Pharma Congress 2009: At the Pulse of Industry

Defying the general melancholy across industries, at the Pharma Congress Production & Technology 2009 taking place at the Rosengarten Congress Center in Mannheim in March the more than 400 delegates, visitors and exhibitors once again showed that they are not intimidated by the prevailing gloomy mood. On the contrary, the Pharma industry is looking ahead positively.

Current reconstruction and new building projects
The impressive reconstruction and new building projects presented by some of the companies at the 11th Pharma Technology Conference demonstrate this industry's positive attitude. Merck in Darmstadt, Germany, for instance, decided to reconstruct its plant for the production of sterile and non-sterile liquids due changed operational requirements. The company aimed at establishing a modern and flexible sterile area including a monitoring system in the existing building, replacing the high-purity medium systems and largely automating cleaning – and all of this in running production. Head of Production Dr Christian Schröter compared it to playing chess: "You always need a free field for your next move. But in this game, none of the partners may be checkmated. "

The first phase of the two-part building project comprised renewal of the clean rooms for the production of ampoules and integration of a new line. In phase 2, Merck concentrated on the remaining sterile area, the compounding rooms and the clean rooms for filling in eye-drops. But phase 2 soon had to be divided again: first, the area around the eye-drop line was reconstructed and then the line was moved. Afterwards this area was rebuilt as well. However, any construction causing vibrations had to be conducted outside production hours – a particular challenge as Dr Schröter underlined, especially since the composition floor had to be redeveloped completely and the on-going sterile production still had to be protected by thick barriers. Still, down times were inevitable: In the course of expanding the WFI loop, the corresponding production on the existing system had to be stopped.

Merz also reconstructed its plant in Reinheim, Germany; in fact, rooms for the production of solid, semi-solid and non-sterile liquids. And this reconstruction was far more extensive.

This project's objective was to fulfil the future requirements of international GMP standards and to optimise process flows, reported Dr Joachim Reineck, Head of Bulk Production/Packaging and Technology. On Merz' agenda were smooth and easy-to-clean floors, ceilings and walls, avoidance of the cross-flows by staff and materials, a pressure stage concept with a clean-corridor philosophy and spatial segregation of the individual production areas. The project also aimed at achieving at least a ten-fold air change rate in the bulk- and primary packaging area and at least a six-fold air change rate in the secondary packaging area to be fit for the future. The former areas were designed in accordance with grade D.

In the production of liquids and semi-solid forms, dispensing and preparation / production as well as the corresponding primary and secondary packaging were located on different floors – not an ideal solution. Hence, the corresponding steps were consolidated on one floor. Alike the Merck project, this project was also entirely realised while production went on. Newly-defined requirements caused disputes with the performing firms. "A terrier as jobsite manager helps a lot to put pressure on the performing firms", added Dr Reineck.

Apart from Merck and Merz, Boehringer Ingelheim also had construction site going on in its plant, building a new packaging centre. The project's clear objective: increasing the productivity in packaging. It was presented by Dr Torsten Mau, Head of Packaging of Solid Forms. Prior to the construction of the LogiPack-Center, 125,000 palettes were moved annually between the high-rack warehouse (withdrawal of packaging material) to production (packaging) and back to the storage of the finished product. Due to the transfer of the packaging lines into the new LogiPack-Center which is directly connected to the high-rack warehouse through conveying equipment, the flow of palettes could be reduced to 7,500 a year. Sixteen runs were necessary before the layout was ready in its final form. Primary and secondary packaging was separated consistently. The E and F zones are strictly separated in terms of space and can only be reached through separate air locks; in zone E with a double bank system and in Zone F through air locks without a bank. As an innovative approach a locker concept was introduced. Zone E only has non-personified lockers based on the system used in swimming pools. In zone F on the other hand, the lockers are personified but they can be inspected through a window from the outside. The lockers are opened using the plant ID cards. According to Dr Mau this new procedure was necessary to stay flexible in terms of staff assignment in primary and secondary packaging and to keep the number of lockers within reasonable limits. As another innovation the packaging material is no longer commissioned. A driverless conveyor system takes the palette containing the packaging material to the line and returns after its withdrawal, enabling cost savings of 30%. The transport flow is entirely SAP-controlled. No materials are moved without systemic transportation orders. After the move it took about three months to reach former productivity. By now, though, overall productivity is nearly 70%.

At Hameln Pharma, a 100% contract manufacturer specialising in the sterile production of vials and ampoules, buildings from the 70s and the anticipated growth necessitated a new building. The ratio of ampoules to vials is 80:20. There's life in the old dog yet! Dr Simone Dahlmanns, the Project Manager responsible for the new building: "Within the old building structures this was impossible". In addition to complying with the currently valid US-American and European cGMP regulations the project goal was to expand the capacities for sterile production and packaging while increasing efficiency and flexibility at the same time. Moreover, the transfer into the new building possibly had a regulatory impact on the marketing authorisation. For that reason the effort relative to this authorisation had to be reduced to a minimum. The solution: "same facility", the same mailing address, same management and a passageway to the old building. The sterile production and the filling processes with the existing and new filling lines were housed in the new building whereas secondary packaging, which was also expanded, remained in the old building.

The total floor area of the sterile plant is 9222 m^2, 4800 m^2 (63%) of which are grade A-D clean room. Divided into three floors, changing facilities, restrooms and technology are located in the basement, sterile operation is on the ground floor and ventilation, cooling, heating and offices are situated on the first floor. It is possible to extend all three floors to the east and west. Therefore, the high-purity media were accommodated in the south-west corner of the new building, to be able to easily connect them with an extension. "Form follows function"– the layout of the plant is now ideally oriented towards processes such as the flows of material and personnel. The colours red, orange and yellow are not only applied as decoration but also indicate the different clean room areas which are 70% constructed of glass. This is an advantage as all areas are visible from the grade D corridor to visitors such as inspectors without posing a risk for products and processes. Dr Dahlmanns states that cleaning the big glass surface represents no problem: "For hygienic reasons, you have to clean closed walls just as often: you just don't see the dirt as easily." In the filling areas a decision was reached to introduce an RABS system. "The authorities would have accepted a conventional clean room but not all of our 50 customers." The use of isolators was not possible because of technical conditions of the lines. There is continuous particle monitoring in grade A and B. Crimping takes place under "real" grade A conditions, as Dr Dahlmanns pointed out. The draft of annex 1 available at construction time did not contain the passage ‚grade A Air Supply" – "But we do not perform routine particle monitoring during crimping", she added. Qualification and validation took place according to a risk-based approach during which the entire production process was analysed. The equipment was subject to a comparative study. Thus it could be clarified that possible influences from new lines and from a change to products sensitive to oxygen need to be examined. This was tested with a model solution against acceptance criteria which had been evaluated from lines of the stock. This procedure was generally accepted. "Only 8% of our customers had additional requirements such as determining stability data. The costs for qualifications and validation made up 6 – 8 % of total costs."
The whole project was realised in only 25 months as an ultra-fast-track project and in adherence to the budget and timeframe. And it was worth it: the Hameln Facility won the Facility of the Year Award 2009 for operational excellence.

Equipment coming from the Far East
The use of low-cost equipment from the Far East has been common in the pharmaceutical industry for a long time. Dr Urs Flury from PharmaConduct and Erich Battanta from Novartis Pharma illustrated this equipment's advantages and disadvantages. Novartis Global Pharma Sourcing demanded savings of 25% in the purchase of supplies until 2010 by developing new sources in developing countries and by reducing life cycle costs. Flury and Battanta explicitly named China, India, South Korea and Eastern Europe. However, the decision should never be restricted to one supplier. Novartis Pharma Global relies on at least two "preferred suppliers".

The starting point of the study was the construction of two solid dosage forms production facilities in India and Singapore. The facility in Kalwe, India was constructed by the generic branch of Novartis as a facility by Indians for Indians. They implemented a consequent low-cost sourcing process. The question was whether the facility in Singapore could be set up with the same resources or whether higher investments could be substantiated. At that point, the difference in orientation of production of both facilities was important. The facility in India is designed for small batch sizes of 20 – 120 kg and for open handling (dry granulation, wet granulation, tableting, coating and bulk packaging of 1 billion units). The individual production operations are neither integrated nor automated and they are not connected to MES either. Moreover, there are no supplies planned to Japan. Cleaning is performed manually and is time-consuming because of the-suboptimum facility design.

The facility in Singapore on the other hand is to supply Japan and the USA, enable very flexible batch sizes of 100-600 kg and contain a WIP cleaning system because of the active ingredients. It was also supposed to be more automated. Furthermore, it had to be designed for closed, integrated product handling. With 3.5 billion units, output was distinctly higher in Singapore. Consequently, a direct comparison of investment costs is rather difficult. According to the calculations, savings of 60% would have been feasible with the purchase of equipment at the price level of India. After adjustments regarding effectivity and additional effort for the preparation and procurement of the necessary GMP documents and material certificates, there would still have been savings of 34%. But if the Indian concept with little automated stand-alone equipment had been implemented in Singapore, higher costs would have emerged for personnel and higher HVAC costs for the larger area. Suppliers from Europe, China and India and from other countries were subjected to a complex assessment. Criteria such as price, customer service, response times to questions, staff training, operator convenience of the facilities, WIP/CIP ability, documentation, and experience in the pharmaceutical industry etc. were considered and weighted differently. This evaluation matrix was then used for different facilities. According to

Battanta, it is also necessary to budget five more months when buying low-cost equipment. The result: as first and second suppliers for mixers, different granulators, tablet pressing machines and coaters European firms were selected. The defects or differences concerning surface and weld seam qualities, GMP documentation and the lower output and grade of automation were too severe in the end. But both Flury and Battanta stress the fact that their results are only a snapshot and that India, for example, is quickly closing the gap. In the case of less critical equipment, huge savings were already possible: a cooling tower bought in Malaysia, for example, led to savings of 45% and a centrifugal pump from China cost 70% less. According to Battanta, 316 L steel is not the same in every country but the Chinese pump runs without causing any problems. It is important to get the local price for the equipment and to guarantee the after-sale-service. This means it is important to buy from firms which presumably will still exist in ten years.

Conclusions
The opportunities associated with to low-cost equipment must be taken into consideration without forgetting the fact that pharmaceutical firms from India still like to buy equipment from Europe.

Energy-saving projects
Merck in Darmstadt, Germany, needs as much energy as a small town with a population of 35,000, said Wolfgang Ritz, Project Head of enerCare at Merck. With rising costs for energy the decision was obvious to get in on a project to save energy, especially since this leads to a reduction in climate-damaging CO_2-emissions. The objective was to save at least 10% of energy. One of the most important factors in reaching the project's objective involved increasing transparency in the use of energy and motivation of the staff. In June 2007, the Energy-Information-System (EIS) went on line. It records consumption every 15 minutes and files the data in a data base. The data can then be recalled via the intranet and can be controlled by the operator and checked for plausibility any time. The eight-fold air change rate required for laboratories could be reduced to a five-fold one at the weekend by implementing organisational measures. With 42 laboratory units or buildings it all mounts up, claims Ritz. In the meantime, 4.7% of savings could be implemented in a way the controller will not object to: in numbers, this amounts to almost one million Euros a year.

Technically relevant changes in the new Annex 1
In line with the date of the congress, the new Annex 1 of the EU Guidelines to GMP became effective on 1 March 2009. The most important changes concern the crimping process, hence the closure of vial stoppers with caps. This change was discussed controversially not only in the run-up to publication but also at the Pharma Technology Conference and at the Conference "Current Technologies of Sterile Production" taking place at the same time. Whereas the first draft suggested that the requirements of Annex 1 concerning crimping / capping would only be applicable to freeze-dried products in vials, it was now made clear that they are valid for the crimping / capping of all vials. The revised Version was presented by Dr Michael Hiob who supervises GMP surveillance in Schleswig-Holstein and is a member of the ICH and EMEA expert committees.

Crimping is a part of the primary packaging process and, according to Dr Hiob, it is one of the most critical sub-processes in sterile filling. As long as the cap has not been crimped into place on the stoppered vial, it is not regarded as being closed. Since crimping itself generates particles, this process has to be separated from filling. The crimping area should be provided with appropriate air extraction. Due to the frequently needed corrective actions from outside it will also be necessary in the future to separate operators and processes more strictly. There are two options: 1. Vial capping as an aseptic process via A in B grade production. Filling, closure with sterilised stoppers and crimping with sterilised caps take place under conventional grade A conditions with a uni-directional air flow. 2. As a clean process outside the aseptic core where filling of the vials and closure with stoppers conventionally take place under grade A. But here vial capping is carried out outside the aseptic core with non-sterile caps in an area with a Grade A supply (Isolator or RABS may be beneficial) to safeguard the none finally closed containers. In this case, grade A only refers to the particles in the supplied air without requiring a microbiological measurement. As pointed out by Dr Hiob, this makes sense in a manual process, though. The disadvantage of the first variant is that particles are created in an the aseptic core, Variant 2 on the other hand requires additional investments in further safety devices in the form of crimping isolators or crimping RABS. According to Dr Hiob, the highest risk lies in a badly-fitting stopper. A poor crimping process will not improve by using an isolator. Therefore he regards 100% control for tightness as a useful process but not as a requirement.

Topic Monitoring: $1m^3$ sample volume air still is required for clean room classification, mentioned Dr Hiob. But during routine monitoring "in operation" it is possible to make an exception to this rule on the basis of a risk analysis. A novelty: at this point the testing procedure according to ISO 14644-2 is referred to. This is probably the first time a legal text in the pharmaceutical environment requires adherence to a standard! Grade A must constantly be monitored for particles whereas this is not required for grade B. However, the sample frequency should allow early detection of particle contamination. Dr Hiob added that it is important for the authorities to have alert limits on a statistical basis. The limits at which the alarms are triggered should be lower than the limits according to Annex I to provide time to react. The occurrence of a 5 µm particle concentration indicates human contamination. According to Dr Hiob, it should be investigated even with a 10 – 12-fold occurrence. The current limit according to Annex I is 20 particles. Summarising, Dr Hiob mentioned that it does not make sense to conduct particle counts during crimping. Measuring in the height of the vial opening can also be problematic after finishing the crimping procedure due to the whirling up of particles with the ventilation. Verifiable observance of a low-turbulence displacement airflow in the range of 0.36-0.54 m/s as well as a regular HEPA filter leak test are important.

Highly-active pharmaceutical ingredients in the production of APIs and drug products
The 5th Containment Conference as the third conference at the Pharma Congress 2009 concentrated on the handling of highly-active pharmaceutical ingredients in the production of APIs and drug products. On the agenda were fundamental topics such as the current perception of the development of limits as well as measurements to prove the quality of a containment system. A much more extensive discussion, though, revolved around various modern solutions and specifically the state of the art in the handling of highly-active pharmaceutical substances in different tasks.

Dr Andreas Flückiger, Head of the Occupational Health Services of the Roche Group, pointed out that the Council Directive 89/391/EEC is important when moving from the thread analysis to the right containment solution. This directive is binding for employers and mandates to guarantee the right protective measures for their staff. To be more precise: technical measures precede personal protective equipment. However, it is impossible to separate highly-active pharmaceutical ingredients and workers completely. There is no absolutely closed system. For that reason it is definitely essential to examine the duration of exposure when performing a thread analysis to avoid an overexposure. Quite frequently, though, there are no detailed substance properties available for new APIs. Therefore the main question is how long a worker is exposed to an API.

A new request by the EMEA demands manufacturers to establish dedicated facilities for defined substance groups – a rather critical request for Dr Flückiger.Pharmaceutical firms would then no longer be able to produce different substances in the same facility or building, not even if this procedure was well substantiated.

How do you proceed when planning a containment facility? The main problem, so Christopher Dohm from Dohm Pharmaceutical Engineering, is the different emphasis in GMP and EHS (Environment, Health & Safety) regulations. GMP concentrates on product safety, EHS rather on personnel safety. Dohm says the heart of the matter are holistic concepts and refers to the development from the inside (product) to the outside (buildings). Doing this, it is essential to exclude risks right from the start. This can be accomplished by using closed systems such as single-pot systems that do not require any transfer between the various procedural steps. Another possibility is to perform automated sampling. Further, processes should already be designed in the planning stages to handle toxic substances in solution or suspension rather than dry. In Dohm's opinion it is also important to allow for possible incidents such as damage to persons, fire or breakdown of the equipment when planning a containment facility. In total the costs for the construction of a facility for processing highly-active pharmaceutical ingredients are at least 1.7 times higher than for a conventional production facility, Dohm concluded.

Dr Harald Stahl, Senior Pharmaceutical Technologist at GEA Pharma Systems, concentrated on different technical solutions for handling highly-active solid substances in the production of APIs and finished drug products. To be more precise: the functionality of double-flap systems for substance transfer and of one-way-systems which can be used for sampling and transfer and which can be disposed completely. An important issue involves cleaning the equipment – to avoid that staff members are additionally exposed cleaning-in-place (CIP) systems are used. According to Dr Stahl, it is also not necessary any longer either to open facilities for sampling. In addition to contained sampling with one-way-systems PAT is the key instrument here. Today inline NIR, UV or particle size distribution measurement are possible and represent the state of the art.

Dedicated facilities and risk analyses for assessing the risk of cross contamination: As indicated by Dr Flückiger until now they were only required for beta-lactam antibiotics but might also soon be mandatory for hormones and cyto-toxic products. However, "Will it then be mandatory to produce thyroid hormones and sexual hormones in different buildings? Is vitamin D a hormone? What does cyto-toxic mean?" are the logical questions in his view. "In his opinion, the requirement of a dedicated facility is only appropriate if it can not be shown that parallel processes are segregated sufficiently and that cleaning is sufficient. Everything else leads to dedicated mono-product facilities for each critical product. And this is scientifically indefensible. The RiskMaPP approach based on an ISPE COP can provide some support, though. It shows how a sufficient segregation and cleaning can be accomplished and how it can be proven. According to this approach, limits of cross-contamination are defined based on ADI values and on scientifically-based risk analyses. It is the industry's decision whether to dedicate or not. The outcome of this discussion is still uncertain. The FDA indicated that it is willing to discuss the issue. In contrast, EMEA, WHO and ANVISA are apparently reinforcing dedication.

Containment measurements are carried out to measure the quality of a containment solution. According to Andreas Znidar from Diosna & Dierks and Christine Theus from Infraserv, these data are extremely important – at the latest in the event of damage, i.e. when the employer is obliged to prove that the long-term injuries of an employee are not attributable to insufficient operator safety measures. An appropriate test using alternative materials is defined in the Standardised Measurement of Equipment Particulate Airborne Concentration (SMEPAC) guide, allowing to compare different containment technologies. It is necessary to use substitute materials since on the one hand the active ingredient is only available in small amounts and is naturally highly toxic. On the other hand validated sampling and frequently analysis methods as well are lacking. Therefore, the SMEPAC guide proposes to use lactose and to determine it through particle measurement. An alternative is represented by the swab sample, but there are no standardised procedures in place.

According to the Council Directive, technical means precede individual protective equipment. Rudolf Heimerl from Delta Vertrieb believes, though, that protective clothing and respiratory masks are also needed – e.g. in the case of an accident. In his opinion, the right path leads from thread analysis to the right protective clothing. To be able to employ these systems however, the requirements regarding media and technologies in the building have to be clearly defined.

Dr Patrick Jeger, Head of Process Research and Development at Carbogen Amcis, concentrated on the production of highly-active pharmaceutical ingredients from development to production. The underlying risk analysis has to include substance-specific data as well as the thread potential of the various production steps. According to Dr Jeger, it is often difficult to obtain data concerning the toxiticity of new substances. Instead you have to resort to information from literature or to aspects of preclinical studies and for distinguishing between acute and chronic as well as between reversible and irreversible effects. The individual process steps' thread potential depends on the amount of the substance, the duration and complexity of the activity, the formation of dust and cleanability. Subsequently, through the material flow it is possible to define the process steps such as sampling, preparating etc which require special safety measures. Starting from the determined risk, these can afterwards be allocated to different protection cascades.

What can be the solution for handling highly-active and sterile drug products? In the opinion of Thomas Huber, Sales Manager at SKAN AG, filling of cytostatics in an isolator line is problematic. The isolator has to be operated with excess pressure as far as the safety of the product is concerned, but considering personnel safety reasons with low pressure. He is convinced, though, that it is possible to fill and load the vacuum freeze drier with excess pressure and to unload the closed vials with low pressure: The contaminated air in the crimping machine and in the external washing machine is extracted and cleaned using HEPA filters. Since the total airflow in the isolator has to be cleaned, a high air flow rate emerges. Hence changing the filters is crucial, and it is important that this change can be carried out with a low grade of contamination. According to Huber, three systems are available for this. Equally important is a thorough cleaning of the areas between the filling zone and the filter. And here, Huber referred to two methods: the manual cleaning by swiping after moistening the interior and the automatic cleaning where the isolator is cleaned through firmly installed aerosol bombs. Critical parts are cleaned separately using spray guns and drying is performed with the air supply.

According to the description of Dr Günter Nykamp, Head of Manufacture and Formulation Development at Haupt Pharma in Münster, Germany, applied an innovative production design for the production of oral contraceptives. The internal categorisation was made at grade 3 with an OEL value of 0.03 to 10 µg.

In this case, too, the first step involved a detailed risk analysis which considered the physical-chemical properties, process step duration, amount and potency of the highly-active sexual hormones. Based on these results, open and closed equipment could be assigned. This is a crucial step in the design phase. The project was implemented in only 11 months during which period a new dedicated section emerged based on the *house-in-house-concept*. The area of this new section exceeds 1000 m^2 and is divided into 35 rooms according to the *clean-corridor-concept* and is equipped with a dedicated ventilation system. Pressure cascades with $\Delta p > 15$ Pa from -30 to +45 Pa as well as temperature and relative humidity are constantly controlled. In accordance with the exposure risk of the process steps, dispensing equipment, a dry mixer, a wet granulator, tablet presses and coaters were set up. The processing chambers display pressure of 15 Pa. This value is 15 Pa lower than in the clean corridor. A risk analysis for preparating and sampling, transfer of materials, mixing /granulating and tableting, helped to identify criticalities. Then it was decided how the needed equipment such as isolators for preparating and sampling had to be designed. The coating, which is very risky when loading the coater, proved to be uncritical after spreading the first layer.

Pfizer's newly-built NewCon Facility in Illertissen, Germany, was not only awarded a prize in the category "Process Innovation" in 2008, revealed Ernst Sander, Manager at PhC Pharma Consult. The facility was also the overall winner as well as recipient of the Facility of the Year Award 2008.

The detached building has space for three production lines for the production of solid OEB 4 and 5 drug products (1-10 $\mu g/m^3$ and $< 1\ \mu g/m^3$ respectively). This facility is impressive because of its high degree of automation which guarantees the safety of employees through operator-free "one-room-containment" with fully closed equipment. This equipment is managed entirely from one central control room. No manual operations are necessary. Furthermore, a MES system was implemented with incorporation of the equipment by the process guidance system. PAT sensors identify control data concerning mixing homogeneity as well as the drug product's API concentration, its hardness and measures. Synchronised individual machines allow for the process flow of granulating, tableting and coating to be a semi-continuous process. Detailed engineering started in June 2005 and the first vendible batch was already produced in October 2007. That same month, the facility was inspected by the German authorities with the result "passed".

Highlight: Exhibition and Pharma- Technology- Platform

As in the previous year already, the three conferences were once again flanked by an exhibition. After expanding this exhibition over the last few years it included more than 50 exhibitors this time and offered a new highlight: the Pharma-Technology-Forum, enabling exhibitors to briefly present themselves to the interested audience. This innovation was adopted promptly. More than 150 visitors signed up to visit the exhibition and Forum free of charge.

Outlook

On 9 -10 March 2010 the Pharma Congress will be entering a new phase: Delegates, exhibition visitors and exhibitors will experience an entirely new congress. After three years in the Congress Center Rosengarten in Mannheim, Concept Heidelberg decided to move it to Düsseldorf. Oliver Schmidt, Managing Director: “The concept is totally new. The Congress will comprise five conferences instead of three as before, and one of them will be international and will therefore also be attracting an international audience.” The new Congress will also provide more space for the exhibition and the Forum. Moreover, low-priced daily passes and the opportunity to access all five conferences will allow delegates to arrange their individual conference programme and exhibition visit. This will reinforce an active exchange between Congress delegates, visitors and exhibitors.