon is committed to the environmental initiative "Responsible Care" [Vogler 2008]. ChemCon's environmental and safety experts ensure that all safety precautions are adapted to the risk potential of the particular compound. Experts for environment, health and safety (EH&S) review each target compound, check the synthetic route and monitor the manufacturing process (occupational safety, industrial hygiene).

General Management of ChemCon comprises (at least) four CXO positions, specifically CEO, CSO and CKO plus the CFO who is responsible for Accounting/Finances (localized in Ludwigshafen, RP, Germany). A CKO (Chief Knowledge Officer) is in charge of managing intellectual capital and is the custodian of knowledge management practices in the organization with a focus on *technical and regulatory knowledge* and their mutual dependencies.

It is not clear (to the author) whether Business Development is a unit of General Management occupied by a dedicated person or whether it refers to a responsible person of the General Management.

Pharmaceutical and chemical production (common *versus* cGMP and HPAPI-conform) includes toxic substances produced in high purities. Dealing with HPAPIs can only be met by considerable technical efforts as well as related training of employees.

A Workshop (with mechanical and electronic craftsmen) deals essentially with *procurement*, repair, qualification of all technical installations as well as alterations and extensions in laboratories and cleanrooms.

Research and Production are complemented by Analytics – common and special, regulation-oriented chemical analytical operations, but also microbiological operations – and independent

QC- und QA-Departments focused on FDA and EMA guidelines. ChemCon developed and implemented a Total Quality Management System (TQM), which assures the strict compliance with the ChemCon Quality Policy.

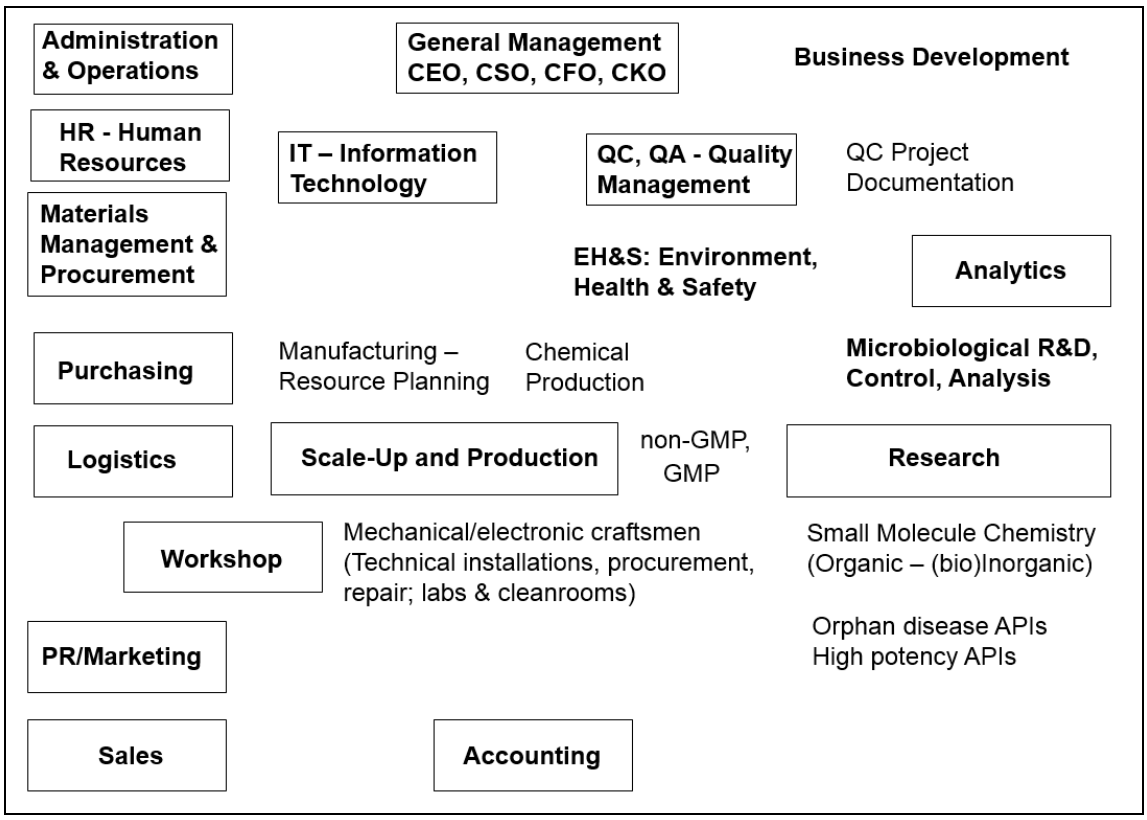


Figure 4: ChemCon's tentative organization – Functions (boxed), units (text in bold face) and employees' roles or activities.

Networking and Cooperation

For ChemCon networks for different phases of its development had different significance. ChemCon was a co-founder of BioValley Deutschland e.V. (and its co-founder acting as an early President) and initiator of the Drug Discovery Net [ChemCon 2006].

Networking was a key element of ChemCon's business success, both in the local (Baden) home area and internationally: BioValley Deutschland is a local biotech association with the specialty of a trinational partnership involving also organizations in France and Switzerland. The Drug Discovery Net corresponds to a *virtual company*. With both networks it built and maintained contacts with potential partners and customers [Vogler and Gockel 2005].

BioValley Deutschland e.V.
President: Dr. R. Vogler

Drug Discovery Net

Chemische Auftragssynthese in Deutschland

According to Wikipedia BioValley (Europe) is a leading life science cluster in Europe, founded in 1996. It connects academia and companies of three nations in the Upper Rhine Valley, namely France, Germany and Switzerland. The main objective is the greater research cooperation between companies and academia involved in the life science sectors, including pharmacology, biotechnology, nanotechnology, medical technology, chemistry and agricultural biotechnology. It comprises the three big universities of Basel, Strasbourg and Freiburg and universities of applied sciences and has a number of Fraunhofer institutes in its area.

With regard to networking for ChemCon's foundation a network played also an important role [Vogler 2006b]. The details are presented in Box 1.

Box 1: A network as an origin and basis of ChemCon's foundation [Vogler 2006b].

Already at the beginning of the company's history a network was formed, which ultimately made possible the founding of the company in its present form.

The common task was that drugs' active pharmaceutical substances whose syntheses were at least partly developed and optimized should be prepared under conditions as required by the rules of the pharmaceutical industry to ensure that the substances could be used in humans to cure diseases.

The precursors of the products were highly toxic, the end products themselves as well, because they should be used as chemotherapeutic agents in cancer treatment. The solvents used were usually inflammable.

The future drugs should be provided as an injection. Therefore, the pharmaceutical ingredients had to be made already under microbiological control in a cleanroom in the absence of possible contaminants.

To achieve this goal the network comprised two different departments of the Freiburg University, the *scientific department* in which the two later founders were active and where the syntheses were partly developed and the Technology Transfer unit of the university and the Founders' Center ("Gründerzentrum") of the university.

The network further comprised facilities of the City of Freiburg and support institutions for economic development as well as finally four American companies. Two of them had distinct requests for products; one was a producer of solutions for injections and the fourth one was a consulting firm specialized in the challenges of legislation of pharmaceutical production. Hence, the network involved four partners and comprised also the two founders with their Start-Up Initiative and their new firm which was just established originally with a different goal.

The common goal of the network partners was essentially to transfer largely known syntheses into commercial production processes. And it turned out that the Freiburg Technology Park at that time under construction would be an ideal place for the required cleanroom-laboratory.

At the beginning the focus was on commercial production of two highly toxic anti-cancer agents. Generally, the level of production should be on a small scale – ca. 100 kg per year for an API. But additionally, despite the very small scale, highest pharmaceutical quality and world standard should be guaranteed.

All the partners of this network definitely had their own goals [Vogler 2006b]. But in the end all partners were satisfied that the common goal was achieved. With one of the two substances

the network managed the fastest approval of a cancer treatment in the history of the American FDA.

One reason to keep the network alive and coherent was the fact that ChemCon's founders, who regarded their partners partly as customers, had the goal the partners to be satisfied. And based on this customers' satisfaction the two founders created a basis for further projects and cooperation and identified being permanently *customer-oriented* (as differentiated from customer-driven [Runge:450]) as the core of their new firm.

The founders became aware that with regard to market requirements their available spectrum of services was not complete. For instance, ChemCon set up rather extensive analytics, but some needed special instruments would not have been utilized fully. Hence, they made use external services providing related analytics. Additionally, ChemCon was not specialized to isolate biomolecules or produce macromolecules. And also facilities to produce large quantities, sometimes requested ton levels, did not exist [Vogler 2006b].

Therefore Dr. Vogler looked pro-actively for companies with which ChemCon could offer together a more extensive service to customers in the field of APIs and ultimate drug production. He called that initiative "Pharma Manufacturing Alliance" and presented that to a number of potential partners. This particular network should cover the whole value system (supply chain), from producing the first samples on a gram scale for testing, via API production of kilogram quantities and scale-up to levels of tons produced by chemical and biotechnological processes, all including analytics, and ultimately manufacturing of the marketable drugs. This would also include producers of related dosage forms, such as tablets, creams, injections, gels, capsules, etc. However, this pharma-service connection did not materialize [Vogler 2006b].

But in 2002 the idea of the "Pharma Manufacturing Alliance" was revived during a biotechnology fair in Canada. With also a founder from the Southern area of Germany Vogler discussed options of marketing their services together. The potential partner which was of a similar age and size as ChemCon was specialized in extracting natural product and optimize seeds [Vogler 2006b].

The two startups were envisioned to become the core of a cooperation which did not cover the whole area of pharma production, but focus on the early development stages of active pharmaceutical agents. Correspondingly, the network initiative was named "Drug Discovery Net". Both firms looked for partners which in the end would make the Drug Discovery Net a *one-stop-shop*. The characteristics of the ultimate connection were a number of new firms which all had a similar age and company size ad were located in Freiburg, the Stuttgart-Tübingen area and Saarbrücken (all in Germany) [Vogler 2006b].

Apart from ChemCon members of the network were Sourcon Pandena AG, EMC Microcollections GmbH, CureVac GmbH and KKS (Koordinierungszentrum Klinische Studien GmbH) (all from Tübinger), from Reutlingen the firms Labor Dr. Glatthaar and Dr. Tetry genmedics GmbH and ActinoDrug Pharmaceuticals GmbH, Hennigsdorf [Biotop 2003].

The connection should view itself as one "*virtual company*". Activities of the network should focus on creating marketing items, coordination of joint appearances on fairs, looking for projects supported by public agencies, etc. In this regard the Drug Discovery Net shows similarities to the "Cooperation-X" network initiated by the founder of NANO-X GmbH [Runge 2015].

Also the new network had problems that emerged when promoting the goals of the network. Addressees of an Internet presentation, a flyer or a brochure on fairs did not grasp the goals and advantage of the network, but rather perceived it as a summary of overviews of the individual firms. These initiative were not sufficient to generate additional sales [Vogler 2006b].

Before 2008 a common project (1/1/2006 – 6/30/2008) of the University Hospital Freiburg (project leading), ChemCon and the Deutsches Krebsforschungszentrum (DKFZ, German

Cancer Research Center) was run. ChemCon's contribution included identification of lead structures, patent search, synthesis of carbohydrate building blocks and verification of structures [Längin and Kümmerer 2008].

By 2008 ChemCon´s *scientific cooperation partners* were rather diverse and included still members of the Drug Discovery Net (Figure 5).

Figure 5: ChemCon's scientific cooperation partners [ChemCon 2006; Vogler 2008].

The orientations of some examples of ChemCon's strategic partners are given in Table 3.

Table 3: Orientations of some strategic partners of ChemCon.

University of Freiburg, research partner	Chemwerth, generics production; sales & distribution cross-agreement
IoLiTec, ionic liquids [Runge 2014b]	Frimorfo, preclinical contract research
EMC Microcollections, combinatorial chemistry	Prestwick Chemical, medicinal/combinatorial chemistry
AQura, GMP analytics	Across Barriers, pharmaceutical testing
Genmedics, gene therapeutics aspects for ChemCon GmbH	KKS UKT, clinical research (Koordinierungszentrum Klinische Studien)
PfizerCapusgel, final dosage forms	CureVac AG: RNA synthesis under GMP conditions [10]

There are no indications on the Web that the Drug Discovery Net is still active as a network. And it is not clear (to the author) whether members of the Drug Discovery Net play a role for ChemCon also presently.

Vogler [2006b] illustrated that a common trait among good technology entrepreneurs is an ability to *build supportive relationships* in an unfamiliar environment. He also describes how being authentic and engaging are key to building a network, as is ensuring alignment with others by explaining how the relationship will benefit them. Finally, from his experience the conclusion

was that for a successful cooperation/networking the specific formulation of common objectives is mandatory, for instance, a product, service or marketing platform.

ChemCon is also an active member in the following *industrial associations or organizations* [ChemCon 2006; 2008]:

After foundation ChemCon's sales doubled every year [Vogler and Gockel 2005] and, despite some significant investment in analytical instruments, profitability could be achieved in 2003. This was possible because there was always only investment, if a new order was present. This principle was valid from the beginning.

At the end of 2004 ChemCon was positioned to even further growth without a major investment in the plant. The original production area grew compared to the first cleanroom from 100 to 2,500 square meters and it had 40 employees. In the business ChemCon became a producer of larger quantities and produced 100 kg APIs per year and could even double this figure in 2005 [BMBF 2005].

Cost control at that time was a challenge seen to extend also into the future. For its optimization an experienced controller could be poached by another company [BMBF 2005].

> But anyhow the long-term vision of the company should always be kept in mind: ChemCon should become the market leader in small-volume pharmaceutical ingredients as well as bio-inorganic agents [Vogler and Gockel 2005].

Innovation Persistence, Expansion and Diversification

According to definition [Runge:16] ChemCon formally ceased to be an NTBF after 2009 (after twelve years of existence) to become a small and then medium-sized enterprise (SME).

After 2009 the core and the orientation of the business did not changed essentially since the early days. ChemCon produced essentially pharmaceutically active substances on behalf of companies of the pharmaceutical or fine chemicals areas. It is a globally operating company claiming to be a leading manufacturer of fine chemicals and small to medium scale APIs used in all clinical stages as well as for commercial use.

Sales are now distributed to 50 percent in North America, 40 percent in Europe and about ten percent in the rest of the world. The orders range from one kilo up to 300 kg [Kramer 2014]. Products are supplied, among others, in the US, Canada, Europe, the Middle East (including Israel), Japan [BIOPRO 2011], India and Australia.

According to its current Web its track record comprises [ChemCon]:

- It has unrivalled chemical expertise
- It already worked for 25 of the world´s major chemical, pharmaceutical and biotech companies,
- 150 customers from small/midsize Biotech and Pharma,
- 25 customers from research institutions and universities and
- more than 10 international trading companies.

ChemCon views its *people to be key to its success*: "The highly experienced, enthusiastic, and motivated team of scientists is committed to delivering your products on time, on budget and in top quality. Over 90 percent of its chemists are qualified to PhD level and have acquired considerable experience in all areas of small molecule synthesis." [ChemCon].

ChemCon's operations are characterized by *investment persistence and innovation persistence* [Runge:625,627,653,681-682]. Recent developments of the number of employees reflect the continuous *organic growth* [Runge:681-682] of ChemCon; revenues show also growth, but with two markedly negative dips around 2005 and 2012 (Table 5).

ChemCon's development after 2009 is characterized by two essential additional orientations:

1. Responding to demand from the market upgrading its technical infrastructure to offer more (and specific types of) HPAPIs.
2. Regulatory allowance to make semi-solid dosage forms (ointments and creams) will address new customers and provide services at all stages of the drug development process (Step 7 in Table 2; Figure 6).

ChemCon produced already for more than ten years highly active ingredients (HPAPIs, Figure 2) and bioconjugates [ChemCon]. Hence, there is currently a focus on

- Orphan disease APIs
- High potency APIs
- Drug product manufacturing in small batches for clinical trials.

Responding to the globally increasing demand for HPAPIs in 2011 and thereafter ChemCon expanded its manufacturing capabilities by a new multi-purpose plant in Freiburg i.Br. for HPAPIs in multi-kilogram quantities by containment down to addressing a limit of 0.1 µg/m3 (OEL) which should start continuous operation in spring of 2012. In 2012 the proportion of HPAPIs would be more than 40 percent of all new active substances [BIOPRO 2011].

The resulting low occupational exposure limit for the product requires special containment during processing. Its award-winning strategy of consistent use of product-specific parts of the plant closes thereby for sure the risk of cross-contaminations. Moreover, rigid waste management is in place [BIOPRO 2011].

Dealing with HPAPIs requires considerable technical effort and corresponding training of staff. To compensate any risk increase possibly connected with higher biological activity, all aspects of the manufacturing process are covered: ChemCon's environment, health and safety (EH&S) experts assess potency of each compound, evaluate synthetic routes and production and monitor practices. They ensure that compound toxicology is accounted for by all applicable procedures [BIOPRO 2011].

In 2011/2012 ChemCon invested more than €1 million in Freiburg [Econo 2011].

A new multi-purpose isolator train was installed at the company site in Freiburg, Germany. Thus ChemCon is in the perfect position to offer custom manufacturing of even the most active cytotoxic ingredients [ABCEurope 2012].

In 2013 ChemCon received approval from the German health authorities to start drug product manufacturing for clinical phases including development services [ChemCon 2013].

Also in 2013 ChemCon had been cleared by German regulators to make semi-solid dosage forms (ointments and creams). The approval will allow to access new customers and provide services at all stages of the drug development process [Bionity 2013].

In the first customer project clinical test samples for a randomized placebo-controlled study of Phase II were produced. After the manufacture of the API using excipients drug and placebo were prepared as a gel, then filled into tubes, randomized and delivered separately to the clinical trial.

The API was a tellurium complex which as an immunomodulator has antiviral activity, particularly against pappilom and herpes viruses. This was one of the first medical tellurium compound used at all [Bionity 2013].

Parallel to its developments ChemCon showed continuity concerning quality and compliance with legal regulations and industry standards.

In 2014 ChemCon´s facility has been cleared for the production of active pharmaceutical ingredients (APIs) by the US Food and Drug Administration (FDA). According to the US regulator, the site is fully compliant with Current Good Manufacturing Practices (cGMP). Overall FDA completed the renewal inspection without any written citation or shortcoming – in 2014 as in 2000, 2007 and 2011 – and, allowing to supply commercial APIs to the US market. “We are very proud of this achievement” stated Raphael Vogler. “It adds to our outstanding track record and is a result of our continuous striving for excellence.” [ChemCon 2014b].

Inspections were also run by German authorities, Regierungspräsidium Tübingen (cGMP) and by DEKRA (DIN EN ISO).

With these permissions ChemCon became able its *offerings to cover the entire value system (supply chain)* [Runge:58-60,1216,1214] in the drug development process. This begins with drug development in the early stages of research, continues with the transfer of the production of active ingredients to the GMP-compliant production and now ends in providing the prepared and packed specimen for clinical testing.

Hence, ChemCon may carry out any concerted development steps from a single source, which are important to provide drugs for clinical trials in phases I to III (Figure 6). And ChemCon can offer completely *integrated* custom manufacturing with associated analytical and regulatory services for supporting critical project milestones as a “good manufacturing partner”.

The services cover all phases of drug development – technical and regulatory. For each project dedicated glassware and equipment is used to eliminate the possibility of cross-contamination, while the cleanroom facilities and manufacturing equipment can be adapted on a project by project basis so that one cleanroom can be used to manufacture a range of different APIs [ChemCon].

CMC (Chemistry, Manufacturing and Controls) considerations are necessary for a successful regulatory submission. The goal of this submission from a CMC perspective is to provide enough information to permit the respective regulatory authority to determine whether the methods used in manufacturing the drug and the controls used to maintain its quality are appropriate and adequate to ensure the drug’s identity, strength, quality, purity and safety and refer to clients' IND, NDA and ANDA filings. [6, 8]

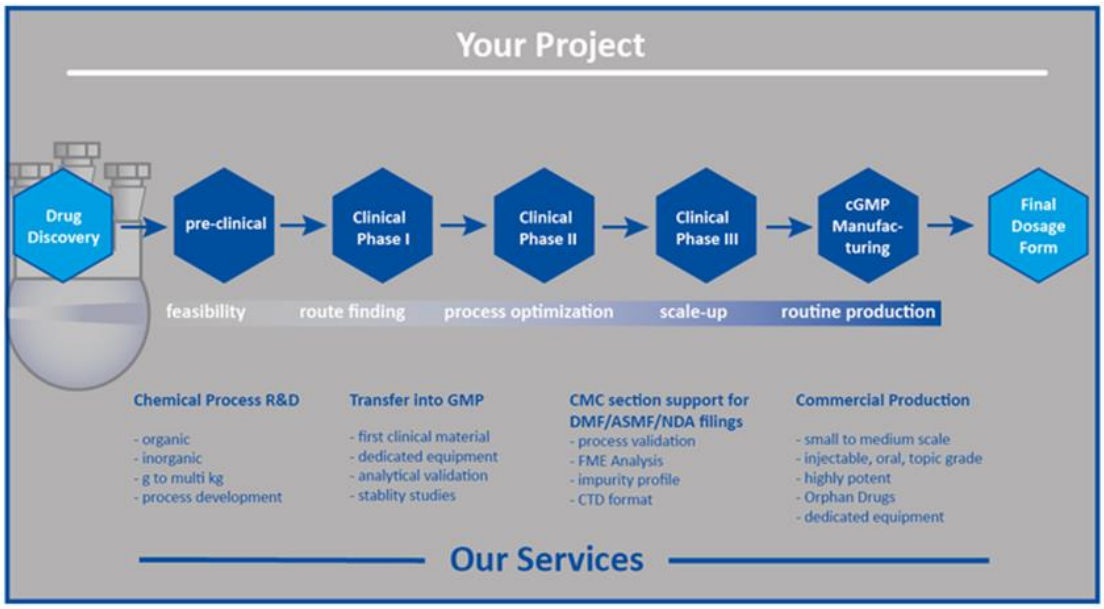


Figure 6: ChemCon's completely integrated cGMP custom manufacturing process and related services emphasizing clinical phases from drug discovery to provision in a final dosage form [ChemCon].

ChemCon has been frequently inspected by US and European authorities. But its customers also regularly audited its quality assurance systems. It passed more than 100 inspections and audits by customers or their agents successfully, *inter alia*, by some of the 10 most successful pharmaceutical companies worldwide. ChemCon is also certified in accordance with ISO 9001:2008 [ChemCon]. All of its processes, equipment and SOPs (Standard Operating Procedure) are regularly checked by its quality assurance unit.

After the fourth successful inspection by FDA in 2014 ChemCon has passed again two inspections successfully in 2015: The Regional Council of Tübingen (Regierungspräsidium Tübingen) awarded ChemCon the predicate "conformity with GMP" ChemCon is holding for the ninth consecutive year since the first survey in 2003. In addition, the DEKRA authority has confirmed the ISO 9001:2008 certificate once again which ChemCon has since 2009 [ChemCon 2015].

Correspondingly, for ChemCon quality means:

- State-of-the-art equipment
- Highest standards of cGMP
- Flawless FDA inspection (and related ones by German authorities)
- ISO certificated
- Exemplary audit history.

Passing US FDA site inspections is vital to attract international clients, a European API supplier (ChemCon) has said. Even among clients outside the US, approval by the US FDA is an important endorsement. They are "*relevant for an awful lot of our customers because they represent one of the best signs of quality*," said ChemCon's sales manager. In ChemCon's case the fourth FDA inspection gave an "*NAI*" (No Action Indicated) to the plant [Barry 2014a]

Tracking regulations continuously is important in the pharma business. Currently API manufacturers are gearing up for changes to regulations on elemental impurities made by the US Pharmaceopeia (USP) and reporting on those impurities. The new rules will come into effect in 2016. Correspondingly, ChemCon has expanded its Quality Control department ahead of changes to the way producers must test for elemental impurities (cadmium, lead, arsenic and

mercury) and inorganic contaminants in pharmaceutical ingredients. One of the reasons for heavy metal contamination in API production is the use of metal catalysts [Barry 2014b].

USP will make compulsory use of inductively coupled plasma mass spectrometry (ICP-MS) to perform these tests. In preparation for the changes ChemCon has invested in a new ICP-MS system as well as a microwave sample digester.

This is a real opportunity. It is reported that a firm talked to a customer which gets some API supply from another company. And this firm is looking for a new supplier as its API has high concentrations of impurities that would fail the new regulations [Barry 2014b].

Key Metrics

ChemCon has been able to successfully complete 98 percent of the chemical developments the company had been commissioned to produce [BIOPRO 2008].

Concerning its output some relevant indicators are given in Table 4. According to the Firmenwissen Database ChemCon's export rate is 90 percent.

Table 4: Development of ChemCon's output, particularly APIs.

Year(s)	Output: APIs in Clinical Phases or on the Market
2003	ChemCon could already look back to more than 250 realized syntheses, 25 APIs in different stages of development and 4 drugs on the market in the US and Europe [BMBF 2005]
2004/2005	The company had 5 APIs on the market, all produced on a custom synthesis basis [Rouhi 2005].

2008	Examples of ChemCon projects (up to 200 kg/year) reported for 2008 were as follows [Muller and Arzt 2008]:
	• 10 APIs and 4 specialty chemicals on the market
	• 12 APIs to be launched
	  • 5 anti-cancer agents in clinical phase II
	  • 6 APIs in the preclinical phase

2013/2014	The company has completed over 1,000 projects since its inception and more than 60 APIs for all phases of drug development including ca. 20 commercial APIs since inception [ChemCon]

From its beginning the fundamental principle of ChemCon's development is "investing after demand": There is always only investment (additional workforce, expansion of offices and lab/production facilities, upgrading production technology, etc.), if a new order was present [Vogler and Gockel 2005].

Since the establishment of the company as a GmbH (LLC) in March 1999 the spatial capacity doubled more than once [BMBF 2005] to achieve 1,000 sqm around 2002. Within six years, the workforce increased to 40 employees and the production area from 100 to 2,500 square meters [MBG 2004].

In 2003 ChemCon's area in Freiburg was 2,500 square meters (27,000 sqft), of which approximately 1,000 sqm (10,800 sqft) – 40 percent – were used as laboratory space [CASID]. Since 2009 ChemCon is occupying 3,000 square meters in the Innovation Center Freiburg [Vogler 2008].

There is sensitivity towards exchange rates of currency, US dollar *versus* the euro [Runge:627]. After the dollar exceeded the €/$ = 1.2 threshold (2004) ChemCon's leaders felt the pain in Germany and worked on shifting their customer base to the euro zone.

During its early phase ChemCon gained 80 percent of its revenue in the US [BIOPRO 2004a; MBG 2004]. "In 2007, we gained 55 percent of our revenues in Europe, and we hope to reach about 70 percent in 2008." [BIOPRO 2008]

However, currently sales to the US is still high. Sales will be achieved to 50 percent in North America, 40 percent in Europe and about 10 percent in the rest of the world. The orders range from one kilo up to 300 kg [Kramer 2014].

Basically, according to Dr. Vogler, ChemCon achieved in 2012 a "nearly double-digit million revenue per year." [Kramer 2014] But, Dr. Vogler also said "we also have experienced phases with severe revenue declines." [Kramer 2014].

This may refer to the time 2004/2005 and 2011/2012 (Table 5). In the last case one may speculate that the striking decline of revenue is somehow related to more than €1 million investment to upgrade its technical infrastructure to offer HPAPIs and related slowdown of finalizing products and corresponding delay of delivering to customers in the planned fiscal year. The 2004/2005 case may result from effects of the dollar/euro exchange rate which turned to become a serious challenge.

There are few references publicly available that provide explicitly early revenue data of ChemCon. Numbers of employees are rather widely available.

Development of ChemCon's revenues during its early phase (2000-2003) can be estimated: "Our sales have doubled every year," said Raphael Vogler [MBG 2004]. Specifically, since 1998 ChemCon has doubled its turnover annually [CASID].

For deriving revenues as an end-point for their "doubling effect" data for 2004 were used: Although 2003 was "a bit quiet," 2004 was "very good," with sales of about $6 million, Gockel said [Rouhi 2005].

When ChemCom had 36 employees "PhD/R&D staff was 7/10" and the turnover was "2006: 3.6 M€". Unfortunately the author missed to note when he last accessed the reference. This was definite before 2009. Accordingly R&D manpower proportion would be 28 percent [BioValley].

Around 2007/2008 the company had about 50 employees (25 PhDs and only certified technical assistants or lab technicians) [Muller and Arzt 2008]. R&D manpower proportion would correspond to 50 percent if all PhDs would work in R&D. Some PhDs may work in other units, such as Production or Project Documentation (Figure 4). Therefore, a ca. 40 percent R&D proportion of ChemCon's employees would be a good guess and in line with the 40 percent lab space of the total space mentioned above.

Until 2008 a notable increase of the number of customers could be tracked:

- 2002: > 30 [Anonymus 2002]
- 2005: > 100 [ChemCon 2006
- 2008: > 200 [Vogler 2008:33].

Revenue and employee data are presented in Table 5.

Table 5: Developments of ChemCon's revenue and number of employees.

Year	Revenue (€, million)	Number of Employees	References and Remarks
1997		2	Founders
1998		4	Founders and 2 brothers of the founders [Vogler 2008:9], [BMBF 2005]
1999		ca. 6 c), 10	[BMBF 2005]
2000	$0.37 a)	13 c)	
2001	$0.75 a)	19 c)	
2002	$1.5 a)	22 c), 25	[Anonymus 2002}
2003	$3.0 a)	36 c), (almost) 40)	[BIOPRO 2004c; BMBF 2005]
2004	$6.0 (ca.. €4.4 mil.)	40	[Rouhi 2005]; [MBG 2005; Gonser 2005]
2005	3.5	42 b)	[Gonser 2005]
2006	3.6		[BioValley]
2007		48 c)	
2008		53	[BIOPRO 2008]
2009			
2010	5.028 b)		
2011	6.052 b)	60	[Econo 2011], >60 employees including 6 apprentices [BIOPRO 2011]
2012	5.270 b)		For 2012 a "nearly double-digit million revenue per year" [Kramer 2014]
2013	6.069 b), 6.2	>60	[Statista 2015]; [ChemCon 2013]
2014	6.600 b), $8 (ca. €7)	65, 70	[InsideView 2015]

a) Estimated on the basis of the statement that "since foundation turnover doubled every year [MBG 2004; CASID] and assuming that it refers to sales in dollars; b) from the Firmenwissen Database; c) [Muller and Arzt 2008].

The issue with the numbers of employees (Figure 7) is on the one hand whether apprentices are included or not and on the other hand that it is not clear whether figures given in public sources are yearly averages or year-end numbers or numbers reported at the date of publication and, finally, whether a part-timer is considered one employee or whether part-timers are converted into "full-time equivalents" (FTEs).

The linear growth of ChemCon in terms of employees' numbers exhibits a change to stronger growth after 2002.

Plateauing of the number of employees from 2004 to 2006 finds expression in the unfavorable revenues' exchange rate (2004/2005: 1 euro = 1.25-1.30 dollar [Runge:626]) plus considerable investments and financing the third GMP manufacturing area. After 2008 one observes a continuous increase of the number of employees.

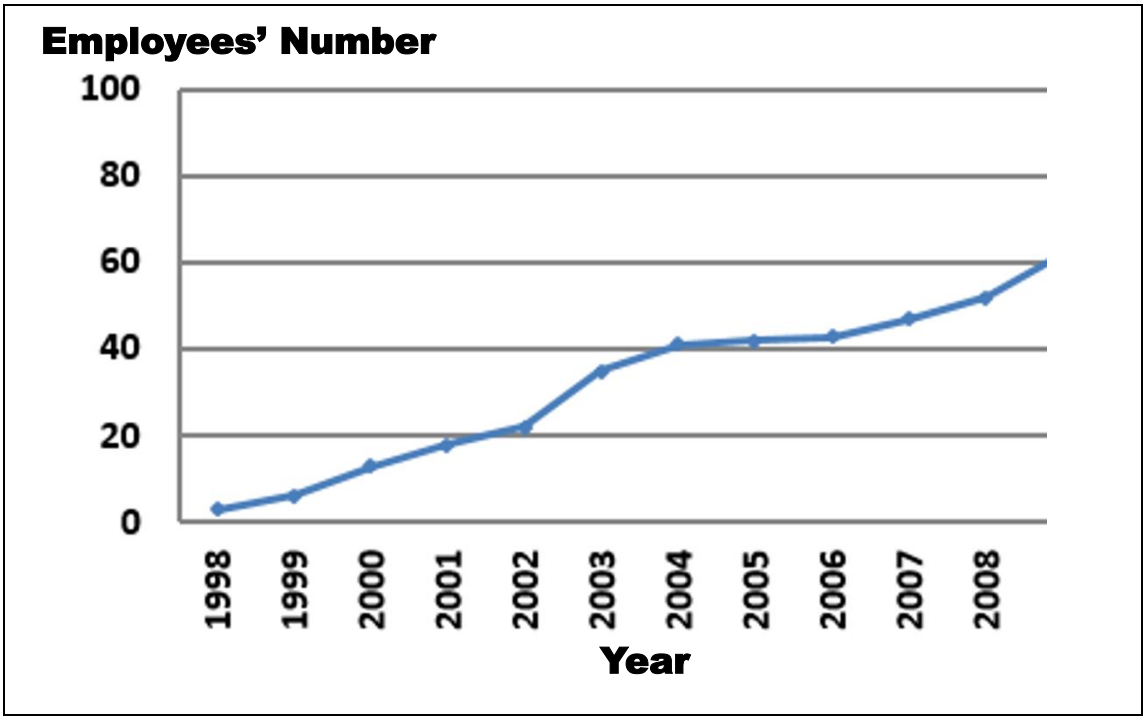


Figure 7: Development of ChemCon's numbers of employees after its foundation [Muller and Arzt 2008].

Vision/Mission, Business Model and Risks

In 1996 ChemCon's founders *vision* was the manufacturing of new metal-containing active pharmaceutical ingredients [ChemCon 2006] and they wanted to develop into the market leader in small-volume active pharmaceutical ingredients as well as bio-inorganic active ingredients [Vogler and Gockel 2005].

Later, already being operational, ChemCon paraphrased its emphasis on cGMP (current *Good Manufacturing Practice*) into its maxim "Chemcon – Good Manufacturing Partner" (also in its logo) – reflecting its *customer and production orientation* as a CRO/CMO.

> "Make us your good manufacturing partner for a broad spectrum of custom synthesis services. We deliver on time, to the required specification and cost-effectively."

They address the market(s) as an independent supplier and service provider and experts for chemical process R&D and small scale cGMP manufacturing (organic and bio-inorganic material for APIs/HPAPIs, clinical trials, or orphan drugs) preferentially for the global pharmaceutical and biotech industry but also fine chemicals for the chemical industry.

According to ChemCon's view of its structural role in industry we read:

> "One can compare our company with a successful automotive supplier in the region. We mainly supply high quality parts that go up into a new product." [Kramer 2014]

ChemCon's *value proposition* and its *key resources* match.

Its *experience* and related *track record* and *core competency* covers producing laboratory-scale amounts (milligrams to grams) and scale-up to multi kg quantities that need to be produced under GMP conditions as typically encountered in preclinical research and all clinical phases of API/HPAPI or (generic) orphan disease drugs' approval.

Whether it is technology or service depends on a customer's specific requirements, but developing a track record for delivering whatever it is a customer needs is key. The added value

comes from many more things way beyond just manufacturing capacity and being the lowest cost provider in a given technology.

Overall ChemCon offers cGMP-compliant API/HPAPI process scale-up and synthetic route development. It manufactures research grade substances, building blocks, reference standards, impurities or verification of scientific claims. ChemCon is also experienced with highly and legally controlled narcotics and fine chemicals.

> It offers an *all-in-one-hand service* including full analytical support, complete documentation and quality management and *operates at just one site* (cf. Figure 8).

It is a service partner for the following *customer segments*:

By Type (Figure 3):

- Pharmaceutical companies,
- Biotech companies,
- Chemical companies
- API trading companies,
- Research institutes
- Diagnostic companies.

By Weight in 2014 [ChemCon]:

- 25 of the world´s major chemical, pharmaceutical and biotech companies,
- 150 customers from small/midsize Biotech and Pharma,
- 25 customers from research institutions and universities
- More than 10 international trading companies.

Key activities comprise services and consulting.

Services:

- Commercial API manufacturing (mg to kg scale)
- Custom synthesis of organic and inorganic chemical specialties and standards (mg to kg scale)
- Elaboration of chemical processes and synthetic routes
- Handling of toxic compounds up to Class III
- Handling of legally controlled narcotics
- Scale-up of chemical processes
- Complete set of GMP documentation
- Ownership of all intellectual properties (IPs) under a contract for the customer.

Consulting

- Synthetic and analytical method development
- Process validation and analytical method validation
- Stability and forced degradation studies
- Drug Master Files (DMF)
- Consulting and investigations.

Key operational factors, activities and strengths comprise specifically.

- A highly qualified team can provide all the needed synthetic services
- Route scouting and optimization
- Feasibility studies
- Custom synthesis (R&D material, intermediates and also synthesis of building blocks, derivatives, analytical services and verification of scientific claims)
- Synthesis or isolation of impurities or degradation products for use as reference standards
- Chemical process development by versatile manufacturing capabilities (Dedicated Equipment Strategy) and process validation
- cGMP material for clinical trials (API manufacturing).

ChemCon uses dedicated equipment for each project once the production is under cGMP. This is the most effective way to ensure that there is no cross-contamination. Moreover, rigid waste management is in place.

Its regulatory affairs staff has extensive experience bringing projects into the commercial phase. ChemCon is currently manufacturing for multiple active DMFs.[8]

This approach allows, even for drug production on the smallest scale, to realize a perfect production design and to provide every customer the perfect chemical plant technology and at the same time eliminating the problem is cross-contamination. To do so ChemCon has developed related concepts in flexible setup of plants and their dismantling and developed the logistics of this equipment.

Marketing and *Customer Relationships* comprise the following aspects:

Gaining visibility:

- The Web (home page, professional social media – Xing, LinkedIn)
- Participations at fairs, exhibitions, international scientific subject-related conferences
- Participations at congresses, meetings, events.

Customer Contacts:

- Consulting
- Customer visits, communication/specification to elaborate chemical processes and synthetic routes (Table 2)
- Inspections by customers
- Test measurements,
- Customization of products.

Concerning customer relationships ChemCon is convinced that “Our customers appreciate ChemCon’s smart and quick handling, speed of problem-solving, flexibility and the quality of our products and GMP documentation services.” And there is the commitment “to serving our customer’s needs.” [ChemCon] Interactions with customers refer also to credibility, reliability and confidentiality.

ChemCon’s address to its customers: “The keys to your success” comprise [ChemCon 2013]

- *Customer orientation*: the customer’s chemical challenge will be solved
- *Experience*: more than 1,000 projects completed,
- Produced more than 60 APIs for all phases of drug development including ca. 20 commercial APIs since inception
- Clear focus on *early R&D stages* and *small to medium scale manufacturing*
- *Quality*: more than 100 different inspections and audits successfully passed (track record).

Risks for ChemCon emerge essentially via the HPAPI business and concerning its API-business by low cost suppliers from China and India. "With India and China we cannot compete in price," Vogler admitted candidly [BIOPRO 2008].

Even so, one challenge a company faces regularly as a CMO with a multi-purpose facility relates to servicing customers ranging from virtual biotechnology firms to very large pharmaceutical manufacturers that have a wide range of expectations regarding handling and cleaning verification [Challener 2015].

And while looking to enter into a strategic alliance with a HPAPI contract manufacturer, pharma multinational corporations (MNCs) need to ensure that the CMO has the potential to provide *end to end services* [Shruthi 2012].

“The variability and uncertainty associated with each compound present the greatest risks. It seems that ‘no two new chemical entities (NCEs) are alike.’ The situation is aggravated by the lack of universally accepted definitions for various compound types, such as highly active, highly potent, and cytotoxic agents, which can lead to confusion between sponsor companies and custom manufacturing organizations (CMOs).” [Challener 2015]

“The manufacture of this expanding field of HPAPIs is challenging and requires specific know-how, facilities, equipment, and procedures designed to mitigate the risk associated with producing and handling potent compounds. Standards and technologies are continually changing, and HPAPI manufacturers must remain vigilant and prepared to adopt and implement the latest designs, equipment, training, and procedures to reduce the risks posed by HPAPIs.” [Challener 2015]

You always have to identify which technology will be required in the future and then pursue the right one, meaning also anticipating developments in regulations – and looking to keep the balance between technology, regulations and customers. But that means continuous investments in new technology and people (training of existing employees, making new employees catch up fast to the current situation) and comply with changing regulations to respond to new requirements of customers.

To sites failing to comply with regulations FDA issues a Form 483. An *FDA Form 483* is issued to firm management at the conclusion of an inspection when an investigator(s) has observed any conditions that in their judgement may constitute violations of FDA regulations. An NAI inspection classification (No Action Indicated) occurs when no objectionable conditions or practices were found during the inspection or the significance of the documented objectionable conditions found does not justify further actions.

Issuing a Form 483 is generally known to the public. For instance, an Indian API facility has received a Form 483 from the US FDA in the latest setback for the troubled drug maker Ranbaxy Laboratories [Stanton 2014].

Furthermore, manufacturing and process continuity are also crucial during scale-up to ensure that risks are minimized. “Laboratories and small-scale GMP equipment should be designed so that they are aligned with the large-scale equipment used for commercial production.” [Challener 2015]

Usually, “as an HPAPI project proceeds through the development lifecycle and into clinical trials, the understanding of the risks associated with the potent compound increases and risk mitigation generally becomes less difficult.” [Challener 2015]

“Since a certain level of risk will always exist when working with HPAPIs, it is important to foster a strong company culture of excellence in protecting employees, products, and the environment.”

Generic APIs are a very attractive segment of the fine chemicals industry. With regard to risk being in the generics business has two aspects: Develop generic APIs and then go out and sell or develop generics only if a customer is interested – as ChemCon does.

In the first case manufacturers of generic APIs take a huge risk. They select a product based on the feasibility of inventing a different manufacturing route, develop the process chemistry, and assemble the drug master file – or registration dossier for European customers. Then they must find buyers. When a generic company is trying to circumvent a patent, how fast the API manufacturer can develop an alternative non-patent-infringing process is critical to the generic company's success in gaining first approval [Rouhi 2002].

But it is not just about technology. It's also about the API manufacturer's competitiveness, regulatory history, and manufacturing capabilities; what other products it manufactures and whether it can provide the API in the specific way the generic company demands.

Furthermore, whenever a drug loses patent protection, the amount of API needed to supply the market more than doubles. "Because of the enormous volumes involved, success in generic APIs requires good understanding of the supply chain, especially where it is weakest and most susceptible to competition." [Rouhi 2002].

Competition

Competition and *differentiation* are on the minds of custom chemical producers as they try to succeed, or at least survive, in a difficult market.

Whether it is technology or service depends on a customer's specific requirements, but developing a *track record for delivering* whatever it is a customer needs is key.

Another factor definitely contributing to ChemCon's success is a business landscape with few competitors. "Our company profile is unique worldwide. There are only approximately 10 to 20 companies that have a slightly similar profile." [BIOPRO 2004a]. In 2008 ChemCon claimed "*In this particular combination no competitor* in the world offers such a range of services! ("In dieser speziellen Kombination bietet dieses Leistungsspektrum kein Konkurrent weltweit an!") [Vogler 2008]. Additionally, it has stable relationships with a broad variety of customers over time (Figure 3) and is strong in the niche with metal-containing APIs.

"The pressure on pharmaceutical companies to adapt to changes in the pharma market is ever increasing. Pharmaceutical innovators have to find novel ways of staying ahead of their competition in terms of delivery, quality and cost. One approach to managing the key success factors … is for pharmaceutical companies to strategically outsource aspects of their drug pipeline. The high potent active pharmaceutical ingredient (HPAPI) industry is a $12B industry, with around 10% of the global market (ca $120B) and a 10% growth rate year on year. This growth has fueled the number of service providers that offer these capabilities to meet the increasing demand." [Heiss 2015; PwC 2011]

APAC (Asia and Pacific) and pharmerging markets like the BRICS (Brazil, Russia, India, China, South Africa) etc. are the major growth drivers of the oncology market, with around 20 percent growth rate. These regions are home to a large patient pool, affected by cancer and other lifestyle related disorders. Unlike the Asian API market, the APAC and pharmerging nations have only a few CMOs with HPAPI manufacturing capabilities, and account for only about 9-10 percent of the global HPAPI production. For instance, only few of the domestic CMOs like Asymchem Laboratories (China) and Piramal Healthcare, India etc. have ventured into establishing manufacturing facilities for HPAPI [Shruthi 2012].

Pharmerging markets rank countries on the basis of their minimum anticipated growth contribution to the global pharmaceutical market between 2009 and 2013.

A few pharmaceutical companies have in-house capabilities, a sizeable proportion of the market is covered by contract manufacturing. Thus, adequate containment strategies and proper classification of hazards is essential for the uptake of this market.

A good proportion of HPAPI/cytotoxics manufacturing is currently outsourced. In fact, specifically for ADCs, the outsourcing proportion is as high as 75-80 percent. Big pharma companies such as Roche, Pfizer and AbbVie have also established in-house capabilities [RootsAnalysis 2014].

Over the last decade a rather large number of firms already working as CRO/CMO/CDMO in the fine chemicals or API businesses upgraded their facilities to exploit the distinct opportunities in HPAPIs.

But, there are high entry barriers to enter the market associated with sophisticated, expensive equipment and production facilities and high quality, highly educated and trained employees.

The cost of technology and processes to establish a plant and comply with the regulations is extremely challenging which means required capital, intensive high containment facilities and a skilled labor force adept at maintaining operational standards.

Concerning ChemCon's competitive situation the supplier slate in custom chemicals [9] comprises both *very large* competitors that have custom-chemicals sales in excess of $300 million such as DSM Pharmaceutical Products (Heerlen, Netherlands) or Evonik Industries from Germany (emerged out of Degussa Fine Chemicals as an API/HPAPI supplier by acquisitions), medium-sized and *large* firms with more than 200 employees and sales of more than $50 million like Medichem SA from Barcelona/Spain as well as small firms with a turnover of less than $10 million, such as ChemCon. Most often, small competitors tend to focus on niches of selected products or technologies.

Many of the medium-sized and *large* firms were founded in the 1970s or 1980s.

There are many sources, mostly referring to market research reports, which provide lists of companies active in the relevant fields [GBI Research 2010; Heiss 2015; PharmaBiz Editor 2014; RootsAnalysis 2014; Transparency Market Research 2015; Research and Markets 2014]. Some of the listed firms are secondary processors of HPAPIs, for example, dosage form scale-up and manufacturing or focusing on specific services rather than covering the whole value system. [9]

An overview of contract manufacturers that picked up Big Pharma's old plants for upgrading or expansion is given by PwC [2011:25]. Heiss [2015] provides also players by listing recent investments for HPAPI capabilities.

As mentioned above the large German pharmaceutical and specialty chemicals firm Merck KGaA recently purchased the Sigma-Aldrich Corporation with SAFC. SAFC – Sigma-Aldrich Fine Chemicals – is the custom manufacturing and services business unit of Sigma-Aldrich. The Company is recognized as a Top 10 global specialty chemicals and biologics supplier which invested heavily in HPAPI production. It had approximately 9,300 employees worldwide and had sales of $2.79 billion in 2014.

A further very large supplier to the pharma/biotech and specialty ingredient markets is Lonza Custom Manufacturing (LCM – sales of CHF3.64 billion in 2014) which is located in Basel (Switzerland) close to ChemCon.

Helsinn Advanced Synthesis SA (Biasca near Lugano) is also from Switzerland which develops and manufactures APIs, advanced intermediates, HPAPIs, and most recently cytotoxic compounds for third parties under cGMP on an exclusive basis. It had 560 employees in 2013 and sales of $348 million in 2013 (cf. Figure 5).

ChemCon produces already for more than ten years highly active ingredients (HPAPIs, Figure 2) and bioconjugates (ADC – antibody drug conjugates) [ChemCon]. It has a notable track record and, hence, a *competitive advantage* relative to those firms that just entered the scene 1-4 years ago.

Furthermore, ChemCon is able to *offer the entire value system (supply chain)* in the drug development process. Hence, ChemCon may carry out any concerted development steps from a *single source*, which are important to provide drugs for clinical trials in phases I to III (Figure 6). The services cover all phases of drug development to regulatory approval and commercial production – fully cGMP-compliant. ChemCon offers an *all-in-one-hand service* including full analytical support, complete documentation and outstanding quality management.

In terms of a current buzz phrase ChemCon's approach is "integrated DS/DP Manufacturing" [Heiss 2015]. DS – Drug Substance – means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body. DP – Drug

Product – is the marketed dosage form designed to consistently deliver the drug substance at the desired rate [Boe et al. 2011].

The advantages of an integrated over a non-integrated approach is summarized in Figure 8. It shows the advantages and challenges for pharma companies in outsourcing using an integrated *versus* non-integrated approach.

There are "specialist expertise and capabilities that can be gained from manufacturing both the DS and DP and the potential complexities that CDMOs need to address for successful outcomes." [Heiss 2015]

> "There are very few contract businesses that offer integrated HPAPI drug substance (DS)/drug product (DP) capabilities and even fewer that have a wealth of experience in this area, though the number is growing." [Heiss 2015]

Streamlining the manufacturing process by integrating DS/DP production can mitigate risk for the client by reducing timelines and decreasing costs whilst maintaining quality.

ChemCon as an integrated DS/DP manufacturer operates at just one site whereas large CMOs/CDMOs may be integrated as a firm, but individual steps of the overall service are often distributed over several separated units of the firm at different locations. This does not make communication easier (Figure 8). This is particularly true if the integrated DS/DP manufacturer evolved through acquisitions of relevant smaller firms which occupy the necessary functions.

Integrated	Non-integrated
Easier path of communication within single organization.	Multiple organizations mean more points of contact.
Project scope changes can be made without impacting overall project timeline.	Changing project scope can have a big impact on the overall project timeline.
DS process optimization and manufacturing activities coordinated with DP inputs.	Technology transfer from one organization to another can increase risk and delay projects.
Single touch-point for all processes.	Management of projects is split between DS and DP sites.

Figure 8: Comparing integrated *versus* non-integrated DS/DP Manufacturing [Heiss 2015:24].

CordenPharma is a representative for such a situation and also Helsinn Advanced Synthesis which runs R&D in Switzerland and manufacturing in Ireland.

Concerning more potential competitors Custom Pharma Services (CPS) operates as a separate business unit of Dr. Reddy's Laboratories Ltd. and develops and manufactures advanced intermediates (cGMP), NCE's, API's and dosage forms on a custom basis for the pharmaceutical industry. It is a service provider with own pharma industry base and knowledge and bases in India, USA, Mexico, Switzerland (Basel), the UK (Chirotech Technology Limited) and Japan.

Dr. Reddy's Laboratories Ltd. was founded by Dr. K Anji Reddy in 1984 and headquartered at Hyderabad, India. It is one of the leading pharmaceutical companies in India and globally an Indian generics giant. Consolidated net revenue in 2014 was $2.38 billion. (Annual Report 2014). Its Pharmaceutical Services and Active Ingredients (PSAI) segment, which consists of its active pharmaceutical ingredients (API) business and custom pharmaceutical services (CPS) business, had revenue of ca. $500 million.

CPS promotes its end-to-end services and integrated DS/DP manufacturing specifically for HPAPIs from development to commercial manufacture of steroids (including androgens, estrogens, glucocorticoids, fluorinated steroids and steroid hormones cf. Figure 1), prostaglandins and cytotoxics [Heiss 2015]. Therefore, concerning chemical orientation CPS addresses applications and markets that are different from those of ChemCon.

Two notable young suppliers founded after 2000, CordenPharma and Aesica Pharmaceticals Limited, have developed in the context of consolidations in the medical/pharmaceuticals field by acquisition activities of large firms.

Aesica Pharmaceuticals is now a Consort Medical Plc Company (UK) which acquired Aesica Pharmaceuticals for £230 million. Aesica is a pharmaceutical CDMOs, providing contract development and manufacturing services essentially for finished dose and APIs to the global pharmaceutical industry. Since the Aesica business was established in 2004 it has grown both organically and non-organically through acquisitions and had established relationships with major global blue-chip pharmaceutical companies. It has manufacturing and development facilities in the UK, Germany and Italy.

CordenPharma formed in 2006 as the Pharmaceutical Brand of the International Chemical Investors Group (ICIG), appears as a CDMO and is organized under six technology platforms. With 1,500 employees total sales were €330 million (2014) utilizing ten manufacturing facilities in Europe and the US (8 GMP plants, 2 R&D labs).

CordenPharma mission focuses on being a *full-service* partner in the cGMP CDMO of APIs and drug products for pharmaceutical and biotechnology companies. Specifically, there are three HPAPI and Oncology Facilities: CordenPharma Colorado – Boulder, CO, USA, CordenPharma Latina – Latina, IT, CordenPharma Plankstadt – Plankstadt, DE.

US firm Aptuit LLC (formed in 2004) grew almost from its start via continuous acquisitions of other firms or divesting firms of the Group, also by JVs and cooperation. In 2006 it acquired Quintiles EDP. The company maintains resources around the world, with facilities in the US, UK and Italy. Aptuit LLC is partnered with Welsh, Carson, Anderson & Stowe, one of the world's leading private equity investors.

It offers fully integrated drug discovery and development services from a single site at The Aptuit Center for Drug Discovery & Development in Verona, Italy. The company maintains resources around the world, with facilities in the US, UK and Italy.

Only recently Aptuit announced expansion of integrated CMC offering (drug substance and drug product) to Phase III and commercial scale. Aptuit LLC now provides a complete set of integrated early discovery to mid-phase drug development services in the pharmaceutical industry including Drug Design & Discovery, API Development and Manufacture, Solid State Chemistry, CMC, Preclinical and IND enabling GLP/GMP programs.

Revenue of $100 to 500 million – most likely ca. $200 million – and employing a staff of approximately 100 to 249 are reported.

> ChemCon obviously has found its niche: Competitors are scarce. "We estimate that we have developed just one percent of the potential market," said Raphael Vogler in 2004 [MBG 2004] – and this is apparently still valid.
> "Who can produce small and smallest quantities of active drug ingredients under absolute GMP conditions is able to occupy a market niche. We have done that," said Dr. Vogler [BIOPRO 2008].

However, as biologics account for over 60 percent of the orphan drug market, the future of the orphan drug industry will also depend heavily upon the entry of biogenerics ("biosimilars"). And as ChemCon is largely focusing on products generated by chemical means biologics may create a challenge for ChemCon in the future.

References

ABCEurope (2012): *ABCEurope Virtual Matchmaking Event on Oncology – Company profiles – 13 and 14 February 2012*. http://www.biocat.cat/sites/default/files/VirtualMatchmakingOncology_ProfilesCatalogue.pdf (last access 7/23/2014).

aiHit Ltd. (2015): *CHEMCON*. Updated January 2015. https://www.aihitdata.com/company/00973495/CHEMCON/people (last access 6/2/2015).

Ainsworth, S. J. (2007): *Pharma Adapts*. Chemical & Engineering News 85 (49), 13-24, Dec. 3, 2007. http://pubs.acs.org/cen/coverstory/85/8549cover.html (last access 12/5/2007).

Anonymus (2002): *Die US Niederlassung im Visier (The US subsidiary is in sight*). Freiburger Uni-Magazin, 2/April 2002, p. 16. http://www.pr.uni-freiburg.de/publikationen/unileben/archiv_uni-magazin/2002/fum-2-2002.pdf (last access 1/31/2009).

Ariyanchira, S. (2008): *BioMarket Trends: Orphan Drug Arena Driven by Biologics*. GENNews, 28 (1), Jan. 1, 2008. http://www.genengnews.com/gen-articles/biomarket-trends-orphan-drug-arena-driven-by-biologics/2318/ (last access 6/19/2009).

Barry, F. (2014a): *Foreign customers look to US FDA as stamp of quality*. In-PharmaTechnologist.com, Apr. 9, 2014. http://www.in-pharmatechnologist.com/Ingredients/Foreign-customers-look-to-US-FDA-as-stamp-of-quality (last access 1/18/2015).

Barry, F. (2014b): *100-hundred year old rules on API impurities to change in 2015*. In-PharmaTechnologist.com, May. 22, 2014. http://www.in-pharmatechnologist.com/Ingredients/100-year-old-rules-on-API-impurities-to-change-in-2015 (last access 1/18/2015).

BCC Research (2007): *Global Markets for Orphan Drugs*. Published September 2007. http://www.bccresearch.com/market-research/pharmaceuticals/orphan-drugs-market-phm038b.html (last access 6/19/2014).

BCC Research (2010): *Global Markets for Orphan Drugs*. Published May 2010. http://www.bccresearch.com/market-research/pharmaceuticals/orphan-drugs-market-phm038c.html (last access 6/19/2014).

Bionity (2013): *ChemCon erhält Herstellungserlaubnis für halbfeste Arzneimittel zur Verwendung am Menschen (ChemCon obtains manufacturing authorization for semi-solid pharmaceutical composition for use in humans*). Published Dec. 6, 2013. http://www.bionity.com/de/news/146082/chemcon-erhaelt-herstellungserlaubnis-fuer-halbfeste-arzneimittel-zur-verwendung-am-menschen.html (last access 5/29/2014).

BIOPRO (2004a): *Wirkstoffentwicklung vom Labormaßstab bis hin zu Medikamenten für klinische Studien und für Arzneimittel auf dem Markt (Drug development from laboratory scale to medicines for clinical trials and for medicinal products on the market*). Published Aug. 14, 2004. http://www.bio-pro.de/standort/unternehmen_bw/index.html?lang=de&artikelid=/artikel/03240/index.html, http://www.bio-pro.de/artikel/03240/index.html?lang=en (last access 1/23/2009).

BIOPRO (2004b): *Mehr Platz für Forschung und Produktion bei ChemCon (More space for research and production at ChemCon*). Published Feb. 2, 2004. http://www.bio-pro.de/de/region/freiburg/meldungen/00313/index.html (last access 10/15/2008), no longer accessible); http://www.bio-pro.de/magazin/wirtschaft/archiv_2008/index.html?lang=de&artikelid=/artikel/01294/index.html (last access 6/3/2015).

BIOPRO (2004c*): ChemCon gewinnt den "Baden - Württembergischen Förderpreis für junge Unternehmen" (ChemCon wins the "Baden-Württemberg Award for Young Companies*). Published Nov. 22, 2004. http://www.bio-pro.de/de/region/freiburg/meldungen/00996/index.html (last access 3/29/2005), no longer accessible; http://www.bio-pro.de/artikel/01063/index.html?lang=de&linkGlossaryTerms=1 (last access 6/3/2015).

BIOPRO (2008): *ChemCon – and how an ideal niche was found and occupied*. BIOPRO Baden-Württemberg GmbH, May 7, 2008. http://www.bio-pro.de/magazin/thema/00143/index.html?lang=en&artikelid=/artikel/01267/index.html (last access 1/12/2008) no longer accessible; cf. http://www.bio-pro.de/magazin/thema/00143/index.html?lang=en&artikelid=/artikel/01267/index.html (last access 6/2/2015); https://www.gesundheitsindustrie-bw.de/de/fachbeitrag/pm/chemcon-die-ideale-nische-gefunden-und-besetzt/.

BIOPRO (2011): *ChemCon baut Fertigungskapazitäten für hochaktive Pharmawirkstoffe aus (ChemCon expands production capacities for highly active pharmaceutical ingredients*). Published Nov. 25, 2011. http://www.bio-pro.de/magazin/wirtschaft/archiv_2011/index.html?lang=de&artikelid=/artikel/07328/index.html (last access 4/12/2015).

Biotop (2003): *Acht Unternehmen bilden virtuelle Pharma-Firma (Eight firms form a virtual pharma company*). Published Jun. 10, 2003. http://www.biotop.de/news/archiv_detail_g.asp?ID=756&QuickSearch=&AbsolutePage=92 (last access 11/23/2007), no longer accessible.

BioValley: *ChemCon GmbH*. http://209.85.135.104/search?q=cache:WXk5pSeJ6GIJ:www.biovalley.com/images_messages/image2/1072.pdf+chemcon+freiburg+revenues&hl=en&ct=clnk&cd=5 (last access before 2009, currently no longer accessible).

BMBF (2005): *Chemcon's Erfolgsgeschichte. Jugend gründet (Chemcon's success story – Youth is founding*). *In* Schülermagazin, 2005. File of 10/11/2005, p. 9-10. http://www.jugend-gruendet.de/barrierefrei/fileadmin/downloads/Sch_lermagazin.pdf (last access 7/27/2006).

Boe, P.; Snyder, B.; Weiss, M. (2011): *Introduction to Regulatory Documents in New Drug Applications*. AMWA JOURNAL 26 (3), 2011, 122-124.; Table 1. http://www.amwa.org/files/publications/regulatory_insights.pdf (last access 6/18/2015).

CASID – Arbeitsgemeinschaft für chemische Auftragssynthese in Deutschland e.V. *Willkommen zu einem kurzen Firmenüberblick bei der ChemCon GmbH. (Welcome to a brief company overview of ChemCon GmbH*). http://www.casid.de/mitglieder/chemcon/index_de.php (last access 12/17/2008).

Cauchi, R. (2015): *State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars*. NCSL – National Conference of State Legislatures, 7/2/2015. http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx (last access 7/7/2015).

Chao Xiong (2011): *API Market Outlook –The market for contract API manufacturing and fine chemicals is forecast to be fairly strong, and growth for generic APIs is expected to outpace growth for innovator APIs*. PharmaTrend, Aug. 3, 2011. https://www.linkedin.com/grp/post/4029475-130640741 (last access 6/30/2015).

Challener, C. A. (2014): *HPAPIs: Fast-growing Segment Presents Challenges and Opportunities*. PharmTech, May 30, 2014. http://www.pharmtech.com/hpapis-fast-growing-segment-presents-challenges-and-opportunities (last access 7/11/2015).

Challener, C. A. (2015*): Minimizing Risk during HPAPI Manufacture*. PharmTech, May 2, 2015. http://www.pharmtech.com/minimizing-risk-during-hpapi-manufacture (last access 6/29/2015).

ChemCon: Web site information – *Facts*. http://www.chemcon.com/en/company/facts.html (last access 6/2/2015);
Chemical development. http://www.chemcon.com/en/services/chemical-development.html (last access 7/23/2015);
GMP. http://www.chemcon.com/de/quality/gmp.html (last access 5/29/2015);
FDA. http://www.chemcon.com/de/quality/us-fda.html (last access 5/29/2015);
ISO. http://www.chemcon.com/de/quality/iso.html (last access 5/29/2015);
Quality. http://www.chemcon.com/en/quality.html (last access 8/23/2015);
Bioconjugates. http://www.chemcon.com/de/services/gmp-manufacturing/biokonjugate.html (last access 8/23/2015);
Advantages. http://www.chemcon.com/en/company/why-choose-chemcon.html (last access 8/23/2015).

ChemCon (2004a*)* – Dr. Monika Schmidt (Ed.): *A successful German-American Partnership*. Chemcon News Letter, Issue 03, Jan. 14, 2004. http://www.chemical-services.de/cc/images/stories/pdf/NL03-englisch.PDF (last access 4/7/2006); no longer accessible.

ChemCon (2004b) – Dr. Monika Schmidt (Ed.): *Throwing a glance at Chemcon's roots*. Chemcon News Letter, Issue 04, Mar. 5, 2004. http://www.chemical-services.de/cc/images/stories/pdf/NL04-englisch.PDF (last access11/17/2007); no longer accessible.

ChemCon (2006): *6 Steps to Success for our Customers*! File of 8/28/2006. http://events.dechema.de/events_media/11+ChemCon.pdf (last access 4/20/2015).

ChemCon (2013): *ChemCon Brochüre (Brochure*). File of 10/18/2013. http://www.chemcon.com/fileadmin/user_upload/Images/Content/ChemCon_Broschuere_2013.pdf (last access 11/4/2014).

ChemCon (2014a): *ChemCon – Prize winner at 'Service Provider of the Year'*. News, Jul. 16, 2014. http://www.chemcon.com/en/news-events/singleview/article/chemcon-prize-winner-at-service-provider-of-the-year-2014.html (last access 3/26/2015).

ChemCon (2014b): *ChemCon GmbH besteht FDA Inspektion zum vierten Mal erfolgreich (ChemCon GmbH passes FDA inspection for the fourth time successfully*). Published Apr. 1, 2014. http://www.chemcon.com/de/neues/singleview/article/chemcon-gmbh-passes-fda-inspection-successfully-for-the-4th-time.html (last access 2/24/2015).

ChemCon (2015): *ChemCon besteht 2015 erneut zwei Inspektionen erfolgreich (In 2015 ChemCon passes again two inspections successfully*). Published Jul. 13, 2015. http://www.chemcon.com/de/neues/singleview/article/continuing-flawless-quality.html (last access 7/30/2015).

CHEMWERTH: *Chemwerth appoints ChemCon as European sales agent*. http://www.chemwerth.com/html/news/chemconPartnership.html (last access 10/3/2008), no longer accessible;
ChemWerth: FIRST TO QUALITY. FAST TO MARKET. http://www.chemwerth.com/news/FDA_Approval_Archive.php (last access 10/3/2008), no longer accessible.

Doyle, J. (2014): *Bringing Orphan Drugs to Market*. Quintiles, August 19, 2014. http://www.quintiles.com/blog/doyle-bringing-orphan-drugs-to-market (last access 6/20/2015).

Econo (2011): *Chemcon investiert in Freiburg (ChemCon invests in Freiburg*). Published Nov. 25, 2011. http://www.econo.de/no_cache/nachrichten/einzelansicht/article/chemcon-investiert-in-freiburg.html (last access 10/17/2012).

EMA – European Medicines Agency: *Biosimilar medicines*. http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000318.jsp (last access 7/7/2015).

EvaluatePharma (2013): *ORPHAN DRUG REPORT 2013*. Published April 2013. http://info.evaluategroup.com/rs/evaluatepharmaltd/images/EP_OrphanDrugReport2013.pdf (last access 3/12/2015).

EvaluatePharma (2014): *ORPHAN DRUG REPORT 2014*. Published October 2014. http://info.evaluategroup.com/rs/evaluatepharmaltd/images/2014OD.pdf (last access 3/12/2015).

FDA: *Biosimilars*. http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/default.htm (last access 7/7/2015).

GBI Research (2010): *The Future of High Potency Active Pharmaceutical Ingredients (HPAPIs), Market Forecasts and Growth Opportunities to 2015 – Growing Demand Drives Investment in Capacity*. Published March 2010. http://www.docstoc.com/docs/64933532/The-Future-of-High-Potency-Active-Pharmaceutical-Ingredients-(HPAPIs),-Market-Forecasts-and-Growth-Opportunities-to-2015---Growing-Demand-Drives-Investment-in-Capacity (last access 7/4/2015).

Gaffney, A. (2014): *EMA Finalizes Major Guideline on Biosimilars*. RAPS – Regulatory Affairs Professionals Society, Oct. 29, 2014. http://www.raps.org/Regulatory-Focus/News/2014/10/29/20643/EMA-Finalizes-Major-Guideline-on-Biosimilars/ (last access 7/7/2015).

Gonser, B. (2005): *ChemCon: Kleine Mengen – großer Erfolg (Small quantities – big success)*. Schwäbische Zeitung, Jan. 3, 2005. http://www.schwaebische.de/home_artikel,-ChemCon-Kleine-Mengen-grosser-Erfolg-_arid,1304896.html (last access 7/10/2008).

Heiss, A. (2015): *HPAPI DS/DP Manufacturing – Industry Trends*. informEX, February 3-5, 2015, New Orleans. http://www.slideshare.net/DrReddysCPS/aaron-heiss-informex-2015 (last access 7/11/2015); cf, also http://gbuweb02.ut.ubm-net.com/informex/webroot/hpapi-dsdp-manufacture-%E2%80%93-advantages-streamlining-manufacturing-process.

Helfand, C. (2014): *Who's king of the orphan drug hill*? *BMS, Merck, Celgene and Roche, to name a few*? Fiercepharmamarketing, Nov. 5, 2014. http://www.fiercepharmamarketing.com/story/whos-king-orphan-drug-hill-bms-merck-celgene-and-roche-name-few/2014-11-05 (last access4 /7/2015).

InsideView (2015): *ChemCon GmbH*. Published 2015-06-04. http://www.insideview.com/directory/chemcon-gmbh/ (last access 6/29/2015).

Kramer, B. (2014): *Klassisch deutsch (Classically German*). Badische Zeitung, Jun. 2, 2014. http://www.badische-zeitung.de/wirtschaft-3/klassisch-deutsch--85688458.html (last access 96/2014).

Längin, A.; Kümmerer, K. (2008): *Systematische Modifizierung von Arzneimitteln auf Basis nachwachsender Rohstoffe als ein Konzept für eine nachhaltige Chemie (Systematic modification of medicines based on renewable resources as a concept for sustainable chemistry*). Final Report of a common project, Freiburg 2008. https://www.dbu.de/ab/DBU-Abschlussbericht-AZ-22597.pdf (last access 4/23/2009).

MBG - Mittelständische Beteiligungsgesellschaft Baden-Württemberg GmbH (2004): *ChemCon GmbH Freiburg*. Geschäftsbericht (Annual Report) 2004. http://www.mbg.de/pdf/Seite_16_39.pdf (last access 4/24/2009, no longer accessible); also http://www.foerderportal.newcome.de/finanzierung/SuccessStories/index.php?oid=21149 (last access 4/22/2009, no longer accessible); https://www.yumpu.com/de/document/view/2215850/geschaftsberichte-2004-mbg-mittelstandische-/39 (last access 6/30/2015).

MBG – MBG Mittelständische Beteiligungsgesellschaft Baden-Württemberg GmbH and Bürgschaftsbank Baden-Württemberg GmbH (2005): *ChemCon GmbH – Gewinner des Förderpreises für Junge Unternehmen 2004 (ChemCon GmbH – Winner of the Baden-Württemberg Award for Young Entrepreneurs*). INFO February 2005. http://www.mbg.de/uploads/tx_bbnewsletterlist/info0502.pdf (last access 6/2/2015).

Muller, T.; Arzt, S. (2008): Exercise “Write the Business Plan of ChemCon” in the context of the Technology Entrepreneurship course. Utilized literature/Internet and discussions with the co-founder Dr. Vogler and project chemists Frédérique Hauss. Related PowerPoint presentation delivered, March 2008.

Patnaik, P. (2011): *HPAPI: When Less is More*. ContractPharma, Sep. 7, 2011. http://www.contractpharma.com/issues/2011-09/view_features/hpapi-when-less-is-more (last access 11/16/2014).

PwC (2011): *Pharma 2020: Supplying the future – Which path will you take*? https://www.pwc.com/gx/en/pharma-life-sciences/pdf/pharma-2020-supplying-the-future.pdf (last access 9/24/2015).

PharmaBiz Editor (2014): *HPAPI market helps drive API market growth*. Published May 29, 2014. http://www.pharmabiz.com/NewsDetails.aspx?aid=82268&sid=21 (last access 7/11/2015).

Pollak, P. (2011): *Fine Chemicals: The Industry and the Business. Global Merchant API Production, Market Share and Growth*. John Wiley & Sons, 2011 (Table 14.4, p. 187). https://books.google.de/books?isbn=1118002229 (last access 9/10/2014).

Raeside, A. (2013): *Worldwide Orphan Drug Market to Grow to $127 Billion by 2018*. Published Apr. 23, 2013. http://www.biotech-now.org/health/2013/04/worldwide-orphan-drug-market-to-grow-to-127-billion-by-2018 (last access 5/21//2014).

Research and Markets (2014): *HPAPIs and Cytotoxic Drugs Manufacturing Market, 2014 – 2024*. Published Sep. 23, 2014. http://www.wallstreet-online.de/nachricht/7028216-hpapis-and-cytotoxic-drugs-manufacturing-market-2014-2024 (last access 3/9/2015).

RootsAnalysis (2014): *HPAPIs and Cytotoxic Drugs Manufacturing Market*. Published Aug. 6, 2014. http://www.rootsanalysis.com/reports/view_document/hpapis-and-cytotoxic-drugs-manufacturing-market/64.html (last access 11/7/2014).

Rouhi, A. M. (2002): *Generic Tide is Rising*. Chemical & Engineering News 80 (38), Sep. 23, 2002, 37-51. http://pubs.acs.org/cen/coverstory/8038/8038biogenerics.html (last access 11/25/2008).

Rouhi, A. M. (2005): *Mixed Outlook for Custom Chemicals*. Chemical & Engineering News 83 (3), Jan. 17, 2005, 52-57. http://pubs.acs.org/cen/coverstory/83/print/8303customchemicals1.html (last access 11/24/2008).

Runge, W. (2014a): *Case WITec GmbH*. August 2014. http://etm.entechnon.kit.edu/454.php.

Runge, W. (2014b): *Case IoLiTec GmbH*. March 2014. http://etm.entechnon.kit.edu/454.php.

Runge, W. (2015): *Case NANO-X GmbH.* June 2015. http://etm.entechnon.kit.edu/454.php.

Sharma, A.; Jacob, A.; Tandon, M.; Kumar, D. (2010): *Orphan drug: Development trends and strategies*. Journal of Pharmacy & Bioallied Sciences 2010, Oct-Dec; 2 (4) p. 290–299. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2996062/ (last access 4/23/2015).

Shruthi P, (2012): *A holistic view of the HPAPI opportunity*. ExpressPharna Jun. 29, 2012. http://archivepharma.financialexpress.com/sections/management/670-a-holistic-view-of-the-hpapi-opportunity (last access 7/11/2015).

Stanton, D. (2014): *Ranbaxy receives US FDA Form 483 at Indian API plant*. in-PharmaTechnologist, Jan. 13, 2014. http://www.in-pharmatechnologist.com/Ingredients/Ranbaxy-receives-US-FDA-Form-483-at-Indian-API-plant (last access 2/12/2015).

Statista (2015): *ChemCon GmbH: Umsatz in 2014 (Revenue in 2014*). http://de.statista.com/unternehmen/217289/chemcon-gmbh (last access 5/29/2015).

STEP Award: *Leitidee (Leading Idea*). http://www.step-award.de/leitidee.16.0.html (last access 7/2/2015).

STEP Award (2009): *ChemCon GmbH – Kategoriensieger 2009 Prozess (Winner 2009 in the Category Processes*). http://www.step-award.de/Gewinner-2009.53.0.html (11/20/2011).

Thayer, A. M. (2012): *Finding new uses for approved drugs and shelved drug candidates is gaining steam as a pharmaceutical development strategy*. Chemical & Engineering News 90 (40), 15-25, Oct, 1, 2012. http://cen.acs.org/articles/90/i40/Drug-Repurposing.html?h=-1031248274 (last access 2/23/2013).

Thayer, A. M. (2006): *Custom Chemicals*. Chemical & Engineering News 84 (7), Feb. 13, 2006, 17-27. http://cen.acs.org/articles/84/i7/Custom-Chemicals.html (last access 7/19/2008).

Transparency Market Research (2015): *HPAPIs Market to Benefit from Increased Demand for Generic Drugs*. Posted on Apr 1, 2015. http://www.transparencymarketresearch.com/article/high-potency-active-pharmaceutical-ingredients-market.htm (last access 6/30/2015).

Van Arnum, P. (2012): *API Market Outlook*. PharmTech, Jan. 12, 2014. http://www.pharmtech.com/api-market-outlook (last access 10/17/2014).

Van Arnum. P. (2013): *The Weaknesses and Strengths of the Global API Market*. PharmTech, Mar 06, 2013. http://www.pharmtech.com/weaknesses-and-strengths-global-api-market (last access 10/17/2014).

Vogler, R. (2008): *Willkommen zur Präsentation der Firma ChemCon: Vom Laborkittel zur Chefkrawatte (Welcom to the Presentation of the Firm ChemCon – From lab coats to a chief's tie*). Technology Entrepreneurship Presentation, Dec. 3, 2008. http://ce.ioc.kit.edu/downloads/Praesentation_Vogler.pdf; http://ce.ioc.kit.edu/75.php.

Vogler, R. (2006a): *Sicherheitsnetz Vertraulichkeitsvereinbarungen (Safety net confidentiality agreements*). In [Zülch et al. 2006] ch. 3, 37- 56.

Vogler, R. (2006b): *Aufbau von Kooperationsfähigkeit. So wird's gemacht! (Building cooperation skills. How to do it!*). In [Zülch et al. 2006], ch. 6, 97-116.

Vogler, R.; Gockel, P. (2005): *Case Study: ChemCon GmbH*. GoingPublic "Biotechnologie" 2005, 126-127. File of 9/22/2005 (no longer accessible).

WIKIPEDIA-1: *Orphan Drugs*. http://en.wikipedia.org/wiki/Orphan_drug (last access 2/23/2015).

Zülch, J.; Barrantes, L.; Steinheuser, S. (2006): *Unternehmensführung in dynamischen Netzwerken: Erfolgreiche Konzepte aus der Life Science Branche* (Corporate management in dynamic networks: Successful concepts from the life sciences industry). Springer-Verlag Berlin Heidelberg: 2006. https://books.google.de/books?isbn=3540346503 (last access 11/23/2014).

Notes

1. *Off-Label Drug Use*. Miller K.: Off-Label Drug Use: What You Need to Know. WebMD. http://www.webmd.com/a-to-z-guides/features/off-label-drug-use-what-you-need-to-know (last access 7/3/2015).
   "Off-label" means the medication is being used in a manner not specified in the FDA's approved packaging label, or insert. Every prescription drug marketed in the U.S. carries an individual, FDA-approved label. This label is a written report that provides detailed instructions regarding the approved uses and doses, which are based on the results of clinical studies that the drug maker submitted to the FDA."
2. *Clinical Trials*: https://en.wikipedia.org/wiki/Clinical_trial; https://de.wikipedia.org/wiki/Klinische_Studie (last access 7/3/2015).
3. *Lead generation*: https://en.wikipedia.org/wiki/Hit_to_lead (last access 7/3/2015).
   Hit to lead (H2L), also known as lead generation, is a stage in early drug discovery where small molecule hits from a high throughput screen (HTS) are evaluated and undergo limited optimization to identify promising lead compounds. These lead compounds undergo more extensive optimization in a subsequent step of drug discovery called lead optimization (LO). The drug discovery process generally follows the following path that includes a hit to lead stage:
   target validation (TV) → assay development → high-throughput screening → hit to lead (H2L) → lead optimization (LO) → preclinical drug development → clinical drug development.
   The hit to lead stage starts with confirmation and evaluation of the initial screening hits and is followed by synthesis of analogs (hit expansion). Typically the initial screening hits display binding affinities for their biological target in the micromolar (10^{-6} molar concentration) range. Through limited H2L optimization, the affinities of the hits are often improved by several orders of magnitude to the nanomolar (10^{-9} M) range. The hits also undergo limited optimization to improve metabolic half-life so that the compounds can be tested in animal models of disease and also to improve selectivity against other biological targets binding that may result in undesirable side effects.
4. *Translational science:* https://en.wikipedia.org/wiki/Translational_science (last access 7/4/2015).
   Translational science is a multidisciplinary form of science that bridges the recalcitrant gaps that sometimes exist between fundamental science and applied science, necessitating something in between to translate knowledge into applications. The term is most often used in the health sciences and refers to the translation of bench science.

   "In translational research, basic research informs the development of a treatment or other forms of interventions, but considerations of practical problems inform what questions basic scientists look at. Ideally, it goes back and forth." (Rebecca A. Clay: Postgrad growth area: Translational science. American Psychological Society. http://www.apa.org/gradpsych/2011/01/postgrad.aspx).
5. *Antibody drug conjugate (ADC*): https://en.wikipedia.org/wiki/Antibody-drug_conjugate (last access 7/4/2015); cf. also https://www.youtube.com/watch?v=GD0gcZoqtcM.

Antibody-drug conjugates or ADCs are a new class of highly potent biopharmaceutical drugs designed as a targeted therapy for the treatment of people with cancer. ADCs are complex molecules composed of an antibody (a whole monoclonal antibody (mAb) or an antibody fragment such as a single-chain variable fragment [scFv]) linked, via a stable, chemical linker with labile bonds, to a biological active cytotoxic (anticancer) payload or drug. Antibody Drug Conjugates are examples of *bioconjugates* and immunoconjugates. By combining the unique targeting capabilities of monoclonal antibodies with the cancer-killing ability of cytotoxic drugs, antibody drug conjugates allow sensitive discrimination between healthy and diseased tissue. This means that, in contrast to traditional chemotherapeutic agents, antibody drug conjugates target and attack the cancer cell so that healthy cells are less severely affected.

6. *New Drug Application* (NDA):
http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm (last access 4/23/2015).
When the sponsor of a new drug believes that enough evidence on the drug's safety and effectiveness has been obtained to meet FDA's requirements for marketing approval, the sponsor submits to FDA a new drug application (NDA). The application must contain data from specific technical viewpoints for review, including chemistry, pharmacology, medical, biopharmaceutics, and statistics. If the NDA is approved, the product may be marketed in the United States. For internal tracking purposes, all NDA's are assigned an NDA number.

7. *Gödecke (Unternehmen – Enterprise)*:
https://de.wikipedia.org/wiki/G%C3%B6decke_(Unternehmen) (last access 4/23/2015).
Gödecke (also: Goedecke) is a former pharmaceutical company in Germany. Today Gödecke is a sales division of the Pfizer Group. In 1994 in Freiburg a completely new solid-factory was put into operation, which should produce all solid drugs of the Group for the whole European market in the future. The FDA allowed also to produce for the US market. In 2000, the Warner-Lambert Group was acquired by Pfizer. The merger of the two companies was officially completed on 19 June 2000. And the Gödecke AG, the Parke-Davis GmbH and Warner Lambert Consumer Healthcare were incorporated into the Pfizer Group Germany.

8. *Drug Master File (DMF*): https://en.wikipedia.org/wiki/Drug_Master_File (last access 4/26/2015).
Drug Master File or DMF (in Europa also called European Drug Master File (EDMF) or new Active Substance Master File (ASMF)) is a document prepared by a pharmaceutical manufacturer and submitted solely at its discretion to the appropriate regulatory authority in the intended drug market.
There is no regulatory requirement to file a DMF. However, the document provides the regulatory authority with confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. Typically, a DMF is filed when two or more firms work in partnership on developing or manufacturing a drug product. The DMF filing allows a firm to protect its intellectual property from its partner while complying with regulatory requirements for disclosure of processing details.

9. *ChemCon's competitors*: Very short descriptions of selected formally potential competitors are based essentially on the firms' Web pages ("About"), recent news or company presentations on the Internet (related searches in September/October 2015), for instance,
http://www.rsc.org/images/Dr-Reddys-CPS-final_tcm18-211154.pdf;
https://simconblog.wordpress.com/2014/01/08/dr-reddys-lab-company-analysis/;
http://www.slideshare.net/ChristianAhlmark/cordenpharma-general-presentation-515?related=1;

http://www.jefferies.com/CMSFiles/Jefferies.com/files/Conferences/060214/Presentations/Helsinn%20Healthcare.pdf;
http://www.medichem.es/wp-content/uploads/2015/03/Medichem_Company-Profile_2015.pdf;
http://www.aesica-pharma.com/wp-content/uploads/2014/09/Aesica-Pharmaceuticals-Company-Brochure-English.pdf.

10. *CureVac AG*: CureVac has been successful in optimizing the natural structure for RNA-based medicine. mRNA, as an active ingredient, can be used in treating cancer and for the prevention of infectious diseases. However, such examples are only a few of the possibilities for its innovative RNA technology platforms. It has raised around €300 million in equity investment. Its lead investors are dievini Hopp BioTech holding GmbH & Co. of SAP co-founder D. Hopp and it recently (November 2015) captured €100 from the Bill & Melinda Gates Foundation. Currently CureVac maintains its own in-house, GMP-compliant, cleanroom pharmaceutical production facility and is able to manufacture all of the optimized RNA-based active ingredients it has developed (http://www.curevac.com/).

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