Near infrared spectroscopy in the pharmaceutical quality control of raw materials

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Introduction

Near infrared (NIR) spectroscopy has, in a very short time, become a very important analytical method for the food and pharmaceutical industries when compared with the implementation of other new techniques, for example, capillary electrophoresis. This phenomenon may be explained by the numerous advantages of NIR, such as negligible sample preparation, non-invasive methodology, very short analysis times and versatile applications (besides identification of raw materials, determination of particle behaviours of powders, monitoring of drying processes, assays of active ingredients in finished products[1] etc.). The importance and the potential of NIR spectroscopy are demonstrated by the fact that this technique, which is only ten years old (due to the commercial availability of processor capacity for statistical evaluations of the spectra), was already included as a general monograph in the *European Pharmocopoeia* 1997.[2] For other pharmacopoeias, such as the USP, drafts of corresponding monographs are under discussion (*Pharmacopoeial Forum*, Volume 24).[3]

In the pharmaceutical industry, NIR is mainly used in quality control (QC) for identification of raw materials (active ingredients and excipients) used in the manufacturing process of medicinal products. Due to the legal requirement that the identity of the contents of each container of raw material should be checked (EC-GMP-Directive),[4] an enormous number of identifications have to be performed in addition to the "normal" release testing. For this single container testing, NIR has almost replaced wet chemical methods as well as the classical instrumental procedures [for example, IR and thin layer chromatography (TLC)].

This article focusses on the applications of NIR in the QC labs of Byk Gulden, with emphasis on the economical aspects.

Raw material supply chain, single container testing of raw materials for medicinal products

According the EC-Guide to Good Manufacturing Practice (GMP) for medicinal products (directive 91/355/EEC, Chapter 5.30, effective since March 1, 1993)[4] the pharmaceutical manufacturer has to prove the identity of the content of each single container of any raw material, in addition to release testing. This additional testing procedure—known as single container identification (SCI)—demands changes in the organisational structures and processes of logistics, QC and pharmaceutical production. In general there are two possibilities of implementing SCI in the raw material supply chain. The main difference between both procedures is the time for performing the SCI. The single container testing can be performed either directly after raw material entry (this bears risk of cross contamination, due to the opening of each container) or it can be implemented prior to the start of production, during

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Table 1. Raw materials, batches and containers received in 1998.

Substance	Number of different raw materials 1. Total 2. Raw materials with more than 1 container	Number of batches 1. Total 2. Batches with more than 1 container (% of total)	Number of containers
Active ingredients	1. 68 2. 53 (78%)	1. Approximately 440 2. 30 (89%)	Approximately 6,300
Excipients	1. 157 2. 122 (78%)	1. Approximately 560 2. 455 (81%)	Approximately 13,700
Total	1. 225 2. 175 (78%)	1. Approximately 1,000 2. 845 (85%)	Approximately 20,000

dispensing/weighing of starting materials. The second alternative has the advantage that only those containers which are needed for the particular manufacturing will be opened. This is why Byk Gulden has implemented the SCI during the dispensing/weighing procedure of raw materials.

Choice of suitable test methods for the single container identification

Besides the decision regarding the implementation of the SCI in the raw material supply chain the choice of suitable identification methods play an important role. In 1998 Byk Gulden used 225 different raw materials for the manufacturing of products. For 175 of these substances (representing 845 lots) supply batch sizes exceeded one container (total number of containers: approximately 20,000, Table 1) and, therefore, needed SCI. The single container identification was performed on 85% which corresponded to approximately 17,000 containers in 1998. The remaining 3,000 containers of raw material are substances which require no SCI process or are not yet needed for production. The enormous number of containers per year to be analysed—which is rising steadily—needs highly efficient analytical procedures which are quick and inexpensive, but which are extremely reliable.

For benchmarking, all suitable methods for the single container testing were compared with each other (Table 2). The assessment criteria used were sample preparation expenditure, instrument purchasing costs (including equipment qualification), cost of reagents/solvents and time needed for mea-

Table 2. Ranking of suitable identification methods.

Analysis technique	Identification method	Ranking of the methods
Spectroscopic methods	1. NIR spectroscopy 2. IR spectroscopy	 Increasing expenditure
Wet chemical tests	Chemical identity tests (for example, according pharmacopoeia monographs	
Spectroscopic method	UV/Vis spectroscopy	
Chromatographic methods	1. TLC/HPTLC 2. HPLC/GC	

surement/evaluation/documentation. As a result of this benchmarking, three identity techniques, NIR (most efficient method), FT-IRS and wet chemistry, have been chosen for the SCI procedure.

NIR measurement techniques and calibration models used for single container testing

In the QC labs of Byk Gulden two identical NIR systems (supplied by Bühler, Uzwil, Switzerland*) are used for single container testing; one for establishing and changing new or existing calibration models and one for routine tests. The measurements are performed using transmission (cuvettes) for liquids and diffuse reflection (fibre optic probe) for solids. Single spectra/cluster models are used for calibration models (spectra library models). These techniques and models are described in the *Pharm. Eur.* 1997, general monograph 2.2.40 "Near-Infrared-Spectroscopy."[2] In order to follow the requirement of a "suitable number of batches" as stated in the same monograph, five samples of each raw material from each supplier are measured for developing or extending of new/existing calibration models.

*Company name and location has changed to Büchi, Flawil, Switzerland).

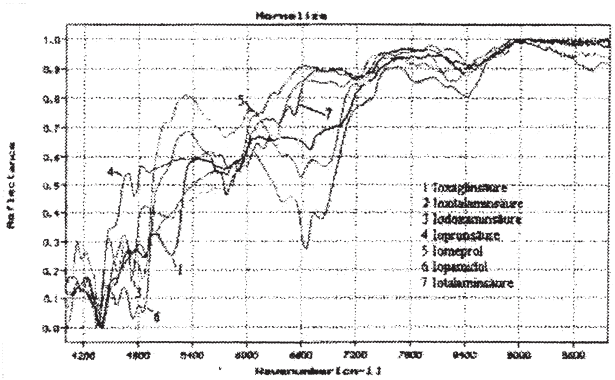

Figure 1(a). Normalised NIR spectra of x-ray contrast media active.

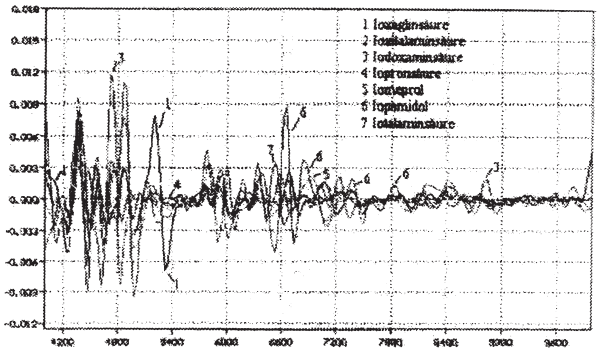

Figure 1(b). Second derivative of NIR spectra of x-ray contrast media actives.

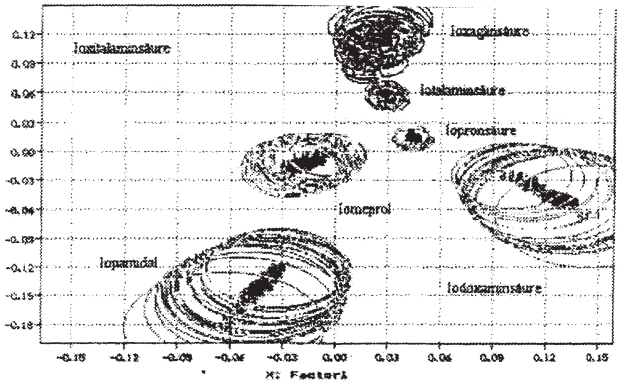

Figure 1(c). 2-factor plot of x-ray contrast media actives.

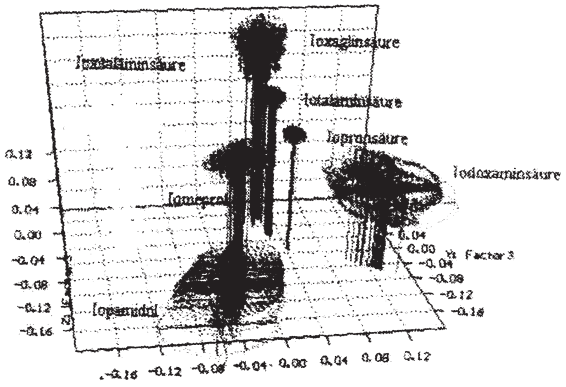

Figure 1(d). 3-factor plot of x-ray contrast media actives.

The calibration models are based on product group-specific classes of substances (for example, actives of x-ray contrast media [Figure 1(a–d)], Mg-/Al-preparations, preservatives and active ingredients of the fine chemical plant). For single container identifications, 45 different classes of substances/calibration models are used with an average content of five substances each. This represents a system with small library models that is contrary to central calibration models which are in use in other pharmaceutical companies. The important advantage of this library model is that necessary changes and re-validations of models (for example, change of supplier and failures in routine testing) can be done properly according to the cGMP rules (change control procedure) in a very short time with low costs.

NIR for single container testing: economical consideration

The result of the qualitative comparison of possible identification techniques (Chapter 3) is confirmed quantitatively by benchmarking over a three year period. This benchmarking shows that NIR is the most efficient technique in terms of costs and analysis times needed. Typical NIR expenditure for routine use may be demonstrated for single container identifications of x-ray contrast media. The cal-

Table 3. Estimated costs for establishing NIR identity methods, for example, x-ray contrast media (active).

Costs for basic establishing of the calibration model		Costs for changing or extending the calibration model		Costs for establishing NIR identity methods used for single container testing	
Action	Costs[a] (% total costs)	Action	Costs[a] (% total costs)	Action	Costs[a] (% total costs
1. Planning, supply of samples and measurements (7 actives, 5 lots each)	Approx. 4,000 DM (80%)	1. Planning, supply of add samples and measurements (for example new/other supplier)	Approx. 1,200 DM (80%)	1. Basic model for routine use	Approx. 5,000 DM (20%)
2. Measurements, establishing calibration model	Approx. 500 DM (10%)	2. Measurements, changing of calibration model	Approx. 150 DM (10%)	2. changes/extensions of the model (assumption: one per year	Approx. 7,500 DM (30%)
3. Validation, tests of the model	Approx. 500 DM (10%)	3. Re-validation, tests of the model	Approx. 150 DM (10%)	3. Qualification of NIR system (7 actives	Approx. 1,600 DM (6%)
				4. Portability[b] (7 actives)	Approx. 10,000 DM (40%)
				5. Training (7 actives)	Approx. 900 DM (4%)
Total costs	**Approx. 5,000 DM ($2,700)**	**Total costs**	**Approx. 1,500 DM ($800)**	**Total costs**	**Approx. 25,000 DM ($13,500)**

[a] Estimated costs for one laboratory hour: 150 DM (approx. $80).
[b] Portability: identical NIR systems, identical sample containers and comparable sample quantities, comparable environment (identical PC configurations, same type of laboratories).

culated costs for establishing and changing or extending the library model are approximately 5,000 DM and 1,500 DM, respectively, (Table 3). Besides these direct costs, additional expenditure—such as proper qualification of NIR systems according to cGMPs, portability of calibration models between spectrophotometers and training for employees—which are not directly substance-related, have to be considered. Taking these additional costs into account and assuming a 5-year calibration model life-cycle, the total cost of the model containing seven substances can be calculated at approximately 25,000 DM ($13,500). This total cost can only be redeemed if the number of containers is high enough, that the contribution of this stand by cost is low and the main advantages of NIR (very low costs and analysis times) are the determining factors. The analysis time needed per container—based on the data from 1996—shows the exceptional superiority of NIR compared with IR spectroscopy and wet chemistry. The average analysis time per container using the NIR is approximately 1 min, which is seven

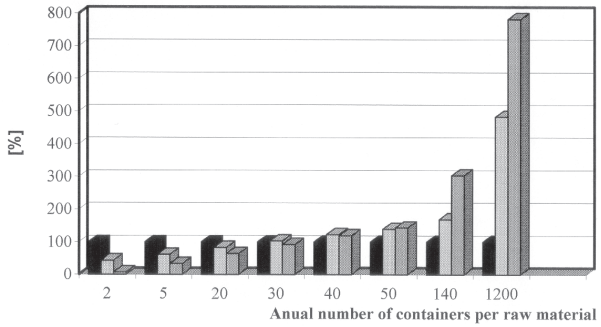

Figure 2. Comparison of the costs of the different identitymethods depending on the annual number of containers.

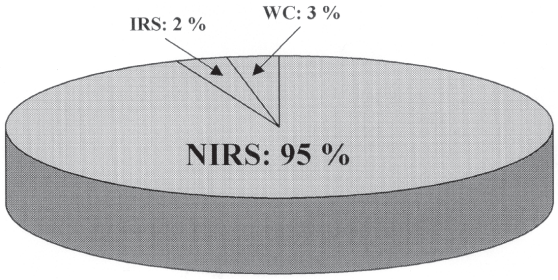

Figure 3. Contribution of the different methods for single container identity testing regarding total number of containers received (data basis: 1996–1998).

times less than for IR spectroscopy (approximately 7 min) and nine times less than for wet chemistry (approximately 9 min).

Using these average analysis times and the above described costs for establishing and change-control of a routine identification model, it is easy to calculate the number of containers per year that are necessary to make NIR profitable for routine testing compared to the other two selected identity methods. This "return on investment point" is reached if the number of containers of raw materials is approximately 40 per year (Figure 2). Based on this cost/benefit assessment a decision tree was implemented in our company for choosing the suitable identification technique for single container testing.

The economical superiority of NIR can also be demonstrated comparing the fictional testing costs for materials with a batch size of 140/1200 (annual average number of incoming containers per material/x-ray contrast medium, respectively). The calculating costs for NIR are 170 / 480% lower than those calculated for IR spectroscopy and 200 / 630% lower than those calculated for wet chemistry. These economical considerations have induced us to test approximately 95% of the incoming raw material containers by NIR (data from 1996–1998, Figure 3).

References

1. K. Molt, F. Zeyen and E. Podpetschnig-Fopp, *Pharm. Ind.* **58,** 847 (1996).

2. *European Pharmacopeia*, Monograph 2.2.40 "Near-Infrared-Spectroscopy", pp. 43–44 (1997).
3. *Pharmacopeial Forum*, Vol. 24, No. 4, pp. 6463 (1998).
4. *EC-Guide to Good Manufacturing Practice for Medicinal Products*, Directive 91/355/EEC, Chapter 5.30.