THE CHOICE OF ACTIVE PHARMACEUTICAL INGREDIENT SUPPLIERS: HOW SUPPLIERS CAN ADD VALUE TO THE DEVELOPMENT, MANUFACTURE AND SUPPLY OF PHARMACEUTICALS

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Introduction

First of all let me give a short introduction to my company, Hovione Sociedade Química and myself, Tom Buggy, Vice President of Quality Operations.

Hovione is an independent chemical company specialising in the manufacture of Active Pharmaceutical Ingredients (API'S). There are two manufacturing sites the largest in Loures, Portugal where I am based and the second in Macau.

Hovione has 40 years of expertise in API chemistry and provides a range of tetracycline antibiotics, corticosteroids, contrast media agents and other API'S to drug product companies. We also have a range of custom synthesis contracts with pharmaceutical companies including large tonnage production of a key registered intermediate used in the treatment of AIDS.

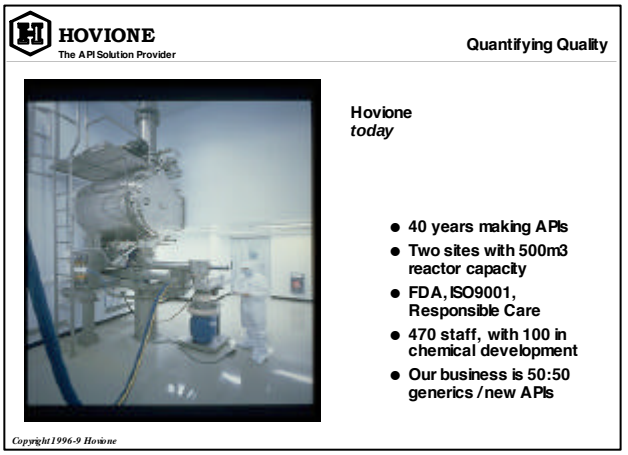
Hovione has approximately 470 employees, provides its products to an international range of clients and has approved regulatory dossiers in all of the healthcare authorities worldwide.

This year we are celebrating 40 years of API manufacture since the company was founded by Ivan Villax. His son Guy Villax is the chief executive.

We have a good record of inspection with the FDA and we are an IS0 9001/2 registered company.

We also have certificates for Environmental Protection.

Below we see the finishing area for one of our injectable products: Iopamidol which I will discuss later.



I joined Hovione in October 1998 having previously worked for 18 years with Glaxo, GlaxoWellcome in the U.K.

I will now summarise the key aspects of API supply and how we in Hovione believe API suppliers can add value to the development, manufacture and supply of pharmaceuticals.

To do this I will answer the following questions:-

Who are the customers and what is the market place?

What is involved in API supply?

What do customers look for during the selection process?

What does the future hold for the industry?

Who are the customers and what is the market place?

The customers for API'S can be divided into three categories.

1. Large Pharma

Multinational Pharmaceutical companies usually have a wide range of products in their development and commercial portfolios. Most of these companies realise it does not make good business sense to retain the manufacture of all steps in the synthesis. Some of the companies prefer to outsource early stages of the synthesis while retaining the final steps in-house. Others look to outsource the manufacture of the API itself.

A custom synthesis partnership is usually identified during the development stages of a new drug candidate when there is a need for significant kilogram quantities but there is still an opportunity to benefit from the development skills of the API supplier prior to registration of the manufacturing process. The pharmaceutical company usually owns the intellectual property but is looking to develop its supply base in the shortest possible time and to minimise capital expenditure. Compliance with a technology transfer package is required.

In terms of a successful partnership the pharmaceutical company is looking for:-
Reliability, Speed, Acceptable Costs, Quality Compliance.

2. Generic Product Suppliers

Generic product companies expect the API supplier to take full responsibility for process development, validation and registration. They require an API which is suitable for formulation, is of satisfactory quality and is provided at a competitive price. Strategic partnerships are often agreed in advance of patent expiry.

Although the emphasis may be different the general requirements are still:-
Reliability, Speed, Acceptable Costs, Quality Compliance.

3. Small Pharma

In recent years a new type of customer has emerged. There is an increasing number of new pharmaceutical companies whose main expertise is in the discovery of new molecules and who require a fully outsourced supply of the API. These companies require full assistance with process development, scale-up and validation of the manufacturing process. They require an API supplier with an extensive knowledge of the quality and regulatory requirements of the industry.

Again the key features of the partnership are :-
Reliability, Speed, Acceptable Costs, Quality Compliance.

We should also note that the business environment is constantly providing new challenges.

The pharmaceutical industry is busy reducing the time taken from discovery to launch of a new product. At the same time there is harmonisation of the regulatory requirements in which the information required to support product quality and process validation is increasing. There is also significant pressure to reduce costs both from API customers and healthcare authorities.

At Hovione, we believe in adapting the partnership to meet the needs of the different customers but still having a common approach to process development, scale up and c-GMP compliance. Consistent product quality, on time delivery and a quality system designed for excellent quality assurance are the keys to a long term successful partnership between the API supplier and their customers.

What is involved in API supply?

Depending on the complexity of the molecule, the API synthesis may involve multi-step complex chemistry from the starting material to the API. A range of process technologies may be required and varied manufacturing capacities will be involved.

The manufacturing equipment must be properly qualified, calibrated and maintained. There must be appropriate environmental measures in place to cope with long term manufacturing on an industrial scale.

The chemical processes must be fully investigated to ensure satisfactory scale-up and validation. A secure supply of raw materials and validated analytical controls must be in place.

As well as providing kilogrammes or tonnes of API or registered intermediates the API supplier provides information in the form of certificates of analysis of product quality and regulatory dossiers to gain approval for their products.

Control of the manufacturing operations must be fully documented and high standards of c-GMP are required to provide assurance of product quality.

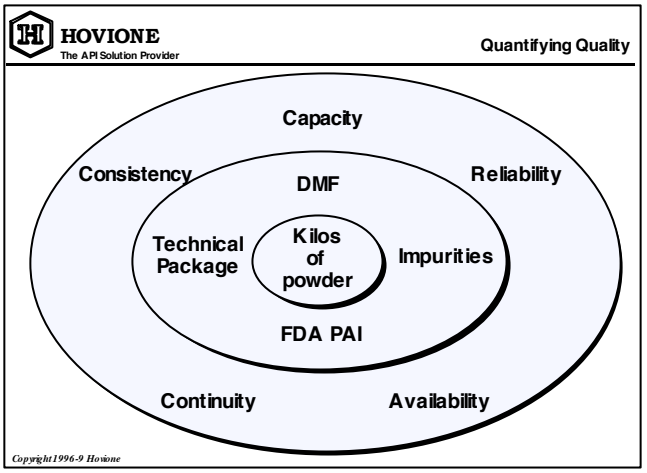
What skills can the API supplier offer?

The core skills of an API supplier are technical expertise in API chemistry aligned with appropriate engineering skills and an understanding of product quality which meets the challenging regulatory requirements.

However equally important are good communication, planning and people skills that will ensure a successful partnership between the API supplier and the customer. The success of a good partnership can be measured by the way problems are managed and resolved.

It is the people who make a difference.

The following quality circles summarise the overall business of API supply starting in the centre with the obvious product- the API as a powder followed by the key information and regulatory approvals leading to reliability and consistency of supply based on available manufacturing capacity.



What do customers look for during the selection process?

So how should the API customer identify the most appropriate API supplier? Based on our experience at Hovione the initial discussions centre on the process chemistry involved in the API synthesis, the manufacturing capacity and availability based on the project timelines.

If there is a basis for a partnership a series of technical meetings and a quality audit of the manufacturing facilities provide a basis for assessment of the API supplier by the prospective customer.

The key people interactions can also be assessed during these meetings. Together with commercial discussions an objective assessment is possible.

The Quality Audit

I will now expand on the quality audit as this provides an opportunity for a structured assessment of the API supplier. Continuing with the theme of the importance of the people, a review of the company personnel in terms of organisation, numbers, experience and training is crucial. If there is a high turnover of staff the reason for this should be investigated and the level of supervision and training should be assessed.

Review of the quality system and operating procedures will allow an assessment of the quality standards. Key procedures which are regularly scrutinised by our customers include change control, equipment calibration and qualification, process validation, cleaning validation and training to name only a few.

A tour of the facilities is always included. This provides not only the opportunity to view standards of installation, housekeeping and c-GMP but also to talk to manufacturing and laboratory staff to assess how well the procedures are operating in practice. Close inspection of randomly selected production and analytical records is also key.

A review of project management systems and the approach to reporting progress on projects is also vital. The willingness of the API supplier to inform the customer of any problems or significant deviations from procedure will also indicate the type of partnership that will be established.

Assessing knowledge of regulatory requirements, experience with regulatory filings and inspection records are also part of any comprehensive audit.

At the end of the audit the response of the API supplier to the audit findings can be quite revealing. Clarification of any misunderstandings is quite acceptable but a willingness to listen and learn from the audit findings should be evident.

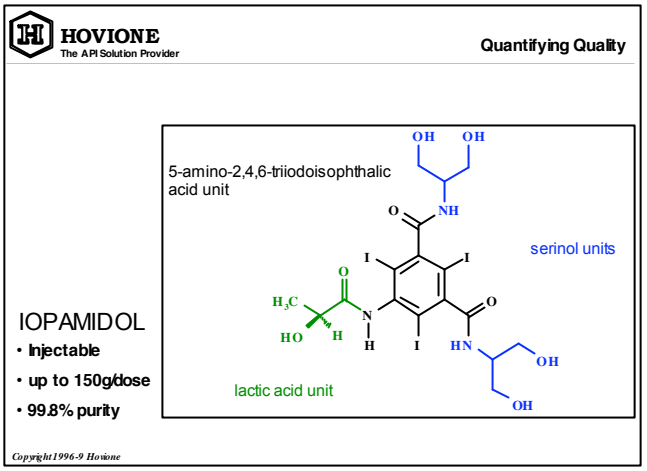
Selection of the API supplier

In conclusion consideration of the technical, commercial, quality and people factors will allow an objective assessment of the API supplier and should lead to a successful and secure long term partnership.

Hovione Case Studies

I will now include the final slides used in my presentation which give two case studies of how Hovione has added value to the pharmaceutical business.

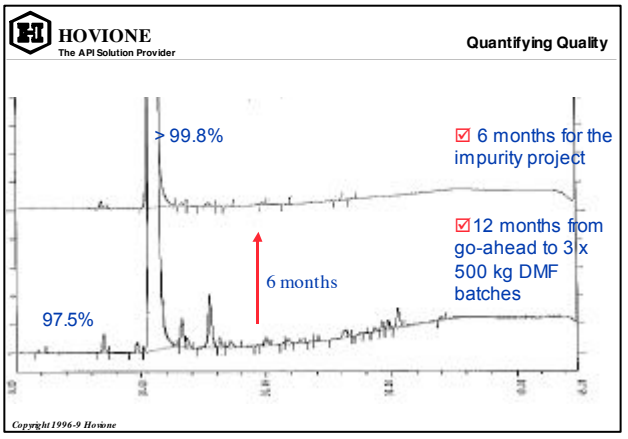
The first example describes the approach taken to produce high quality Iopamidol used as a contrast media in X-ray diagnosis.



The iodine atoms are detected by xray during diagnosis.

The lactic acid and serinol units aid the solubility of the molecule.

The dose can be as large as 150g. 0.1% impurity = 150 mg more than the daily dose of many medicines. Therefore, there is a high quality requirement.

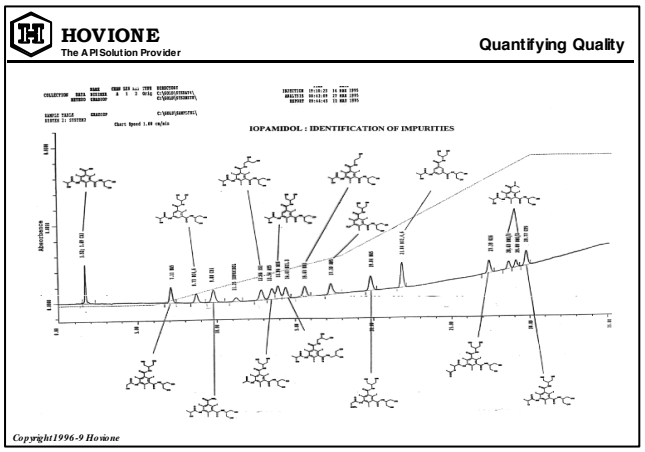


The process development team were given the task of improving quality and reducing the impurity levels by a factor of 10.

The quality of the key starting materials was improved.

In the final step, a special purification process was used to improve product quality.

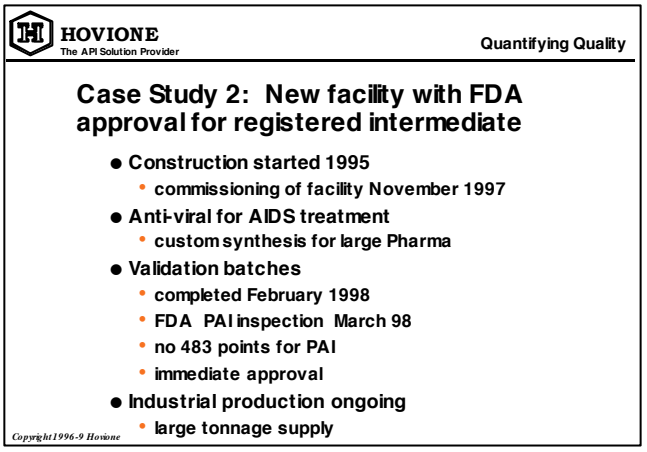
The process was then satisfactorily scaled up to produce the batches for the Drug Master File.



The analytical department also carried out an impurity study to show the selectivity of the method in terms of separating all of the possible impurities.

This task was helped enormously by the availability of the EP method. Based on the successful process development, Hovione can now manufacture Iopamidol to a consistently high standard for supply to the generics industry.

The second study shows how the provision of a new manufacturing facility funded by Hovione was able to help in the fast track supply of AIDS products.



What does the future hold for the industry?

The need for innovative cost effective medicines will continue to increase. There will be a high risk and capital expenditure requirement for new medicines. The API supplier who has considerable expertise in process chemistry allied with appropriate costs, quality compliance and reliability and who has the right people and culture will be able to establish a successful partnership with pharmaceutical companies in the new Millenium.

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