



CUSTOMER CASE STUDY:

The Use of Near-Infrared (NIR) Spectroscopy for Raw Material Identification by a Contract Pharmaceutical Manufacturer

Abiogen Pharma S.p.A is a pharmaceutical manufacturer based in Pisa, Italy. A medium-sized company, Abiogen employs over 385 people and specializes in the manufacture of bone metabolism, anti-inflammatory and respiratory therapeutic pharmaceuticals.

As part of the manufacturing process, Abiogen carries out raw material analysis in its warehouse, and until five years ago each raw material was tested individually. Although an effective method, individual raw material analysis proved to be extremely time-consuming and costly for Abiogen, leading the company to seek an alternative. Already familiar with Thermo Fisher Scientific's proven track record of cost-effective instruments and strong customer support, Abiogen decided to purchase the Thermo Scientific Antaris™ FT-NIR analyzer, enabling the company to carry out analysis of a variety of raw materials with a single instrument. Since the implementation of the analyzer, Abiogen has

seen savings of time and money as well as increased productivity from staff in both its warehouse and its laboratory.

Background

Like all pharmaceutical companies, Abiogen is governed by the Good Manufacturing Practice (GMP) guidelines which take a holistic approach to regulating the manufacturing and laboratory testing environment to ensure that the manufacturing of pharmaceutical products is controlled and managed. A key component of GMP is the documentation of all stages of the manufacturing process. The documentation enables traceability of the product throughout the supply chain. If the

Dr. Nicola Cecconi, Chemical QC Manager, Abiogen, shown using the Antaris FT-NIR analyzer.

process is not accurately documented then the product is considered contaminated and can be recalled from the market. Additionally, GMP requires that all manufacturing and testing equipment has been qualified as suitable for use, and that all operational methodologies and procedures (such as manufacturing, cleaning, and analytical testing) used in the drug manufacturing process have been validated to demonstrate that they can perform their purported functions.

One particular guideline was becoming particularly onerous for Abiogen. Chapter 5.30 of the GMP guidelines specifies that a pharmaceutical company must "...provide suitable procedures or measures to guarantee

the identification of the [raw] material contained in each recipient.” Early versions of Pharmacopoeia methods specified a number of different analysis methods for the testing of individual raw materials including UV-Visible (UV-Vis) spectroscopy, infrared spectroscopy and Gas Chromatography (GC).

Not only was using individual testing methods extremely time-consuming for Abiogen, it also incurred significant costs while reducing the productivity of the laboratory and personnel. Over a period of five years, the company has also seen a significant increase in the amount

and type of raw materials that are used at the site, all of which need to be analyzed according to the GMP guidelines.

To continue sampling each different raw material individually, it would have been necessary for Abiogen to employ additional personnel to cope with the workload. This would have caused an increase in cost to the company, in addition to the increase in time consumed by the growing number of samples to analyze. Carrying out separate analyses for each raw material also takes a huge amount of planning and organization, taking scientists away from the laboratory and increasing their workload.

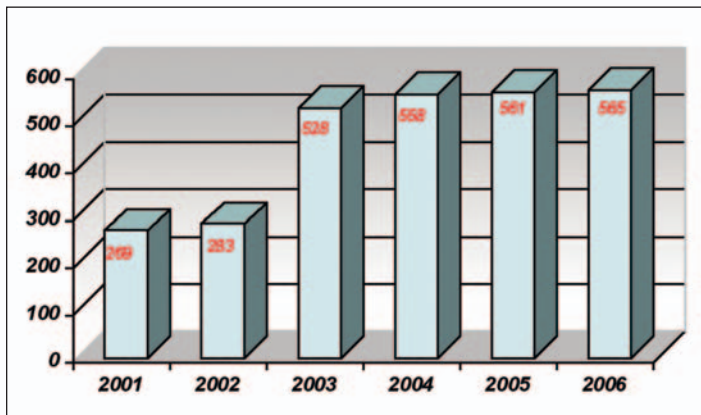


Figure 1: The total number of raw materials (different batches) received at Abiogen has doubled over the last five years.

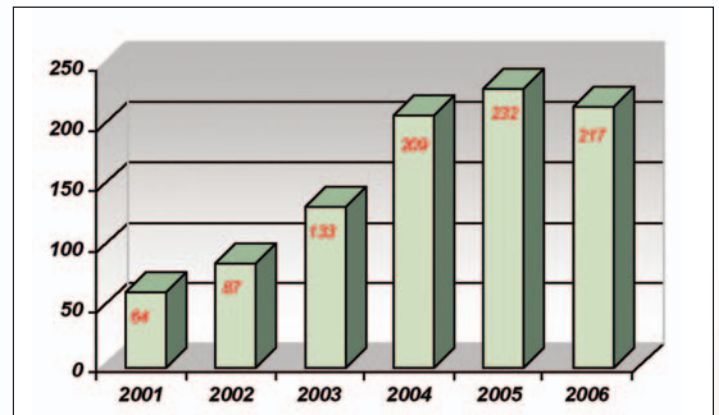


Figure 2: The types of different raw materials received at Abiogen has tripled over the last five years.

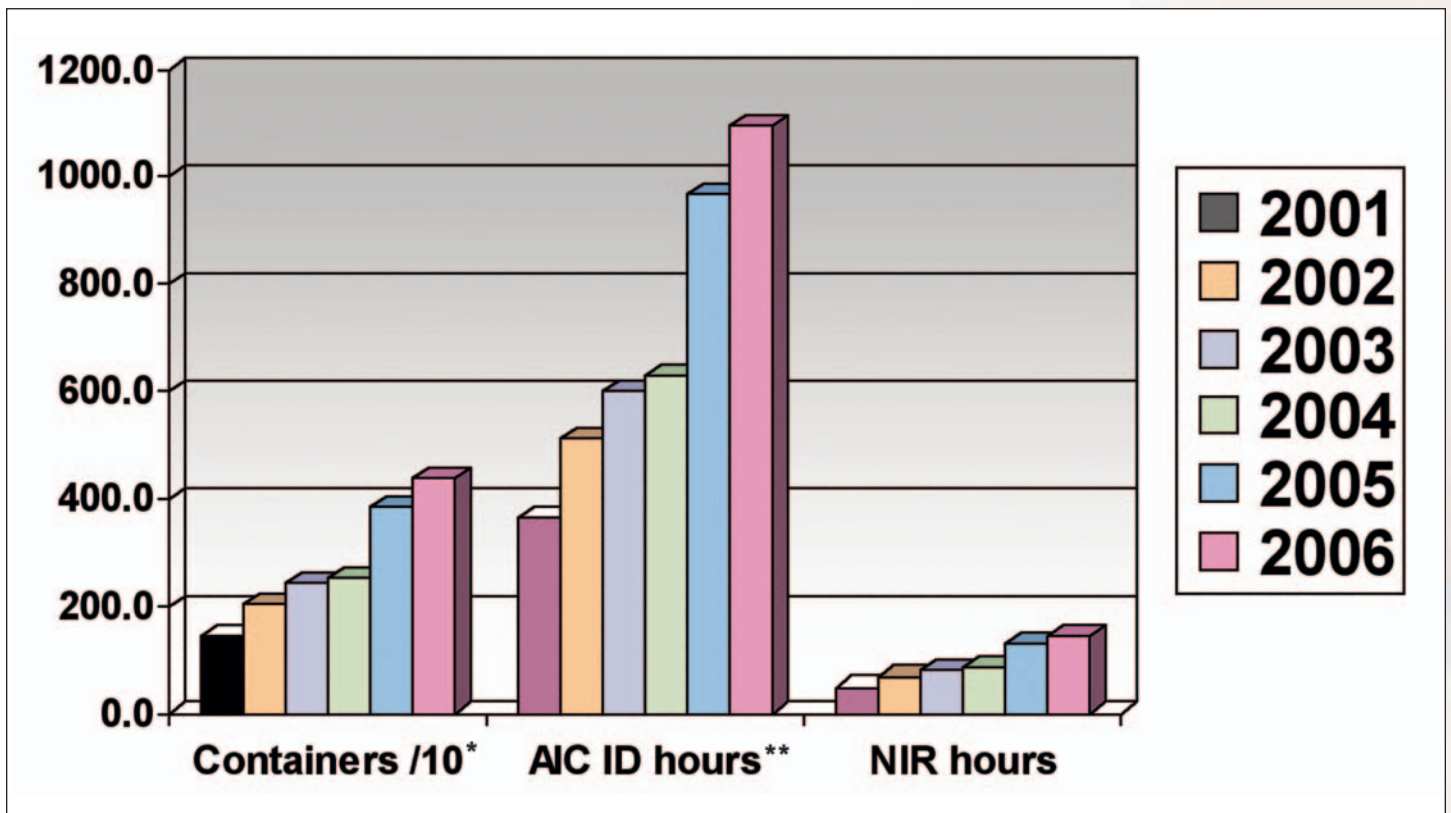


Figure 3: Time required for raw material identification, comparing AIC testing with NIR analysis

* Containers/10 = number of containers divided by 10

** AIC ID hours = number of hours for identification using traditional pharmacopoeia methods

Choosing NIR

A number of recent sets of guidelines now advise the use of NIR spectroscopy as a universal method suitable for the identification of raw materials:

- European Pharmacopoeia 5 (2005), page 59
- EMEA – CPMP/QWP/3309/01 and EMEA/CVMP/961/01 Note for Guidance on the use of Near infrared spectroscopy by the pharmaceutical industry and the data requirements for new submissions and variations, EMEA, London, 2003.
- USP 29 (2006) page 2979

“...NIR Spectroscopy is a well established technique in the food, chemical, agrochemical and petrochemical industry, and has now also been used for many years in the pharmaceutical industry. The technique appears to be useful for the identification and assay of pharmaceutical substances, the identification and assay of such substances in the finished products, as well as for in-process control and for monitoring purposes.” EMEA, Note for Guidance.

Faced with the problems of maintaining regulatory compliance with an increasing amount of raw material analysis, Abiogen looked to NIR with the goal of saving time and cost, and increasing productivity. The company purchased an Antaris FT-NIR analyzer which enabled Abiogen to avoid engaging an additional analyst, resulting in a significant time and cost saving. Abiogen also aimed to improve problems of planning and organization by unifying the raw material analysis on the Antaris.

Abiogen was already familiar with Thermo Scientific products as its laboratory used a Nicolet™ FT-IR spectrometer and an Evolution™ UV-Visible spectrophotometer. **Dr. Nicola Cecconi, Chemical QC Manager at Abiogen**, became aware of the Antaris analyzer when one of his customers bought one, and so decided to trial the instrument.

The decision to adopt an Antaris analyzer was made because of the company's proven track record of strong technical support. Dr. Nicola Cecconi comments, “We were impressed as we were given all of the information and help needed, enabling us to begin the project in the best possible way. Thermo Fisher Scientific strives to be a partner rather than a supplier, and this makes them stand out among competitors.

“We quickly established a good relationship and developed a positive impression which was reinforced when company representatives took the time to give me a full tour of the analyzer factory.”

In addition to manufacturing highly respected scientific instruments, the company operates a strong after-sales program, from helping customers to initially implement their new instrument to training staff on how to operate the analyzer. In Abiogen's case this involved a training period in between ordering the Antaris and the installation of the instrument. Training took place in a demonstration laboratory that is customized to match each customer's actual needs. After the initial training, NIR courses are available periodically with Thermo Scientific representatives.



Abiogen saved significant time using the Antaris FT-NIR analyzer for the analysis of Metformin Hydrochloride, a raw material used in the manufacture of the drug, Metfonorm®. Results are shown on the following page.

Implementation

Initially Abiogen considered three possible applications for the Antaris analyzer – the dispensing area, the QC laboratory and the raw materials warehouse. If the analysis is carried out in the warehouse, no sampling is required by GMP guidelines and therefore the time per analysis is reduced. There are also practical advantages, as raw materials can be analyzed as they arrive in the warehouse, and do not have to be transported for analysis, ensuring improved workflow. However, placing the analyzer in the raw materials warehouse means that the analysis may not be carried out by specialized personnel. This can be remedied by using correct training for staff, and by appointing an instrument manager to oversee the raw material identification.

If the analysis takes place in the dispensing area, there is again no need for sampling, which results in a reduction in analysis time. There are also cost savings on reagents and other chemicals, however the analysis is again carried out by non-specialized personnel and the flow of raw materials through the manufacturing plant is interrupted. Another option is to place the analyzer in the QC laboratory, where specialized personnel can carry out NIR spectroscopy analysis. Although time per analysis would be reduced, in order to comply with GMP guidelines, it would be necessary to sample again, interrupting the flow of raw materials. After considering these issues, Abiogen chose to install the analyzer in the raw materials warehouse, where the instrument was used for the analysis of each container of raw materials that arrives in the warehouse.

After purchasing the Antaris analyzer, Abiogen created a library of active pharmaceutical ingredients (API) and excipients, initially choosing 10-11 ingredients to maximize the return on investment. This library is continuously increased and revised to reflect the growing number of API and excipients analyzed with the Antaris.

The implementation period was overseen by Nicola Cecconi and the QC team at Abiogen, and included support from the Thermo Scientific product team specialists. After implementation, an instrument supervisor in Abiogen's chemical control department runs validation samples on the Antaris according to a rigorous protocol developed by Abiogen.

Actual Benefits

Abiogen has calculated that the investment in an Antaris analyzer was returned after a period of only 18 months. This is in part due to the time saved by using NIR for raw material analysis in the place of testing each raw material individually using multiple analysis techniques.

To demonstrate the results obtained, the analysis of the raw material Metformin Hydrochloride, which is used to make the drug Metfonorm, is described. Metformin Hydrochloride arrives at the warehouse in a standard weight of 25kg per container, and Abiogen has seen a significant increase in quantity, container numbers and time spent analyzing the raw material. This culminated in the hours spent analyzing this particular raw material being trebled from 2001 to 2006.

Year	Quantity (Kg)	Containers	AIC ID hours
2001	36500	1456	364
2002	51000	2040	510
2003	62000	2408	602
2004	63100	2524	631
2005	96600	3864	966
2006	109500	4380	1095

Table 1: Increase in quantity, container number and hours of analysis for Metformin Hydrochloride

Abiogen had examined a range of solutions to solve this problem including increased container sizes and material self-qualification from suppliers. Increasing container sizes was not a viable option, as it can be implemented only for low-cost raw materials, and would have had a significant impact on manufacturing processes such as transport and weighing systems. Although GMP allows a lower number of tests on raw materials supplied by qualified vendors, this was not a suitable alternative for Abiogen as the implementation process can be lengthy, and there is a periodic vendor re-qualification requirement which could result in the necessity to change suppliers. Having considered these alternatives, Abiogen chose to implement NIR spectroscopy with the Antaris analyzer to save time and costs and to increase productivity.

The time taken for analysis using the Antaris analyzer is significantly lower than the time taken using alternative techniques. With the Antaris it is not necessary to sample each container, meaning a savings in cost and a huge increase in productivity.

Year	Containers/10	AIC ID hours	NIR hours
2001	145.6	364.0	48.5
2002	204.0	510.0	68.0
2003	240.8	602.0	80.0
2004	252.4	631.0	84.1
2005	386.4	966.0	128.8
2006	438	1095.0	146.0

Table 2: Hours required for raw material identification, comparing AIC testing with NIR analysis

Future Projections

Impressed by the time and cost savings associated with using the Antaris analyzer and the streamlined production line it has achieved, Abiogen is now planning to purchase another Antaris that will be placed at a different point on the production line. As there are different advantages to placing the analyzer in the laboratory from placing it in the raw materials warehouse, Abiogen is interested to see how it can further streamline its manufacturing processes using the analyzer.

Conclusion

Using the Antaris FT-NIR analyzer it is possible to carry out extremely accurate analysis and QC of raw materials in the pharmaceutical manufacturing plant. In addition to helping laboratory and manufacturing workers to improve productivity by reducing analysis time, the analyzer can also aid regulatory compliance. By using the Antaris for raw material analysis, Abiogen has saved a significant amount of time in the laboratory, as well as improving productivity, and reducing operating costs.

References

- Chapter 5.30, GMP guidelines
- EMA, Note for Guidance on the Use of NIR Spectroscopy by the Pharmaceutical Industry and the Data Requirements for New Submissions and Variations.

In addition to these offices, Thermo Fisher Scientific maintains a network of representative organizations throughout the world.

Australia
+61 2 8844 9500
Austria
+43 1 333 50340
Belgium
+32 2 482 30 30
Canada
+1 800 532 4752
China
+86 10 5850 3588
Denmark
+45 70 23 62 60
France
+33 1 60 92 48 00
Germany
+49 6103 408 1014
India
+91 22 6742 9434
Italy
+39 02 950 591
Japan
+81 45 453 9100
Latin America
+1 808 276 5659
Netherlands
+31 76 587 98 88
South Africa
+27 11 570 1840
Spain
+34 91 657 4930
Sweden/Norway/Finland
+46 8 556 468 00
Switzerland
+41 61 48784 00
UK
+44 1442 233555
USA
+1 800 532 4752

www.thermo.com



Thermo Electron Scientific Instruments LLC, Madison, WI USA is ISO Certified.

©2007 Thermo Fisher Scientific Inc. All rights reserved. Metfonorm is a registered trademark of Abiogen Pharma S.p.A. All other trademarks are the property of Thermo Fisher Scientific Inc. and its subsidiaries.

Specifications, terms and pricing are subject to change. Not all products are available in all countries. Please consult your local sales representative for details.

CS51440_E 07/07M