PHARMAGEN Sintesi della relazione

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Final Report Summary - PHARMAGEN (Innovative multidisciplinary approach to pharma generic production)

Executive Summary:

The motivation of PHARMAGEN stems from a recognition that bulk Active Pharmaceutical Ingredients (API) manufacturers need to employ new synthetic routes and better manufacturing techniques for the manufacture of generics drugs. It is also recognised that a key enabling technology for achieving this goal entails greater use of continuous processes. A successful outcome will deliver processes which are more energy efficient, have higher yields, better controllability and quality, greater flexibility of output and faster development time. Most importantly, development of effective continuous processing methods will give European manufacturers a significant competitive advantage over Asian producers who have been progressively eroding the European know how and market share leadership in the API market.

The PHARMAGEN project aims to improve the competitiveness of the participants by developing continuous production routes for three specific APIs selected by the SMEs.
Batch pharmaceutical processes and continuous petrochemicals source their raw materials from the same basic chemical pool. Despite this, yield indexes (= wt reactants/wt final product, representing the effectiveness of the processes) for high throughput plants are typically in the region of 1, 2-1, 5, compared to more 10, for pharmaceutical batch processes.

Thus, traditional pharmaceutical processes are characterised by waste levels of 90 % plus.
The PHARMAGEN project enabled participating SMEs to develop new and better chemical synthesis methods based on continuous processing. Further innovative modelling and process control will be developed. This will give European pharmaceuctical manufacturers a competitive advantage.

It was demonstrated that continuous processes can allow very high control level respect discontinuous ones, and this aspect is of paramount value for quality assurance in the manufacture of products for the human consumption.
PHARMAGEN project delivered the expected results, consisting in 3 different APIs receipts with continuous steps integrated, validation, study of two innovative reactors layouts; the results are in line with the expected results identified in Annex I; the future steps for the exploitation are mainly consisting in standards requirements, and investments at the SMEs level.
Project background and objectives:

PHARMAGEN concept arises from the idea to couple petrochemical continuous processes, characterised by high volumes and yield indexes (= wt reactants/wt final product, representing the effectiveness of the processes) of 1, 2-1, 5, and traditional batch technologies of the pharma industry with typical indexes of processes of 10.

PHARMAGEN merged advantages from the 2 sectors avoiding the bottlenecks of both. This will be done thanks to the RTD expertise, that it is recognised in both petrochemical and pharma industry.

This kind of approach was unfeasible in the past years, not only, or mainly because of technological barrier, but most because of the contingency moment that the markets were facing.

The increasing globalisation and the changes of the sector above explained make this approach not only feasible, but potentially of paramount importance for the medium to long term competitiveness of the pharma generic industry and in particular for API bulk manufacturers SMEs.

The objectives of the PHARMAGEN project are illustrated in the following table.

GENERAL RESULTS

General Result: Increasing knowledge about continuous processes for PHARMA sector-Owner: All SMEs;

General Result: Boosting high throughput research through the introduction of continuous process in the PHARMA sector-Owner: All SMEs;

General Result: Improving process control through process understanding and models, as well as through the development of appropriate control strategies-Owner: All SMEs;

SPECIFIC RESULTS

Specific result: Anti HIV production recipes (with continuous steps integrated)-Owner: FLAMMA (SME); FLAM (SME);
Specific result: Anti epilectic production recipes (with continuous steps integrated)-Patent-Owner: MERCHAV (SME);
Specific result: Anti diabetic production recipes (with continuous steps integrated)-Owner: CARBOP (SME);
Specific result: Continuous reactor prototypes: variable channels and agitated cells reactors-Owner: All SMEs;
Specific result: Development of appropriate control strategies for sample processes-Owner: All SMEs;
Specific result: Personnel training for the use of continuous processes-Owner: All SMEs.

Project results:

The project is marked with several confidential information; in fact part of the foreground is patentable, but part of it is not, even if it represent a core aspect for the exploitation; for this reason it is not possible to proceed to a full description of the foreground and a summary of it will be provided.

The first year of the project has been dedicated to:
1. Identify the specifications for three APIs, one for each participating SME
2. Develop process chemistries for each one of them, suitable for a continuous mode implementation in the key step (s)
3. Perform preliminary design of reactors
4. Perform simulation assessment of APIs processes and control strategies
5. Experimentally check the entire synthetic process at lab scale, with special care for continuous steps

Results achieved:
1. APIs recipes developed for all three APIs, 1 patent already filled and deposited, 1 patent currently under preparation
2. Identification of best innovative reactor for the trials phase
3. Identification of control methods compliant with GMP requirement

The main goal of the project second period was that of demonstrating that the continuous processes studied in the first period can be used at the industrial scale and that they afford definitive advantages on the equivalent batch processes.

Two issues have to be considered in the industrialisation of a process know how:
-Demonstration of the possibility of successfully scaling up the processes from the lab scale to the industrial scale, passing through the pilot experiments (technical acceptability);
-Demonstration of the compliance of the developed processes and plants to the regulatory requirements of production of pharmaceutical substances (regulatory acceptability).

Both the two issues were faced during the period. Focus was given to the continuous steps of the developed processes, disregarding the obvious batch sections, for which a well assessed methodology is available in the technical and regulatory documentation.

Special reference has been done to the ICH guidelines that rule good manufacturing practice (GMP) for the manufacture of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. Methodologies and documents compliant with those guidelines were worked out in order to be sure that no relevant points exist that can doubt the industrial use of the work done.

Technical acceptability is basically related to scaling up aspects of continuous processes. It passes through a deep analysis of the performances of continuous unit operations used, and on a full characterisation of the apparatuses constituting the plant, namely the equipments that perform those operations. A preliminary survey of the technical aspects of the used unit operations showed that reaction operations and reactors represent the more complex steps of the entire processes, while other operations do not require special considerations in their use for API manufacture.

Obviously operational limits of each step, related mainly to chemical stabilities of substances, have to be considered, but the invariance of residence times, characteristic of continuous processes in front of the batch ones, guarantees that the results obtained at the small scale can be reproduced at the industrial scale.

As an example, liquid-liquid continuous counter current extraction requires that the number of theoretical equilibrium stages do not change passing from the lab to the industrial scale and that the residence time of each one of the two liquid phase is conserved. For solvent evaporation a strict control of operative time and of utility temperatures is required.

A more complex analysis had to be done for reaction and reactors (see WP1 results). Two basic types of continuous

reactors can be used: the CSTR (continuous stirred tank reactor) and the PFR (plug flow reactor). The first one is suitable only for instantaneous reactions, like neutralisations; the second one is the principal reactor that can work up the large part of chemistries occurring in the API processes. From the kinetic point of view PFR is the continuous analogue of the batch reactor, that means that the concentration profiles that occur during a batch reaction as a function of time are realised in a PFR along the length of the reactor. In a batch reactor the initial and final conditions occur at the beginning and at the end; in the PFR they occur at the inlet and at the outlet of the reactor. This spatial segregation is at the basis of the efficiency of the PFR.

In all real reactors perfect segregation is a conceptual limit: some back mixing always occurs. In order two PFRs are kinetically equivalent, they have to present the same back mixing degree, which has to be known.

Due to so strict requirements, Pharmagen developed a complete methodology for reactor characterisation, and applied it to the reactors used to study and validate the 3 production processes considered.

The validation criterion of continuous operations was a principal issue of this part of the project. A common misunderstanding is due to the definition of the production unit in the official guidelines for GMP. They define the "batch" as "a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture" but usually it is intended as a batch production. However "batch size refers to the quantity of material and does not specify the mode of manufacture". The more clear statement about batch is given by Q7 document of ICH, which states that batch is:

"A specific quantity of material produced in a process or series of processes so that it can be expected to be homogeneous. In the case of continuous processes, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. "

In order to avoid confusion, it is our opinion that the word "lot" has to be preferred to that of "batch".

Having previous definitions in mind, procedures have been designed to check that the process (and the plant) guarantees reproducible quality passing from a time period to the next. All validation runs were carried out sampling the lots produced in consecutive time intervals, and checking their qualities.

The Drug Master Files for the three developed products were worked out and they constitute the basis for specialisations on the future production plants.

Once the regulatory compliance of the continuous processes has been demonstrated, the economic and operational value of the developed processes should be appreciated.

Ritonavir is a very important anti HIV drug. The developed process is based on a original chemical path, different from the chemical routes published and patented by Abbott, who is the drug originator. The new chemistry is particularly suitable for continuous process exploitation, because the very short reaction time can be completely valorised only operating in continuous. Thanks to this chemical and technological innovation the reaction productivity was increased by a factor of 1000 respect to the original process, and the reactor volume needed to obtain the same hourly capacity has been reduced 1000 times. This outstanding result allows savings in:
-Equipment costs;
-Safety explosion proof requirements
-Building costs;
-Utility costs;
-Safety standards
-Emission containment costs

Moreover a saving of about 15 % in raw material cost was obtained.

Gabapentin is one of the high volume APIs, globally produced at the level of more than 1000 tons/year. The last step of the process is based on a very exothermic oxidation reaction, runaway type. The developed process carries out this quite dangerous reaction in a very safe way, avoiding the well known problems of scaling up of exothermic reactions. The big improvement of safety obtained with the continuous process can be fully appreciated considering that the hold up of reactive materials is reduced by a factor of 40. Moreover safety in the batch process is dependent on instrumental control, while the continuous process presents intrinsic safety characteristics.

The continuous reaction affords very high yield and selectivity, giving substantial savings on the raw material cost: this is a very important advantage, because, due to the high competition on this API, low production cost is a key to obtain a serious market share.

The product recovery section from the reaction crude is formed by a series of continuous operations fully integrated: reaction quenching, l-l product extraction and crude crystallisation are parts of a train where recycles from one operation to the previous one determine the efficiency of the overall process. Recycles are integral part of the process and they can be conveniently operated only using continuous operations.

In order to take all advantages from this kind of approach also the crude crystallisation has to be performed in

continuous mode.

Rosiglitazone has a quite different connotation. Chemistries of the major part of process steps do not take great advantage by the continuous approach: obviously they can be operated in continuous mode, but without outstanding improvements. The only one exception is a condensation reaction used to prepare one of the two final synthons. In this case the continuous approach affords a very big increase in reaction yield, that cannot be obtained with batch reaction. Maximum yield in batch is about 60 %, while in continuous more than 90 % was consolidated. That is dependent on the particular chemical characteristic of the reaction, and demonstrate that there are case where the continuous approach can improve not only technology, but also chemistry.

A complete process for the manufacture of Rosiglitazone was developed, and it will be used by Carbopharm according to the opportunities offered by the market of this product.

As a conclusion, all the main goals of Pharmagen were achieved:
-from the methodological point of view, a positive assessment of the power of the use of continuous processes for the API manufacture;
-from the point of view of results immediately useful for market exploitation, new processes for three generics were developed, each one offering definite advantages over the usual published processes, giving the opportunity to the participating SME of increasing their product list.

It is the case of underlining that in the last 2 years an explosive interest on continuous processes applied to API production arose, being object of a great attention both from the multinational pharma companies and from bulk producers. All the companies participants to Pharmagen can praise a deep experience in this field, so that their participation to the project will be a starting point for the development of new business.

Potential Impact

GBI Research has released its Chemical research, "Active Pharmaceutical Ingredients (APIs) Market to 2015-Rise in the Generic and Biotech Sector will Sustain Growth". According to the report North America and Europe together account for more than 60 % share in the global API market revenue. Asia-Pacific is the fastest growing API market in the world. The global API demand is led by China, India and Brazil. The innovator APIs are increasingly losing market share to generic sector APIs. On the basis of synthetic route, the synthetic APIs continue to dominate the global revenues. However, the growth in biotech APIs is expected to be faster in the forecast period.

The global API sales revenue was $91 billion in 2009 and is expected to grow at a CAGR of 5. 9 % from 2010 to 2015. The growth will be driven by the rise in demand of generic sector drugs and biological drugs. The recovery from economic slowdown will help the global API market to grow. The global API sales revenue is expected to reach $126. 3 billion in 2015.

The Global API Market will Sustain Considerable Growth in the Forecast Period. Due to the impact of the economic slowdown, the global API market's growth has slowed down in the past 2 years. However, the worst is thought to be over for the pharmaceutical industry. The API market globally will witness significant growth in the next 5 years. The growth rates will be much higher in the developing countries such as China, India and Brazil than in the mature markets of the US, Germany and Italy.

The strong growth in the generic drugs segment may enable the global API market to grow. The growing incidence of diseases more prevalent in the elderly and lifestyle diseases worldwide will sustain the global API market's growth rates. The global API market is expected to grow at a CAGR of 5. 9 % from 2010 to 2015.

The global API market is dominated by synthetic APIs. The share of biotechnology APIs is small as the use of biotechnology in the pharmaceutical industry is a relatively new trend.

Generics are increasing their market share in the global API market as many innovator drugs are losing their patents in the regulated markets. Also, due to the impact of the global economic slowdown, the focus on innovation has reduced, giving way to the growth of generics. Generic drugs are also increasingly preferred because of their lower cost in comparison to the highly expensive innovator drugs. As a part of cost containment measures, the governments of many countries are encouraging the generic sector.

Due to the emergence of a large number of generic API-producing companies and innovator companies venturing into the generic market, the generic sector API is set for high growth.

As evidenced by the above paragraph, the PHARMAGEN objectives represent more than ever a strategic issue for the generic market sector, and most of all for the SMEs working in the field. The results achieved represent a unique opportunity for the SMEs to gain substantial advantage over their competitors and to bring a breakthrough on the market.

In the following paragraphs the APIs are considered per se, and an outline of their market representativeness is provided.

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Informazioni correlate

Risultato in breve	Europe optimises drug-making

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