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INHALT

TITELBILD

75 Years Interpharma – 75 years in the service of research for tomorrow

Cooperation with all participants in the health-care system and representation of interests of Switzerland's research-based pharmaceutical industry, in Switzerland and abroad

Interview with Thomas B. Cueni, secretary general and managing director of Interpharma, the association of research-based pharmaceutical companies in Switzerland, Basel

Actelion, Merck Serono, Novartis, Roche and the two associated companies, Cilag Switzerland and Vifor, represent the current members of Interpharma, the association of research-based pharmaceutical companies in Switzerland. The industry association was founded in 1933 and has since continuously adjusted to a changing environment. Today, in its 75th year of existence, Interpharma is mainly concerned with the constructive cooperation among all stakeholders in health care and with representing the interests of Switzerland's research-based pharmaceutical industry in Switzerland and abroad. On the occasion of its anniversary year, Interpharma published "Knowledge – our natural resource", a comprehensive review of the history and present of the Swiss pharmaceutical industry.[1] At the end of the anniversary year, Thomas B. Cueni, Interpharma's secretary general since 1988, was kind enough to meet with Swiss Pharma for an interview.

◆ **Interviewer: Dr. Felix Wüst**

Mr. Cueni, thank you for agreeing to this interview at your offices here in Basel. Last year, 2008, you celebrated Interpharma's 75th anniversary and took that opportunity to publish a history of the Swiss pharmaceutical industry aptly entitled "The Swiss pharmaceutical industry – past and present – in motion" ("Knowledge, Our Natural Resource", Neue Zürcher Zeitung Publishing). Turning to more current issues, would you give us an overview of the anniversary year? How did you benefit from it and how did you enjoy it?

T. C.: Our anniversary year gave us the opportunity to pause for a moment and to look back as well as forward. In looking back, the title of the book you mentioned, *"Knowledge, Our Natural Resource",* says everything about both the pharmaceutical industry and the chemical-pharmaceutical industry in Switzerland. When the dyestuffs industry laid the foundation for the Swiss chemical industry in Basel, Switzerland was one of the poorest countries in Europe. Thousands of Swiss men and women emigrated to North and South America. Today, many towns and villages in Brazil, Argentina and North America carry Swiss names, bearing witness to the Swiss immigrants who left Switzerland due to poverty and hunger. Today, Switzerland is one of the world's richest countries although we have practically no raw materials. Knowledge is our raw material. I believe that no other industry in our country symbolizes the use of knowledge better than does the pharmaceutical industry. In looking back, I recognize a perpetual battle to obtain something better from what was already good. In other words,

[1] Lüönd, Karl: Knowledge, Our Natural Resource, The Swiss pharmaceutical industry – past and present – in motion, 222 pages, ISBN 978-3-03823-485-2, Neue Zürcher Zeitung Publishing, Zurich 2008.

The new Actelion headquarters in Allschwil near Basel, currently under construction, was designed by Herzog & de Meuron architects (completion 2010).

from low added value to higher added value, from dyestuffs to agricultural chemistry, to specialty chemistry, to pharmaceuticals, and from pharmaceuticals to biotechnology and diagnostics; a readiness to continue developing. We wanted to throw light on Switzerland as a pharmaceutical location. Switzerland has a lot of potential, now and in the future. That is why on the occasion of our anniversary we launched Vision 2020, which communicates the premise that should the parameters in Switzerland remain favorable, and provided we can make further use of this potential, the pharmaceutical industry will, in twelve years, be significantly more important than it is today.

Were you able to express the change in Interpharma activities? I remember, about 20 years ago, one of Interpharma's priorities was to publish glossy brochures, to promote the teaching of chemistry and biology in schools, etc.

T.C.: Our activity has become much more intensive, a lot faster, because the environment we operate in has become tougher and more demanding, not only in Switzerland, but also in other countries. In Switzerland, Interpharma is often considered to be a powerful lobby group for the pharmaceutical industry. Lobbying is an integral part of a society that is built on direct democracy, such as in Switzerland. In that sense Interpharma is not alone. With the increasing significance of the civil society there are interest groups representing many interests, from the environment to animal protection and the like. As the association of research-based pharmaceutical companies in Switzerland, we represent the interests of Switzerland as a research location and the production location for the pharmaceutical industry in Switzerland. That, however, is only a small part of our mission. A significant share of our work is disseminating information in general. I should think that most people in Switzerland who work in health-care know our brochures on health-care and are informed about the significance of medicines for health-care. Everybody in health-care works with documentation developed by Interpharma. In 1996, we started conducting a comprehensive annual survey among the population concerning the health sector. A Bern-based research organization managed by Claude Longchamps, gfs.bern, conducts these surveys for us. We published the results right form the start; in other words, we provided transparency to all circles interested in health-care issues. Many among my professional acquaintances utilize these results. In that sense, our work far exceeds our lobbying efforts. The promotion of education and natural sciences continues, in fact, we recently expanded our activity in this field. In this respect we are completely detached from lobbying. A little more than a year ago we employed a former teacher who works in the field of educationals and networking with other teachers.

So, the word "lobbying" does seem to have a rather negative image. Despite the difficult message that you have to disseminate, are you able to achieve openness, readiness to communicate and credibility?

T.C.: In terms of lobbying, when looking around the political environment, I notice that parliamentarians as well as government open their doors to us for one simple reason: we possess factual information, we can provide experts, and we have argued consistently for many years. I am very much in favor of transparency in this field. Both right-wing and left-wing politicians value that everybody knows who we are. We do not do covert lobbying. When I enter the Houses of Parliament, I do not have to hang a big sign around my neck. We are well-known and, accordingly, everything is transparent. Also, we have for years shown that we are interested in finding solutions. For instance, we have offered support to implement price comparisons among comparable countries in Europe. Until recently, we were confronted with a situation where some drugs showed large price differences in comparable countries. However, these medications still enjoyed patent protection. These price differences have now been eliminated. With regard to patent legislation, we worked closely with university professors. For months we met for round table discussions with the Swiss Academies of Arts and Sciences. Our aim was to forge a link between the interests of industry and those of the universities. The outcome of these discussions has had an effect on legislation in that patent protection for biotechnological discoveries was maintained, albeit very narrowly defined, while on the other hand the broadest research privileges anywhere in the world were introduced. Research will never hurt patents. In Switzerland, that has now been put into law. This openness and quest for solutions have provided us with much respect.

It is obvious that you do not wait for a problem to come up and then confront the situation. You try to avoid the problem from the start by providing information.

T.C.: One has to differentiate. On the one hand, you have to analyze a problem. Animal testing, for instance, is still an issue. It must clearly be a concern of the research-based industry to carry out as few animal tests as possible, and whenever possible to reduce, refine and replace them. Before my time, Interpharma founded the 3R Foundation – Reduce, Refine, Replace – a pioneering act in Europe. We fought and won not just one, but several referendum campaigns on issues put to the vote in our direct democracy. Animal testing continues to be permitted in Switzerland. We sat down with politicians and protectors of animal rights to promote alternatives to animal testing. In 2007, the 3R Foundation marked its twentieth year of existence.

You established a further foundation, Gen Suisse.

T.C.: Gen Suisse was established very early on in the debate concerning genetic engineering. I was one of its founders, while the 3R Foundation was established before my time. As early as 1990, eight years prior to the big referendum on genetic engineering, we realized that we had to initiate dialogue. We put it very clearly that a ban would be ineffective. That is why we fought the Genetic Engineering Initiative, which was clearly dismissed by the voters. In turn, however, we supported the inclusion of stringent controls in subsequent genetic engineering legislation. Today, Gen Suisse is an institution that enjoys

wide acceptance and even organizes an annual "Day of Genetic Engineering" which is supported by the Swiss National Science Foundation, several academies, many universities and other organizations.

Now to your members, Actelion, Merck Serono, Novartis, Roche and the two associated members, Cilag Switzerland and Vifor. Are these really the only companies in Switzerland that carry out pharmaceutical research?

T.C.: Only companies that cover the complete value-added chain in Switzerland, i. e. from research to production, can become an Interpharma member. That clearly limits the scope for membership. There is another association in Switzerland, the Swiss Biotech Association (SBA), with which we cultivate good contact. However, only a minority of the SBA members have products. So, the differentiation between companies with the entire value-added chain and those without makes sense. It is therefore remarkable that as of January 1, 2008, for the first time, a former startup company, Actelion, became a full member of our association. Actelion had been an associated member for several years. Actelion's membership enriches the association, because what Jean-Paul Clozel and his co-founders achieved in Allschwil within only a few years is an expression of entrepreneurship and pioneer thinking, proof of the potential inherent in Switzerland as a pharmaceutical location. It also shows that "Big Pharma" and start-up companies can successfully exist side by side. Our association was originally founded by the pharmaceutical industry located in Basel and Wander. Three of the four founding companies – Geigy joined later – are today combined as Novartis. Today, we are a national association. Serono joined in 1997 and later merged with Merck to form Merck Serono, a company with its worldwide headquarters in Geneva, and it has remained an Interpharma member. Cilag was the first instance of a subsidiary of a non-Swiss company joining as an associate member. That became possible because Cilag, a Johnson & Johnson subsidiary in Switzerland, not only operate an enormously important biotechnology production in Schaffhausen but also carry out research in Switzerland. The same goes for Vifor, a company highly specialized in the production of iron preparations. Vifor also covers the entire value-added chain in Switzerland.

And what about the pharmaceutical companies in the Italian part of Switzerland?

T.C.: As far as I know there is currently no company in the region that meets Interpharma's requirements. We have never recruited members. When someone knocks on our door, we will check to see whether or not they fulfill the necessary criteria for membership.

Interpharma's organizational structure shows the function of "Issue Management". What does that mean?

T.C.: Issue management means recognizing issues at an early stage. At Interpharma, the range of topics for issue management is wide, for instance, the discussion circle "Church–Industry–Ethics", which has been meeting for more than ten years now. Originally, the circle was established in connection with genetic engineering, but then discussions veered off to north-south issues, stem cell research, etc. Interpharma experts on research, law and public affairs meet with representatives of church organizations and university ethics specialists. Both sides consider the circle to be of great interest and usefulness. They discuss questions ranging from ethics to patent law, economic issues, the financing of the health-care system, financing of pharmaceutical research and even antitrust law. The number of potential topics for discussion is infinite.

Basel, 17. December 2008: Thomas B. Cueni (left), secretary general and director of Interpharma, the association of research-based pharmaceutical companies in Switzerland, speaking with Dr. Felix Wüst, editor of SWISS PHARMA.

Church–Industry–Ethics: Really quite a surprising discussion circle.

T.C.: Our fascination of the pharmaceutical industry may be due to the fact that it really is a very incestuous industry. There are very few people who once on board leave the industry. It is an enormously interesting and many-faceted industry. On the one hand, it is an industry in which Switzerland is de facto leader worldwide, and Swiss companies enjoy an enormous respect around the globe. Fortunately, these Swiss companies remain successful in a difficult economic environment. On the other hand, our member companies cover areas ranging from research to ethics, and marketing issues to the financing of health care. There are very few questions that interest the people equally as much and that are of such significance. In our value system, health is one of the most important concepts of all. Not only are people growing older today, they are also growing older while remaining healthier. The healthy years of life have grown faster than life expectancy as a whole, to which the pharmaceutical industry with its new therapies has made an essential contribution.

So far, you have spoken primarily about the domestic environment. How well positioned are you internationally?

T.C.: Switzerland is one of the leading pharmaceutical countries in the world, after the USA and the United Kingdom. While Germany has a longstanding pharmaceutical tradition, it is no longer strong. I would say that the USA, England and Switzerland are the three largest pharmaceutical countries. You can deduce that by looking at the companies. And correspondingly, an association that represents the research of companies in these countries will enjoy international recognition. We were a founding member of IFPMA, the International Federation of Pharmaceutical Manufacturers and Associations; and we were a founding member of EFPIA, the European Federation of Pharmaceutical Industries and Associations. The CEOs of Swiss companies have traditionally played an important role in these associations. Until recently, Daniel Vasella, CEO and Chairman of Novartis, was the president of the international pharmaceutical association (IFPMA), while Franz B. Humer of Roche was president of the European pharmaceuti-

cal association (EFPIA). And I have for many years been a board member of both associations, so we cultivate good contacts. On an international level, the fact that we practice direct democracy in Switzerland plays a role. Direct democracy provides us with the experience of dealing with difficult social issues and a performance record which is internationally recognized. The genetic engineering debate held in Switzerland with the clear rejection of the initiative whose goal was to ban genetic engineering enjoyed wide international interest. But that was true also for the so-called Denner initiative concerning drug pricing. We also gained a great deal of experience in issues concerning animal testing. On an international level, the direct democracy we practice is unique and provides us with certain benefits in the field of communication. That is why taking advantage of this experience on an international level is very important to us. This year, for instance, I managed a European association task force concerned with the anti-trust investigation of the European Commission. I am engaged time and again in meetings with the OECD. In fact, I was the representative of the European pharmaceutical industry in a working group of the High Level Pharmaceutical Forum of European Commissioners Verheugen and Vassiliou.

Having heard all of this, I assume you have no problems on the international level.

T.C.: To put it another way, if I may, the problems are the same as in Switzerland. How can one improve patients' access to therapeutic progress, reward innovation, and at the same time take into consideration the budgetary limitations of government health systems? That is possible only in a dialogue with the stakeholders, and the opinion of Switzerland is definitely sought after.

Let us take a look at the future. You mentioned the year 2020. Are you referring to the survey that PriceWaterhouseCoopers published recently?

T.C.: No. At Interpharma we drew up our own paper with which we aim to demonstrate what the pharmaceutical industry in Switzerland can deliver economically, the issue of research in Switzerland, better solutions in health care, etc. We presented all of these issues within the parameters of our anniversary. We shall take further advantage of the survey results in 2009. From an economic perspective, the pharmaceutical industry has been the fastest growing industry in Switzerland for more than ten years. Historically, the chemical industry consisted of 90% dyestuffs. Today, 75% of chemical exports consist of pharmaceuticals and some 120,000 jobs in Switzerland directly or indirectly depend on the pharmaceutical industry. The pharmaceutical industry offers high quality jobs, in other words, jobs for well-educated people with high added value. If we are able to take advantage of this potential then it is possible to make available about 200,000 jobs in the year 2020 that directly or indirectly depend on the pharmaceutical industry, of which 50,000 in the pharmaceutical industry itself. If we take a look at exports in 1990, Switzerland exported pharmaceutical products worth 8 billion Swiss francs, and many people feared that the pharmaceutical industry would move to the USA. Today, we export clearly more than 50 billion Swiss francs. There are no reasons why growth should not increase accordingly, provided the parameters remain attractive and companies can continue to successfully carry out research. These two factors play a decisive role. One also has to recognize that a company like Actelion created more than 800 jobs in Switzerland within a period of ten years. But Roche, Novartis and Merck Serono have also created several thousand additional jobs in Switzerland. In economically difficult times as those we are experiencing at present, we have to be grateful to work in an industry with healthy and long-term growth.

Was this survey published on the topic of "2020"?

T.C.: We presented the survey briefly at the media conference, but if you are interested you may gladly publish it in SWISS PHARMA.[2]

A summary of the PricewaterhouseCoopers "Pharma 2020" survey which I mentioned was published in SWISS PHARMA 10/08, pages 8 and 9.[3] The authors of the survey believe the pharmaceutical market will double by 2020. Do you consider that possible?

T.C.: Forecasts concerning growth rates are always tricky. You become aware of that when you see how other industries are being hit by the recession. However, the pharmaceutical industry is well prepared for the future if it is able to continuously market new and better therapies. The stability of the pharmaceutical industry, especially in difficult times, is based on the major significance of health, particularly in societies that are aging. Although in the pharmaceutical industry the times of double-digit growth have probably been left behind, we will remain a growth industry. I assume that medical research will remain of such importance to us in the future that we will continue to take good care of it. Alright, we have had changes in growth for several years. For many years, the USA has provided the largest share of growth. Today, that is no longer the case. However, there are emerging markets, such as Brazil, China, Korea and Russia, which are growing at an enormously high rate. Growth in Europe is relatively stable, albeit not at 8% or 9%, as experienced before, but still at a respectable 4% to 5%. I do not think that will change because research at our companies over the next 10 to 15 years will continue to provide patients with significant therapeutic progress. To mention one example: At the start of the 1990s, only ancient chemo-therapy was available for

Interpharma throws light on important health issues in brochures, books and other publications.

[2] Pharmaceutical Industry: 2020 and Beyond. Driving prosperity, growth and competitiveness in Switzerland. A contribution by Interpharma, Association of research-based pharmaceutical companies, Basel, SWISS PHARMA 5/09, p. 9–12.

[3] Hotz, Dominik, Pharma 2020: "Virtual R&D – Which path will you take?", in: SWISS PHARMA 10/08, p. 8f. (in German!)

the treatment of most types of cancer. In the mid-1990s, therapies were introduced that are more precise and more effective, achieving significant progress. Swiss companies are at the forefront of this development with such drugs as Glivec and MabThera, Herceptin, Avastin, Velcade and Erbitux. Thanks to these drugs, certain kinds of lymph-gland cancer or breast cancer are no longer mandatorily terminal. There is absolutely no reason why we should not have more progress of this kind in the next ten to fifteen years. We have achieved enormous progress with the application of modern biotechnological medications in the field of rheumatoid arthritis. There is significant progress for MS, as well. Today, the focus is no longer on the classical areas, such as blood pressure, asthma, etc. And when I think of such health issues as, for instance, adiposity and diabetes type II, then the need for better medical solutions is nearly unlimited.

Last question: Let us return to Interpharma. What does 2009 look like in terms of events? And, can you see any problems cropping up?

T.C.: Our concern for many years has been to represent not only the narrow interests of the pharmaceutical industry, but to actively participate in the discussion about long-term financing in the health-care sector. This is an issue of relevance to Switzerland and to the whole world. In this connection, in 2008 we co-published a book with Elizabeth Olmsted Teisberg, a professor in the USA, by means of which we strove to open people's minds and eyes as to how the efficiency of the health-care system can be vastly improved through quality-oriented and results-oriented measurements. A second topic for us is that the pharmaceutical industry must remain a consistent industry. One can only take advantage of knowledge as a raw material if this knowledge is protected. In other words, in Switzerland and on an international scale, the meaning of patent protection is of enormous significance. In Switzerland, in December 2008, we have had to accept a set-back in that patent protection is no longer generally relevant in the case of parallel imports. At least, patent protection remains unlimited with respect to medicines, for which the government determines the price. I would imagine that defending patent protection will remain a central issue for the pharmaceutical industry even in 10 or 20 years time. Without the protection of patents, the investments required until a new medication is finally approved in 10 or 20 years cannot be justified.

Mr. Cueni, I would like to thank you very much for this very informative interview. ◆

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Member companies
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Roche
Merck Serono
Actelion

Associated members:
– Cilag Switzerland
– Vifor

Partnerships

Switzerland
SGCI Chemie Pharma Schweiz
Swiss Society of the Chemical and Pharmaceutical Industry

Vips
Association of Pharmaceutical Companies in Switzerland

Europe
EFPIA
European Federation of Pharmaceutical Industries and Association

ABPI
Association of the British Pharmaceutical Industry

BPI
Federal Association of German Pharmaceutical Industries

Farmindustria
Association of Pharmaceutical Companies in Italy

Pharmig
Association of Pharmaceutical Companies in Austria

LEEM
The French Pharmaceutical Companies Association

VFA
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Pharmaceutical Industry: 2020 and Beyond Driving prosperity, growth and competitiveness in Switzerland

A contribution by Interpharma, Association of research-based pharmaceutical companies in Switzerland, Basel

1. Interplay of three factors: social acceptance, successful research and a favorable operating environment

All industries face the challenge of fostering social and political acceptance by operating responsibly and demonstrating a willingness to engage in dialogue. This is particularly true in an industry like pharmaceuticals that operates in healthcare and whose research gives so many people hope that disease can be prevented, healed or mitigated. The challenge for pharma is to create openness and transparency on the goals of its research efforts, the potential of new therapies, and the findings of clinical trials. The industry must be willing to provide evidence not just of the efficacy and safety of new drugs and diagnostic agents, but of their cost-effectiveness as well. Both in Switzerland and internationally, the pharmaceutical industry's license to operate depends on its social acceptance.

Research-based pharmaceutical companies in Switzerland have a vision: they want to confirm and reinforce Switzerland's leading position in pharmaceutical research – not just in economic terms, but above all in pharmaceutical terms. For this vision to come true, companies need to be able to do successful research and development in a climate of social acceptance, and they need the state to ensure that the best possible operating environment is in place.

Research-based pharma can best exploit its opportunities and harness its potential as a driver of prosperity, growth and competitiveness in Switzerland if the country also provides a world-leading operating environment. For pharmaceuticals, a favorable operating environment includes the following:

Excellence in education, training and research

Investment in education, training and research is important if Switzerland is to retain its competitive edge in the global marketplace. The following priorities are key for research-based pharma companies:

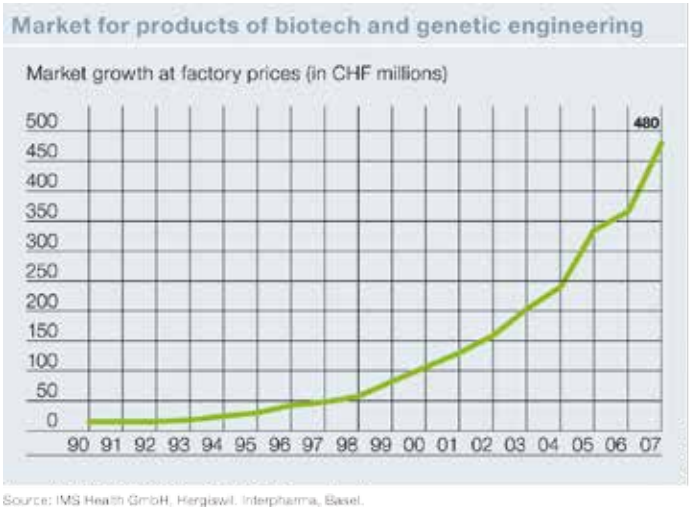
- Switzerland has to improve the **quality of its schools.** There is an urgent need to **step up the teaching of natural sciences** in the final years of high school (Sekundarstufe II). More intensive support should be given to gifted students. Vocational training should be fostered as an important pillar of the education system.
- Switzerland's current position in the global chemical and pharmaceutical industry is built to a considerable extent on the quality of education, training and research at its universities, particularly the Swiss Federal Institutes of Technology. For its universities to remain internationally competitive, Switzerland needs centers of excellence to attract top international researchers. The universities also need **more solid funding.** Global credits for training and research must not be allowed to fall victim of cutbacks. While Switzerland has an outstanding record of private research funding, in recent years it has fallen behind in terms of public investment in training and research.
- Although Swiss research policy should continue to focus on fundamental research, there are also opportunities to be exploited by supporting and enhancing the transfer of technology, particularly in biomedicine.

Innovation the focal point

Innovation is the motor driving the free market economy. However obvious this might seem, it is a reality too often neglected in the economic debate in Switzerland. Switzerland's ability to compete does not depend on low prices or wages. It hinges on the economy's ability to innovate and deliver high valued-added products and services. Just as there are now audits and reports on the environment and sustainability, government should **increasingly be judged by whether it helps or hinders innovation.**

The following factors are key:

- **Access to international markets.** The export industry is the backbone of the Swiss economy. It relies on international trade and open markets. Alongside a functioning world trade system within the framework of the WTO, an important goal must be to



Source: IMS Health GmbH, Hergiswil, Interpharma, Basel

expand the network of free trade agreements with clear priorities. The most important thing, however, is improved access to emerging markets. Here special care must be taken to safeguard intellectual property.

- **A flexible labor market** able to adapt to structural change and provide access to top talent. The continued free movement of persons with the European Union is vital for the research-based pharmaceutical industry. But pharma must also be able to recruit top people from outside the EU.
- **A fiscal environment that is attractive** for research-based pharma firms, including start-ups, and which is constantly monitored and adapted to ensure it remains competitive.

From the point of view of research-based pharma, any economic and industrial policy must also contain the following:

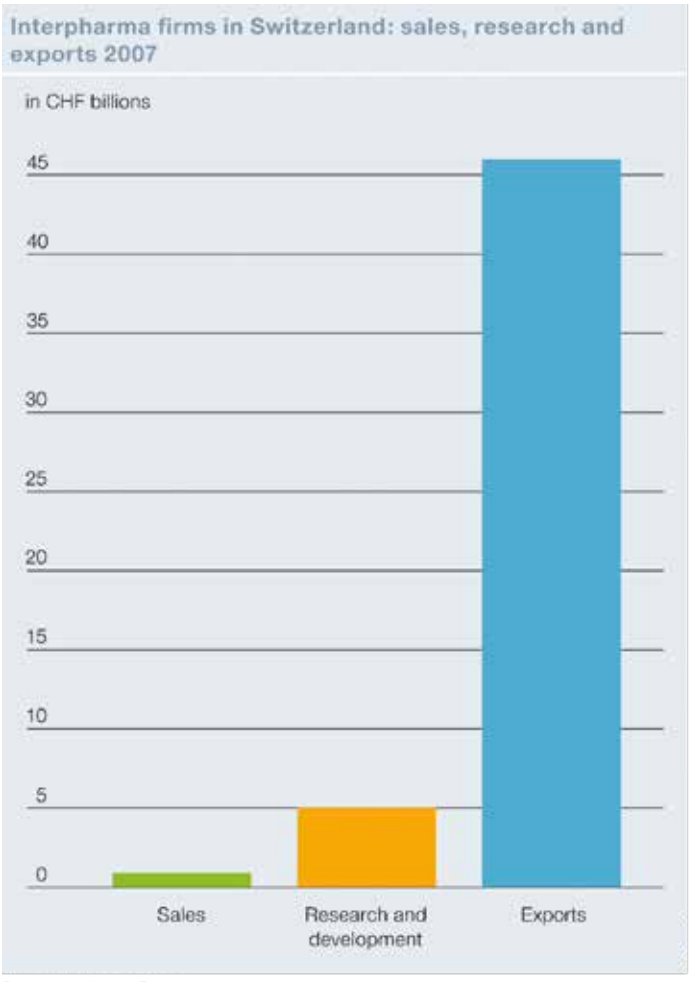
- **An improved approval process:** Swissmedic has to ensure quicker turnaround. As things stand at present, Swissmedic is generally slower than the FDA and EMEA when it comes to approving new drugs. The approval of new, innovative drugs in Switzerland should be back up to speed by 2010 at the latest, and as a rule it should never be slower than in the US or EU. If it requires additional resources to reach this goal, the industry is prepared to take on part of the expense itself by way of fees. There has to be increased cooperation with the EMEA, the European drug administration, and a means of exchanging confidential data such as that which already exists with Canada and the United States.
- **An internationally top-ranking framework for biomedical research:** The procedures for initiating clinical trials need to be accelerated and harmonized, and obstacles to preclinical and clinical research need to be eliminated – something that also applies to experiments on animals.
- **Rapid access to innovative drugs under health insurance:** The process for inclusion on the list of insured drugs has to be streamlined and made more patient-friendly – focusing on a comparison with prices abroad – and once patents have expired potential efficiencies have to be exploited by systematically encouraging and harnessing competition from cheaper generic drugs.
- **Efforts to effectively safeguard intellectual property both in Switzerland and abroad:** Few industries are so reliant on effective patent protection as research-based pharma. To ensure that Switzerland continues to play a leading role in the international debate surrounding the WTO, WIPO and the European Patent Agreement, there also have to be effective safeguards in place to protect intellectual property within the country itself. An urgent priority is the creation of a federal patent court; however, it is also important to preserve the existing rules on parallel imports, particularly with respect to drugs subject to government price administration. Data protection also has to be stepped up – for example in the case of rare disorders or pediatric indications – to created incentives for research.

Switzerland's research-based pharma companies are well aware that it is only possible to dynamically develop the operating environment for pharma in dialogue, and on the basis of a common understanding between policymakers, the universities, and business. If Switzerland succeeds in harnessing the opportunities and potential of biomedical research, it will continue to play an important role in ensuring high-quality healthcare, employment, prosperity and competitiveness in this country.

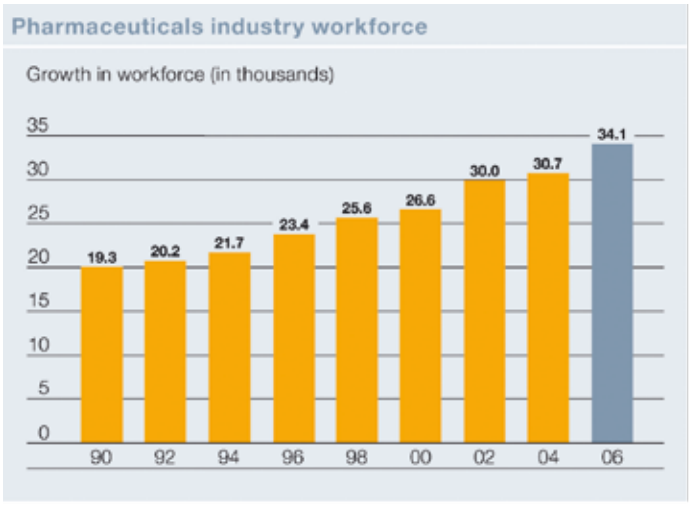
2. Firm commitment – both in principle and in practice – to Switzerland

The desire for an outstanding operating environment goes hand in hand with a firm commitment on the part of industry to **Switzerland as a center of production and research.** This commitment is not just a declaration in principle; it is manifest in research-based pharma's **major investment, current and planned,** in the expansion and ongoing development of centers of production and research in Switzerland that will enable Switzerland to survive and prosper in competition with other regions such as the dynamic Asian markets. :

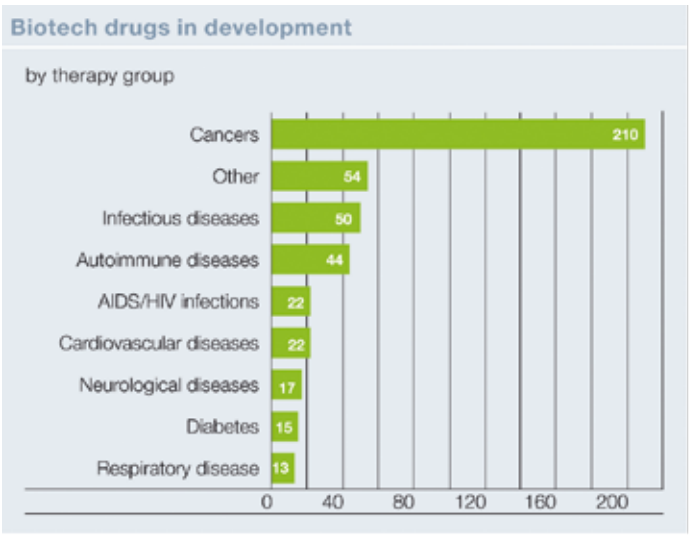
- The Novartis Campus project in Basel – which according to the Financial Times features the most exciting corporate architecture since Chicago and New York in the 1960s – will run until 2030, and involves investment of more than two billion francs.
- In recent years Roche has built new facilities for research and the manufacture of biotech drugs, as well as plowing considerable investment into the headquarters of its diagnostics business in Rotkreuz, Canton Zug. There will be a number of new buildings also transforming the site in Basel. Its investment in Basel alone comes to around 550 million francs.

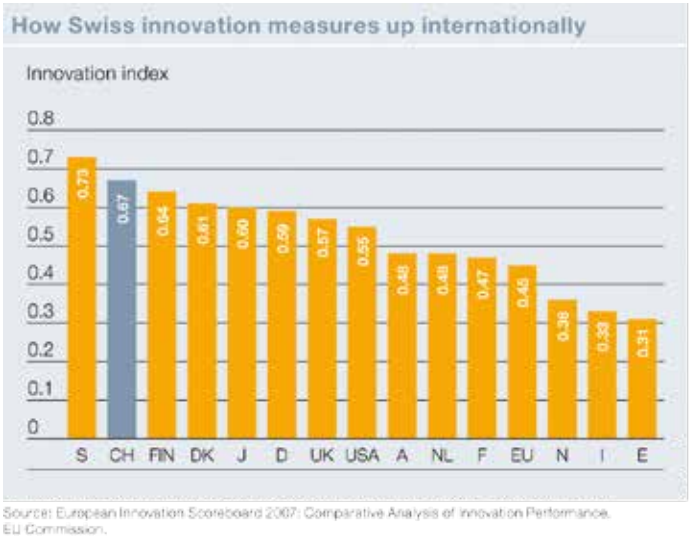


Source: Interpharma, Basel.



Source: Plaut Economics, 2007.





- Merck Serono, founded in the 17th century and the oldest pharmaceutical company in the world, is planning the largest investment in its history in Corsier-sur-Vevey. In the next few years the company will pump 600 million francs into biotech production in Canton Vaud.
- In 2010, Actelion will move into its new corporate center in Allschwil. The building provides workspace for 390 people. Planning is already under way for a new Actelion research facility at the same site that will house several hundred researchers.
- This year Vifor parent Galenica commissioned its new distribution center in Niederbipp. The investment came to 85 million francs.
- Cilag employs more than 1,300 people in Switzerland. In 2008, it commissioned a new 30 million-franc pilot biotech production facility in Schaffhausen.

This considerable investment is rooted in the conviction that Switzerland has a future as a center of production and research. If the environment is right, Switzerland can be a rich source of knowledge – a priceless commodity in its efforts to compete internationally. All in all, the current operating environment is good. Keeping it that way, and improving it, will be key to success.

3. The economic vision for 2020

Despite increasingly tough competition internationally, Swiss pharma is well equipped to meet the challenges. The proportion of high-revenue drugs whose patent is just about to expire is relatively low at Swiss pharmaceutical companies. And the portfolio of drugs at an advanced stage of clinical development is rated positively by external analysts.

With **start-up firms, large multinationals and leading universities all in such close proximity,** Switzerland also boasts a cluster of biomedical research with great potential for spawning and hosting new businesses.

This means that Switzerland's ability to harness its potential as a center of production and research will depend to a large extent to how the local operating framework measures up to the international competition. If Switzerland manages to develop dynamically as a center of pharmaceutical research and production, we could see the following economic vision becoming reality by 2020:

1. Around 55,000 people could be employed directly by the pharmaceutical industry, with another 200,000 or so Swiss jobs indirectly dependent. This would be an **increase of 21,000 in the number of highly qualified people employed** directly by the industry.
2. Pharma's **direct contribution to value creation in Switzerland could total around 20 billion francs,** almost double the figure in 2006.
3. **Annual pharmaceutical exports could double** to well over 100 billion francs, compared with 50 billion at present.

4. Benefits for patients: the pharmaceutical vision for 2020

Swiss pharmaceutical researchers are currently working on drugs and treatments that will be available to patients in 2020.

The results of genome research are increasingly coming into play, and knowledge and understanding of biomarkers is growing all the time. Biomarkers enable the development of even more targeted therapies; they help speed up clinical development and match the use of new drugs even more closely to the needs of patients. By 2020 stem cell research, systems biology, and nanobiotechnology will have substantially expanded the options for using biotechnology in researching and manufacturing drugs and vaccines. New forms of drug delivery will enable active ingredients to be targeted at the diseased organ or tissue more accurately, making drugs safer and reducing the side-effects.

New scientific insights and the successful development of new drugs, vaccines, diagnostics and therapies will lead to **substantial advances that will benefit patients, the healthcare system and society as a whole.**

1. Doctors will be able to use new types of therapies for forms of cancer, dementia, metabolic, inflammatory and infectious diseases and other symptoms that were previously untreatable or difficult to treat, and progressively make existing treatments safer, easier to tolerate and more effective.
2. Doctors will be able to offer patients customized programs for the early detection, prevention and treatment of common diseases with serious health implications.
3. A healthier population, the ability to avoid handicaps, lower healthcare costs and reduced absenteeism will increase the value of pharmaceutical products to society.
4. Drugs, vaccines and diagnostics will thus be a key pillar of an effective and cost-efficient healthcare system.

5. A framework that has made Swiss pharma what it is today

The recognition of the need to maintain a favorable operating framework for the future stems from the realization that the current position of the Swiss pharmaceutical industry is not merely

The Swiss pharma industry today

Research-based pharma is an important factor for Switzerland as a center of production and research. Given this country's lack of natural resources, high-added-value industries and rich innovation are the keys to its economic future.
The industry has developed well in terms of international benchmarking: in the last 15 years Swiss pharma has not only flourished in the face of international competition, but has made an above-average contribution to Switzerland's prosperity, growth and competitiveness. Thanks to successful research, Swiss pharmaceutical companies have been able to build on their international position. They currently hold a share of around 10 percent of the global market. While the EU, for example, debates the declining competitiveness of its drugmakers, Swiss pharma is posting above-average growth in terms of creating new jobs, value creation and exports.

- In 2006, the pharmaceutical industry contributed, directly and indirectly, around 22 billion francs – almost 5 per cent of gross national product – to value creation in Switzerland. At 304,000 francs in 2006, Swiss pharma's GNP per employee was above average – and around three times the average GNP per employee for Switzerland as a whole.
- Most impressive is Swiss pharma's export performance. The industry has seen its exports multiply almost sixfold since 1990. Pharmaceuticals is now the most important exporter in Switzerland, with exports of more than 51 billion francs accounting for one quarter of the Swiss total. An export surplus of 27.9 billion puts the industry at the top of the world rankings.
- Research-based pharmaceuticals is the most important source of private research funding in Switzerland. With R&D investment of more than 5 billion francs in 2007, drugmakers spent many times more than sales (878 million francs) on R&D in Switzerland.
- Pharmaceuticals companies are the leading representatives of Swiss innovation, with two Swiss drugmakers, Roche and Novartis, even figuring among the global top twelve in terms of research spend.

The industry is also a major employee: 118,000 Swiss jobs depend directly or indirectly on the pharmaceuticals industry. The number of people employed directly by pharma has grown 77 percent since 1991 to 34,000

the result of business acumen. Its leading position also has to do with the generally stable and innovation-friendly environment that prevails in this country. This includes factors such as:

- Pharma's traditionally high degree of acceptance among the population, reflected not just in opinion polls, but in referenda as well. No other industry has been challenged by referenda more often than pharma. In referenda on vivisection, genetic technology, in vitro fertilization, drug prices (the Denner initiative) and stem cell research, Swiss voters have demonstrated great support for the aims of research and the quality of the Swiss healthcare system.
- Parliamentary support for the status of research-based pharma on issues of research and healthcare policy and intellectual property, most recently the revision of patent legislation safeguarding biotech inventions.
- High quality education and training at schools, vocational training establishments and the universities. This provides access to a highly qualified workforce, which together with a flexible employment market is key to the industry's competitiveness.
- Stable fiscal and monetary policy and a financial market that gives start-ups access to venture capital.
- The bilateral (and so far successful) approach to relations with the EU, and a trade policy geared to open markets. Of key importance to the highly export-dependent pharmaceuticals industry are access to the international markets and the ability to hire the necessary talent abroad.

A striking feature of the way the Swiss pharmaceutical industry has developed is that growth has come both from large multinationals and from start-ups. Particularly in biotech, the last ten years have seen a whole series of university spin-offs, especially around Zurich and Lake Geneva. The cluster of start-ups that has emerged in the Basel region is unique and the densest of its type anywhere in the world. Discontinued internal research projects have led to the creation of whole new companies. These companies – which include Actelion, Arpida and Basilea – make Switzerland one of the leading centers of biotechnology in Europe, with enormous growth potential.

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Development of a cold distribution chain – the narrow path between product stability requirements and unpredictable temperature challenges on the journey to the patient

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A robust and still affordable cold chain distribution system is developed by considering in parallel the product stability requirements and the actual challenges of the distribution chain.
Based on the current health authority expectations, this article reviews stability test programs suitable to establish the so-called 'Transportation Control Strategy Document'. Examples are given how to construct an ambient temperature profile of the distribution chain, and outlines some specifics of different logistics channels. Examples on what frequently goes wrong illustrate that, besides qualification of the distribution system, the process implementation including appropriate training of all stakeholders is key for success.

1 Introduction

With the growing market share of liquid biopharmaceuticals and vaccine formulations, the number of temperature-sensitive drug products requiring refrigerated storage and cold chain shipment has significantly increased over the past few years. Some insulin preparations, vaccines and biotechnology products additionally require protection from freezing, as even a brief period at sub-zero temperatures may irreversibly denature the protein and lead to a loss of efficacy.
On the other hand, the supply chains tend to become longer and more complex due to the global consolidation of manufacturing. Increased security requirements are also reported to more and more cause unpredictable product holds at airports and borders.
The rising complexity of the transport chain is reflected by the increased focus of health authority inspections on the pharmaceutical supply chain [8]. In 2004/2005, 43% of all critical and major deficiencies in Good Distribution Practices Inspections recorded by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) related to the control and monitoring of storage and transportation temperatures [23].

2 Legislation and Guidelines

While the PIC Guide on Good Manufacturing Practices includes in §1.3 the requirement for 'suitable storage and shipment' [21], it does not give further guidance on implementation of this topic. The same is true for the European Directive 2001/83/EC Title VII on the wholesale distribution of medicinal products [5]. The European Guidelines on Good Distribution Practice of Medicinal Products for Human Use [6] state that 'the quality system operated by distributors (wholesalers) of medicinal products should ensure that storage conditions are observed at all times, including during transportation'. It further advises that 'medicinal products requiring controlled temperature storage should also be transported by appropriately specialized means'. The WHO Draft of revised GDPs [28] recommends 'where special conditions are required during transportation that are different from or limit the given environmental conditions (e.g. temperature, humidity) these should be provided, monitored and recorded'.
In its 2006 revision, the German Medicinal Products and Active Pharmaceutical Ingredients Production decree ('Arzneimittel- und Wirkstoffherstellungsverordnung' [7]) also started to include legally binding requirements on the transport of medicinal products.
More relevant information can be found in the USP Chapter 1079 'Good Storage and Shipping Practices' [26], describing procedures to maintain proper storage environments for individual articles and to ensure a preparation's integrity until it reaches the customer. The risks addressed in this monograph are besides exposure to temperature excursions also humidity, light and oxygen. On European side, the 'Guide to control and monitoring of storage and transportation temperature conditions for medicinal products and active substances' of the Irish Medicines Board [10] provides helpful advice.
A high level guidance on the essential principles and practices of transporting temperature-sensitive medicinal products and an approach how to develop and implement specialized packages and systems that will protect temperature-sensitive products during transport can be found in the PDA Technical Report 39 [20]. Although this document is legally not binding, it has received cGMP approval from the US Pharmacopoeia, FDA, MHRA (UK) and Health Canada being a leading guidance document for cold-chain distribution practices, and is a reference document among the regulatory authorities conducting audits for manufacturing and distribution practices.

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The main building blocks of a Cold Chain Management Process as outlined in this guideline are:

- the proper identification of the requirements, especially investigation of the product stability profile, thorough understanding of the transportation process flow and identification of a suitable temperature protective packaging.
- Development and especially qualification of the cold chain distribution system.
- Implementation of the cold chain management process by setting up the quality systems and training of all stakeholders.

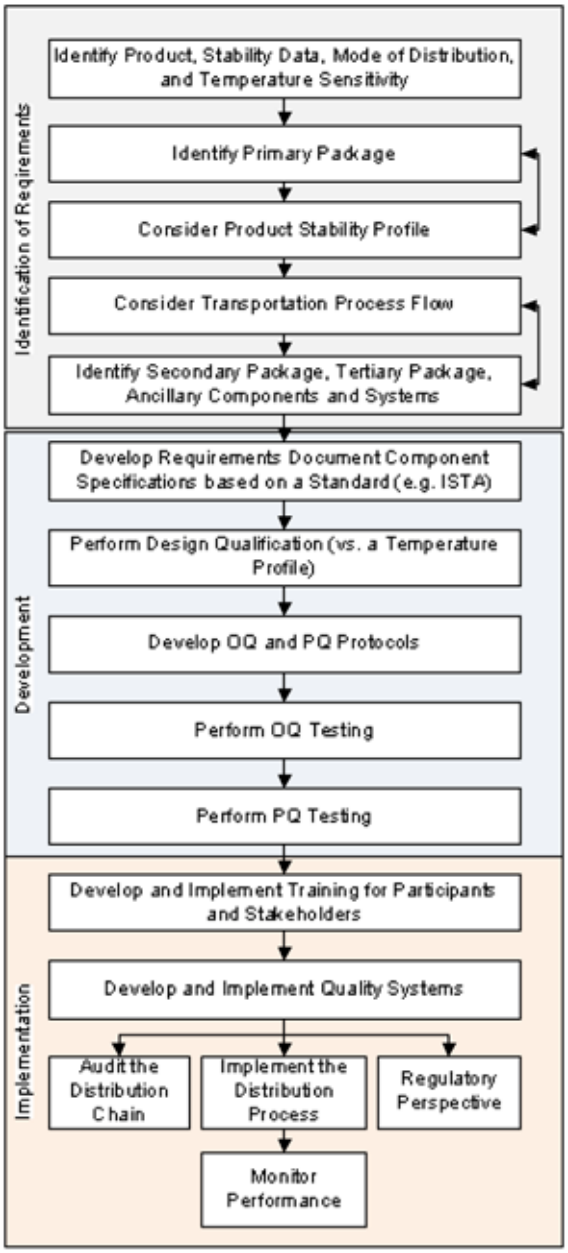

Figure 2-1 Process Flow Diagram of a Cold Chain Management Process according to PDA Technical Report 39 [20]

3 Product Stability

Even with the highest degree of precautionary measures during shipment, temperature excursions from a refrigerated storage condition cannot fully be avoided. This mainly relates to preparation of goods for shipment, operations at receipt and transfer into cold storage chambers, as well as the final use in the hand of the patient or health care giver. It is therefore commonly accepted that the range acceptable for shipment may be outside of the conditions specified for long term storage.

However, excursions need to be supported by stability data or technical justifications demonstrating that the product is not affected, as articles labeled 2–8 °C may widely vary in their tolerance of short term exposure to cold or heat.

The need to evaluate the effect of temperature excursions and consider whether cold chain shipment is mandatory for a refrigerated product, is emphasized by the CPMP Note for Guidance on Declaration of Storage Conditions for Medicinal Products in the Product Particulars [4], which recommends to use the statement to ship the product at 2–8 °C 'only in exceptional cases where necessary'.

The basic requirements for stability testing are laid down in ICH Guideline Q1A, 'Stability Testing of New Drug Substances and Drug Products' [9]. The extent of testing required to define transport conditions is addressed in Paragraph 2.2.7, Storage Conditions: 'A drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use. (…) Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short term excursions outside the label storage conditions (such as might occur during shipping).'

For drug products intended for storage in a refrigerator, further guidance is given for assessment of potential excursions during shipment: 'If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the drug product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through 6 months when a significant change has occurred within the first 3 months.' With other words, if results from routine studies indicate that the product is very stable, then one may decide that distribution studies are not warranted.

Although withdrawn in the mean time, the FDA 'Draft Guidance for Industry: Stability Testing of Drug Substances and Drug Products' [25] gives valuable advice with regard to temperature excursions and suggests to consider 'a study of the effects of temperature variation, particularly if appropriate for the shipping and storage conditions of certain drug products (…). Drug products susceptible to phase separation, loss of viscosity, precipitation, and aggregation should be evaluated under such thermal conditions. As part of the stress testing, the packaged drug product should be cycled through temperature conditions that simulate the changes likely to be encountered once the drug product is in distribution.

- A temperature cycling study for drug products that may be exposed to temperature variations above freezing may consist of three cycles of two days at refrigerated temperature (2–8 °C) followed by two days under accelerated storage conditions (40 °C).
- A temperature cycling study for drug products that may be exposed to sub-freezing temperatures may consist of three cycles of two days at freezer temperature (–10 °C to –20 °C) followed by two days under accelerated storage conditions (40 °C). (…)

Alternatives to these conditions may be acceptable with appropriate justification.'

This guidance may be interpreted that for products requiring refrigeration, the accelerated conditions valid for 2–8 °C storage (25 °C/60 % RH) can be taken instead of 40 °C, the accelerated condition for controlled room temperature storage.

The PDA Technical Report 39 [20] recommends additionally a short term challenge study under severe stress conditions for assessment of potential temperature excursions during transport.

Storage Condition	Testing Condition
Controlled Room Temperature (20–25 °C)	1) –20 °C for 2 days 2) 60 °C/75% RH for 2 days
Refrigerated Condition (2–8 °C)	1) –20 °C for 2 days 2) 40 °C/75% RH for 2 days
Freezer Condition (–20––10 °C)	25 °C/60% RH for 2 days

Table 3-1 Temperature Excursion Study

It appears beneficial upon completion of the temperature excursion and cycling studies to subject these batches to long term stability testing conditions to verify that the exposed product meets shelf life requirements.

Biopharmaceutical products often not only show sensitivity to freeze-thaw phase transitions, but also to shear stress. One may therefore decide to amend the transport studies for liquid products with an agitation cycle covering the shear stress the product is expected to be exposed to during shipment.

Analytical methods should be selected such that any change in chemical (e.g., assay, related substances, aggregates), biological (e.g., potency) or physical properties (e.g., dissolution, particulates, and physical appearance including primary packaging) of the drug product can be evaluated. The validated stability indicating methods should be applied. Results should not show significant changes and must meet the pre-determined end-of-shelf-life specifications. Although some authors tend to use ICH definitions for significant changes [9] to establish the threshold level for acceptable degradation [16], it is recommended to set on a product-specific basis significantly tighter criteria which ensure the product staying within its specifications during the whole shelf life. In freeze-thaw cycles of liquid parenteral products one additionally might want to evaluate container–closure integrity to ensure that the freezing conditions did not lead to any damage of the container closure system.

If a significant change occurs, short term temperature and/or thermal cycling excursion studies may be repeated using less stressful conditions. Samples pulled at intermediate time-points should be tested to determine the maximum allowable temperature excursion and/or time range. Results may indicate the need to implement product protective shipping methods (e.g., expedite shipping, more protective packaging).

If major changes are seen even with more moderate excursions, one may shorten the desired shelf life to increase the amount of potential excursions allotted. To avoid setting too restrictive limitations for the transport conditions, a detailed knowledge on the ambient temperature times needed for routine processing as well as a sound estimate on the almost unavoidable excursions to be expected in the actual supply chain appears mandatory. Time needs for processing outside refrigerated conditions should be included from the point the samples for release analysis are pulled. This may include final processing steps like visual inspection (if release samples were pulled and inspected separately) as well as labeling and secondary packaging operations. To avoid write-offs due to premature consumption of the ambient time allowed for the product, not only the routine production, but also potential deviations requiring additional activities, foreseeable delays, and moderate human failure should be considered.

Experience shows that most of the temperature excursions during the refrigerated transportation segments go only slightly outside the 2–8 °C range. Therefore inclusion of a test segment at an intermediate temperature (e.g. 15 °C) to cover such excursions without consuming too much of the shelf life may be considered.

Process step	Temperature	Duration (normal production)	Time potentially needed to handle deviations
Visual inspection including 4 h warm-up ramp to ambient temperature	25 °C	8 h	8 h (re-inspection in case of quality relevant deviations)
Labeling, Blistering, Secondary Package	25 °C	12 h	12 h
Assembly for transport, split of palettes if necessary	25 °C	4 h	4 h
Transport to country organization: loading and unloading operation (each 2 h)	25 °C	4 h	
Transport to wholesaler: loading and unloading operation (each 2 h)	25 °C	4 h	
Transport to public pharmacy: loading and unloading operation (each 2 h)	25 °C	4 h	
Pickup by customer	30 °C	6 h	
Use	25 °C	1 day	
Temperature excursions during the transport segments	15 °C –5 °C		3 days 3 times for up to 1 day

Table 3-2 Example: Expected ambient temperature challenge for product XYZ

In the example given in Table 3-2, the absolute minimum temperature excursions needed would be 3 days at 15 °C, 3 days at 25 °C and 6 h at 30 °C, combined with 3 freeze/ thaw cycles to sub-zero temperatures, e.g. for up to one day.

Combination of the stability data from long-term, accelerated, short-term temperature, and thermal cycling excursion studies provides the information needed to predict the effect of temperature excursions on drug product quality during distribution.

From these results, a Transportation Control Strategy document can be derived. This document records acceptable transit time limits and temperature ranges for which it was shown that the product quality at the end of the shelf life is not negatively affected. Thus, this document provides also a guidance from which point on more detailed investigations on temperature excursions observed due to failures in routine distribution would be required. It is obvious that the Transportation Control Strategy Document needs to be constructed for each product based on product specific stability data. Usually the information contained in the Transportation Control Strategy Document is kept company-internal, in order not to stimulate processing within the tolerated excursions thus limiting the safety margin for un-planned temperature events.

Temperature range	Time
< –20 °C	Do not use
–20–2 °C	2 days
2–8 °C	Until expiry
8–25 °C	6 days
25–40 °C	2 days
> 40 °C	Do not use

Table 3-3 Example of a Transportation Control Strategy Document [20]

The above example is constructed for a product to be stored at 2–8 °C that was stable towards all temperature excursion studies and cycling tests as proposed in the PDA Technical Report 39 (temperature excursions according to FDA guidance, cycling test acc. to PDA)

Assessment of deviations by use of the Mean Kinetic Temperature (MKT)

The assessment of temperature excursions by evaluation of the mean kinetic temperature is often applied to products stored at controlled room temperature. However, this approach is not always accepted for products requiring refrigerated storage. A guideline of the Irish Medicines Board [10] explicitly states that MKT is not appropriate to be applied for products requiring controlled low temperature storage. This may be due to the observation that especially biopharmaceutical products often are significantly less stable at elevated temperatures than would be expected by applying the Arrhenius equation.

4 Development and selection of a robust temperature controlled transportation system

The environmental conditions under which the drug is to be transported, will change significantly according to the season and other variables, such as the mode of transportation. Even for a given time of the year, the distribution environment can vary markedly from country to country and within countries.

Based on the stability data obtained and the environmental conditions expected, a risk assessment for the cold chain transportation can be developed. This risk assessment will result in a decision on the preferred type of shipping system. The selection of the system will be primarily based on the temperature control necessary, the amount of material per shipment, and the transport route (by land, sea, air or a combination of these). Also transit times and locations should be addressed.

There has been a rapid rise in the use of insulated shipment containers, that are available commercially in a variety of sizes from very small containers used for shipping of clinical trial materials to large containers that fit into aircraft holds. On the market, container systems with active or passive refrigeration systems are offered.

- Active systems, with active temperature control, for example, air / sea freight containers or refrigerated trucks. These systems have the advantage that they react to internal temperature variations, are of large capacity and in almost all cases have integral data recording. On the other hand, because of their capacity, failure may be expensive, special in-transit facilities may be needed and battery life may be limited. In addition, as they often use dry ice as a coolant, they may present hazards to handlers, particularly if they have to be replenished in transit.
- Passive systems without active temperature control, commonly based on polystyrene or polyurethane containers with or without refrigerants. Refrigerants used are cooled elements like eutectic plates or phase-change materials to maintain the required internal temperature range. They are available in a broad range of sizes and costs are comparatively low. The cooling elements however require a high level of control, especially the temperature to which they are cooled, and subsequent conditioning and stabilizing procedures of the container system.

4.1 Development of Ambient Temperature Profiles to qualify Shipping Systems

Basis for qualification of systems that have to maintain a defined temperature range during the transport is an environmental temperature profile that is typical of the conditions the package will encounter during shipment. This should include

- Anticipated temperatures during shipment
- Extremes at origin, throughout the route, and at destination to challenge the effectiveness of the temperature-controlled packaging system
- Seasonal variations (winter versus summer)
- Total duration of transit
- Transport routes and modes (overnight transport, air shipment, shipment by trucks, international shipments)
- Duration, temperature and handling at various stopover or handling points along the route

This is easiest accomplished by breaking the actual transportation route including all intermediate steps and potential deviations into single basic steps, allowing to assign to each segment the expected

Transport step	Time needed	Expected temperature (worst case temperature of first 3 weeks of January)
Packaging for shipment	6 h	25 °C
Loading of truck	2 h	–11 °C
Transport to Frankfurt Airport (refrigerated truck)	6 h	2–8 °C
Waiting for pickup	24 h	2–8 °C
Staging on Frankfurt apron. Incoming flight delayed by 6 h	10 h	–16 °C
Flight to Singapore	12 h	2–10 °C (no animals on board) 18 °C (animals on board)
Unloading	1 h	33 °C
Waiting for connecting flight (not recognized as cold chain product, therefore failed to put in refrigerated storage)	20 h	25 °C
Staging on Singapore apron	4 h	33 °C
Flight to Sydney	7 h	2–10 °C (no animals on board) 18 °C (animals on board)
Customs Control (may be delayed up to 1 day if problems arise with local customs broker)	6 h	45 °C
Staging for pickup by truck	24 h	2–8 °C
Transport to wholesaler	5 h	2–8 °C
Loading/unloading operations 2*2 h	4 h	45 °C

Weather data obtained from www.weatheronline.co.uk

Table 4-1 Example: Temperature profile for a transport from Basel to Sydney in January

duration and temperature range. Temperature data can be obtained from different sources, e.g. by using past or actual shipments done with external temperature monitors, or by getting data from freight forwarders, airlines, trucking companies or packaging personnel. Historical data, especially insight into extremes can be obtained from meteorological websites, e.g. www.weatheronline.co.uk, or www.noaa.gov. An example for a shipment from Switzerland to Australia is given in Table 4-1 (artificial construct assuming coincidence of significant amount of human failure).

Using real transportation temperature data, worst case conditions can be constructed by adding 3 standard deviations to the combined average of summer temperature profiles collected, and subtracting 3 standard deviations from the average of the data collected during winter time.

Several organizations have developed temperature test cycles that also can be taken as a basis. Examples for such temperature cycling tests are test procedures 5B and 7D of the International Safe Transit Association (ISTA) [11, 12], ASTM (American Society for Testing and Materials) Standard Test Method D3103-07 [2] or Cold Chain Committee (C3) Guidance Document "Insulated Shipping Containers" [3]. Neither one addresses all of the potential issues involved in a given transport chain, especially not timing of very complex supply chains, but all include useful information on testing procedures. The tests should be modified based on the specific system adopted by the shipper.

Package Route or Segment	Duration of Segment	Temperature Range Winter	Temperature Range Summer
Pick/Pack	1–6 h	15–25 °C	22–30 °C
Palletize for Pickup / Dock Loading	2–3 h	15–25 °C	22–30 °C
Load/Transit to Sort	1–6 h	15– –10 °C	22–50 °C
Unload / Sort / Hold	1–4 h	15–25 °C	22–30 °C
Load / Transit to Regional Hub	4–12 h	15– –10 °C	22–50 °C
Unload / Sort / Hold	1–4 h	15–25 °C	22–30 °C
Load / Transit to Destination City	1–12 h	15– –10 °C	22–50 °C
Unload / Sort / Hold	1–4 h	15–25 °C	22–30 °C
Load / Transit to Delivery Address	1–12 h	15– –10 °C	22–50 °C
Unload at Destination Prior to Unpacking	1–4 h	15–25 °C	22–30 °C

Table 4-2 Exposure Profiles proposed by ISTA Guide 5B [11, 14]

Test Type (Scenario)	Constant Temperature Test		Cyclic Test
	External Temperature	Duration	
1 (Mild Summer to Mild Summer)	20 °C	48 hours	12 hrs at 20 °C, then 6 hrs at 40 °C, then 12 hrs at 20 °C, then 6 hrs at 40 °C, then 12 hrs at 20 °C.
2 (Mild Summer to Summer) or (Summer to Mild Summer) or (Summer to Summer)	20 °C	48 hours	12 hrs at 25 °C, then 6 hrs at 45 °C, then 12 hrs at 25 °C, then 6 hrs at 45 °C, then 12 hrs at 25 °C.
3 (Mild Winter to Mild Winter)	20 °C	48 hours	12 hrs at 20 °C, then 4 hrs at –5 °C, then 12 hrs at 20 °C, then 4 hrs at –5 °C, then 16 hrs at 20 °C.
4 (Mild Winter to Winter) or (Winter to Mild Winter) or (Winter to Winter)	20 °C	48 hours	12 hrs at 20 °C, then 4 hrs at –10 °C, then 12 hrs at 20 °C, then 4 hrs at –10 °C, then 16 hrs at 20 °C.
5 (Mild Winter to Mild Summer) or (Mild Summer to Mild Winter)	20 °C	48 hours	12 hrs at 20 °C, then 4 hrs at –5 °C, then 12 hrs at 20 °C, then 6 hrs at 40 °C, then 14 hrs at 20 °C.
6 (Summer to Mild Winter) or (Mild Winter to Summer)	25 °C	48 hours	12 hrs at 25 °C, then 4 hrs at –5 °C, then 12 hrs at 20 °C, then 6 hrs at 45 °C, then 14 hrs at 25 °C.
7 (Winter to Mild Summer) or (Mild Summer to Winter)	20 °C	48 hours	12 hrs at 20 °C, then 4 hrs at –10 °C, then 12 hrs at 20 °C, then 6 hrs at 40 °C, then 14 hrs at 20 °C.
8 (Winter to Summer) or (Summer to Winter)	25 °C	48 hours	12 hrs at 20 °C, then 4 hrs at –10 °C, then 12 hrs at 25 °C, then 6 hrs at 45 °C, then 14 hrs at 25 °C.

Table 4-3 Environmental Test Programs as proposed by C3 [3, 27]

4.2 Elements of the transport chain: specific considerations

4.2.1 Air transportation

To keep standing times of aircrafts on ground as short as possible, freight is generally placed on the apron up to 3 hours prior to the planned departure [15]. During this time it is fully exposed to the environmental temperature conditions. The same is true for stopovers if the aircraft has to be changed. In the case the flight is delayed, the time in uncontrolled environment may be further extended. Only in times of bad weather the containers are covered with a tarpaulin. Shipments further may be split to optimally use the aircraft hold, and parts of the goods may be re-routed if the flight capacity is lower than expected in case of high passenger and baggage volume.

Aircraft cargo compartment temperatures can be set by the pilot to 2 °C–18 °C if the load affords such temperatures (e.g. transport of animals). However, depending on the cargo compartment used, temperatures may even vary between –6 °C and 30 °C [13]. Cargo aboard an aircraft parked in freezing or very hot weather may be subjected to further unusual cold or heat conditions [1]. Goods using dry ice as coolant are not accepted if animals are being carried, which may then cause rescheduling to a different flight.

Not all airports do have cold storage facilities for perishable goods or segregated areas for safe storage of high value products.

IATA as the umbrella organization of most commercial airlines got aware of the specific pharmaceutical requirements although healthcare products requiring cold chain transportation represent only ~0.05% of their revenues [18]. In early 2008 they have instituted together with representatives from the pharmaceutical industry a 'Time and Temperature Task Force' to establish a quality management system and to create common standards among air transport companies and health care industry [22]. This institution currently develops and implements guidance material to maintain drug quality and efficacy when moving time and temperature-sensitive materials through the logistics chain.

Besides temperature excursions, also the effect of ambient pressure and radiation should be considered when evaluating the stability of the product during air transport.

In large commercial aircrafts, pressure is normally kept at about 750 mbar equivalent to a flight height of 2500 m. The hold of smaller feeder aircrafts is not pressurized and therefore may go down to 550 mbar. The impact of low pressure, especially on container closure integrity of semi-rigid containers like pre-filled syringes, should be considered.

During pre-flight security checks, the product will be exposed to x-rays, and further exposure may occur during the flight, especially in times of high solar flare activity. Therefore the sensitivity of the drug product to radiation should be checked. Besides sensitive chemical entities, especially biotech products, tissues, cells or tissue engineered products may be affected.

4.2.2 Transport between different climatic zones

In the case that different packaging configurations have been defined for summer and winter shipment, for global shipments the question arises which variant to use. Experience shows that outbound shipment in most cases is well under control, while delays in the destination place, either due to customs hold or misunderstandings at the receiving site can not always be avoided. Therefore it is often the better choice to use the packaging adequate to the destination place and to take the additional precautions to protect the drug product during the outbound shipment.

4.2.3 Wholesalers and Public Pharmacies

While responsibility for the cold chain management ultimately resides with the manufacturer until the product has reached the patient, the distribution steps beyond the wholesalers are outside the influence of the pharmaceutical company.

For transport of small volumes of cold chain products, mostly insulated containers with ice packs are used. Products damaged by freezing must not come in direct contact with ice packs at sub-zero temperatures. Therefore one should alert the wholesalers that their shipment containers should have compartments or baffles to separate the product from the temperature stabilizing material such as ice packs or eutectic plates. As minimum standard addition of a minimum/maximum thermometer is expected by the health authorities. It is also important to advice the receiver to unpack the products that have been delivered in insulated containers before storing. Refrigeration upon receipt of small parcels in insulated boxes with ice packs could negatively impact the product contents causing the internal temperatures of the package top drop below the minimum allowable [10].

It is expected that upon receipt of the goods they are transferred to the correct environment without delay. A maximum of 2 h can be assumed for this step, as this is the maximum lead time required e.g. by US regulations on Good Shipping Practices [26]. This is normally taken into account by the pharmaceutical wholesalers in delivering cold chain products only during normal business hours. The public pharmacy is expected to be equipped with a refrigerator for drugs (e.g. complying to DIN 58345). Such equipment ensures a temperature range of 2–8 °C at an environmental temperature range of 10–35 °C and has alarms for excursions above and below the operating range.

4.2.4 The last mile: Delivery to the patient

From a quality point of view, the fate of the product starting with the pick-up in the public pharmacy is probably the one prone to undergoing most severe temperature excursions in the entire supply chain. This should be taken into consideration when designing the appropriate stability programs.

Very sensitive drug products are best handed out to the patient in insulating containers using e.g. ice packs as coolants. Such systems are available on the market, and are usually defined and distributed by the pharmaceutical company.

Conveying appropriate handling recommendations to the patient may best influence the likelihood of exposing the drug outside the desired temperature range. This may include an advice to collect the drug just before the appointment with the health care giver, to be sure that the product has been kept the longest possible time under controlled conditions in the pharmacy's refrigerator. Storage in domestic refrigerators should only be recommended for products that are not sensitive towards sub-zero temperatures. Generally, due to missing air circulation and the variability in the temperature setting, the inside temperature may vary at least between 0 and 10 °C. If the product is stored in contact with the chiller plate or coil, freezing of the product may occur [24].

5 DQ/OQ/PQ of the temperature controlled shipment

With the product stability studies described above and the to-be-expected ambient temperature profiles, the requirements for robustness and capacity of temperature protection can be defined and a suitable transport system or package can be development or selected. It is not unusual to define different transport systems or packaging configurations according to the shipment destinations, and also to create a summer and winter packaging configuration.

The selected product shipment configuration will be subjected to a Design Qualification (DQ) to ensure that the functional requirements are met with that system. The qualification should cover the expected duration as well as the ambient temperature profile. It should include the required quantity, temperature conditioning, and location of the refrigerant or air conditioning system with minimum as well as maximum load (i.e. minimum and maximum thermal mass). Also, the location of the routine temperature monitoring devices should be defined.

Operational qualification (OQ) is usually done in the laboratory by subjecting the designated transport configuration to the ambient temperature profile, which should be worst case with regard to the temperature as well as its duration. The testing should reflect actual load conditions and configurations including the minimum and maximum configurations. The qualification can be performed either with the product itself or a comparable surrogate. Sufficient positions within the load should be monitored by temperature loggers to detect any temperature variances within the shipment.
Performance Qualification (PQ) as last qualification step consists of consecutive replicate field transportation tests to demonstrate that the process is effective and reproducible. As the transport conditions may vary over time, PQ should be verified in certain intervals. Further guidance and points to consider for the qualification protocols can be found in [20].
Transportation processes can only be qualified rather than validated, as it is not possible to control in the real world all parameters that could affect the transportation process (e.g. weather, delays, mechanical failures). A qualified process may change over time. Therefore, periodic and appropriate monitoring of the actual shipment process is recommended to decide whether corrective actions have to be taken.

6 Process Implementation

The Quality Management System adopted by freight forwarders is often not yet as well developed as in pharmaceutical companies [15]. A mutual understanding of the partner's specific needs and the quality requirements for the pharmaceutical product is essential to reach a high quality standard besides operational efficiency and low costs. A close and long lasting cooperation of the pharmaceutical companies with the shipment contractors can further help to improve the quality standards.
Transportation contractors should be integrated into the quality system of the pharmaceutical company, and quality assurance agreements should be established like they are already state of the art for suppliers of raw materials. Forwarders often co-operate with subcontractors to better adapt on the ever changing shipment amounts. This should be specifically addressed in the contracts, as the sub-contractors so far often are not yet optimally integrated in the forwarder's quality management system.
To ensure that the contractors are actively implementing their quality management systems, regular audits may need to be scheduled.
Besides edition of the relevant SOPs, a key element of the process implementation is the training of all stakeholders involved in the transport chain. Some examples on what can go wrong are described below.

Transport by truck
Cold chain conditions in trucks are generally obtained by active air conditioning of the load room, while temperature insulating packaging is kept at a minimum. Therefore correct setting of the truck's reefer plays an important role. A specification of 2–8 °C sometimes is misinterpreted that the reefer set point may be adjusted to 8 °C instead of 5 °C. The hysteresis of the actual temperature is either not known or neglected. Sometimes, the reefer is further set to a fuel saving instead of a continuous mode, which lets the temperature hysteresis go significantly outside of the desired range.

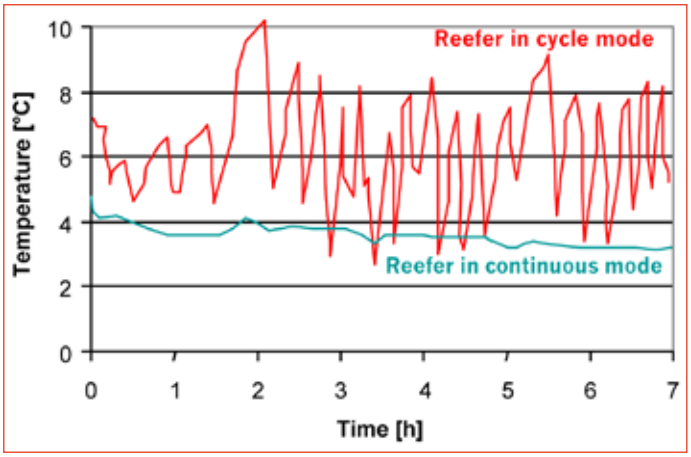

Figure 6-1 Typical temperature pattern with reefer set to cycle or continuous mode

Proper loading of the hold is key to keep the product temperature within the defined range. Main task of the cooling system is to remove the heat that has penetrated through the insulating walls of the load room. Centerline loading keeping a gap between wall and product prevents heat conduction between the wall and the product. This allows the airflow to remove the heat that penetrated the walls. Also, allowing at least one foot air space above the load is necessary to ensure sufficient circulation of the air to the rear of the truck. It has been shown that by overloading of the truck and placing the pallets directly in contact with the wall, the product temperature may rise up to approx. 15 °C due to heat conduction through the walls [17].

Transport by air freight
Handling failures often occur during air transportation because the operators do not recognize cold chain products and therefore do not preferentially bring them to appropriate storage conditions. As theft and pilfering still appears to be a major problem in air transportation [1], harmonized specific warning labels so far have not yet been established. The 'Time and Temperature Task Force' of IATA has recognized this weakness and one of their deliverables is the design of a harmonized alert label for temperature-sensitive health care products [19, 22]. Applying such a harmonized label hopefully in the future reduces the time the product is kept in a highly uncontrolled temperature environment.

Figure 6-2
Proposals for harmonized labels for temperature sensitive products [19]

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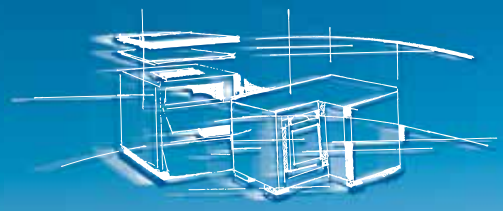

COLD CHAIN CONTAINER

HIGH PERFORMANCE CATEGORY: 2° C – 8° C

Type	TTE 72	TTE 144
Outer container dimensions	1010 x 810 x 805 mm	1210 x 1010 x 805 mm
Inner container dimensions	600 x 400 x 300 mm	800 x 400 x 300 mm
Volume	72 lt	144 lt
Empty weight	87 kg	128 kg

MIDDLE PERFORMANCE CATEGORY: 2° C – 8° C

Type	TC 64	TC 144	TC 288	TC 432
Outer container dimensions	1200 x 800 x 750 mm	1200 x 1000 x 800 mm	1200 x 1000 x 1100 mm	1200 x 1000 x 1400 mm
Inner container dimensions	825 x 425 x 225 mm	825 x 625 x 325 mm	825 x 625 x 625 mm	825 x 625 x 925 mm
Volume	64 lt	144 lt	288 lt	432 lt
Empty weight	105 kg	130 kg	191 kg	252 kg