Attention: European Commission
Enterprise and Industry Directorate-General
Consumer goods, **Pharmaceuticals**

Re: Key ideas for better protection of patients against the risk of **counterfeit medicines**

Contribution: **PANalytical BV**
Almelo, the Netherlands

Authors: Dr. D. Beckers, U. Riedl

Contact: Dr. D. Beckers,
PANalytical B.V.
P.O. Box 13
7600 AA Almelo
The Netherlands
Tel.: +31 546 534239
FAX: +31 546 534571
Email: detlef.beckers@panalytical .com

Subject: Unambiguous identification of packaged counterfeit drugs by X-ray Powder Diffraction (XRPD)

1) Introduction

In recent years, X-ray powder diffraction (XRPD) has become a key analytical technique in the pharmaceutical industry and is being used for the discovery, development and manufacture of drugs. XRPD allows, for example, qualitative and quantitative phase analysis of the various constituents of the complete solid drugs, including the active pharmaceutical ingredient (API) and the fillers, with very low detection limits and control of the final dosage form.

To date, reliable differentiation between fake and authentic product has required the application of analytical techniques following removal of the tablet from the blister. Recently, we (PANalytical) have been able to demonstrate the effective, quick and reliable screening of pharmaceutical tablets **without removing them from their original blister packing**. The high penetration depth of X-rays means that these investigations can be carried out on even fully opaque blisters, with only a moderate attenuation of the signal from the tablet. In most cases, scattering from the mainly amorphous polymer used for the blister material produces only a slightly increased background; the aluminum lidding is evidenced by just two characteristic Bragg reflections at higher angles. Thus the signal from the tablet itself is disturbed very little by the packaging material. This opens new doors for non-invasive screening of packaged drugs, where the technique's unique fingerprinting mechanism allows differentiating between counterfeit and authentic products. Furthermore, the technique allows monitoring of structural changes, taking place during the final production steps of tabletting and packaging or during storage of the packaged drugs.

Unlike other techniques, like hologram or bar code screening, or various analytical techniques which provide specific surface or superficial characteristics, XRPD looks at the tablets themselves and gives a unique fingerprint of the contents.

2) The Technique

X-ray diffraction (XRD) is a versatile, non-destructive technique that reveals detailed information about the chemical composition and crystallographic structure of natural and manufactured materials. The technique is extensively used in the pharmaceutical industry to:

- determine crystal structures
- screen for and unambiguously identify polymorphs or hydrates
- detect changes in morphology or crystalline state of active ingredients (e.g. during processing or at non-ambient conditions)
- detect and quantify crystalline impurities (in some cases down to 0.05%)
- determine the crystallinity or the crystallite size of a compound
- analyze and optimize final dosage forms
- Detect and analyze the used fillers in tablets/capsules

3) Proof of our screening solution to fight counterfeit drugs

In this work we present X-ray diffraction studies on blister-packed tablets. The method has been developed in close co-operations with the pharmaceutical Institute of the University of Bonn, the department of Pharmaceutical Technology and the department of Drug Regulatory Affairs.
The tablets investigated are commercial products purchased in European pharmacies. For the commercial products investigated, the original, intact blister cards were used as received, without any sample preparation or further treatment.
The typical measurement times of such tablets within blister packaging are between 10 and 30 minutes, mainly depending on the thickness and properties of the tablets/capsules.

The following schematic drawing (Figure 1) is an explanatory example of the typical representation of crystalline and amorphous constituents from a powder/solid form material in an X-ray diffraction diagram.
All peaks and background features in such diagram provide qualitative and quantitative information on the constituents, allowing characterizing the total composite.

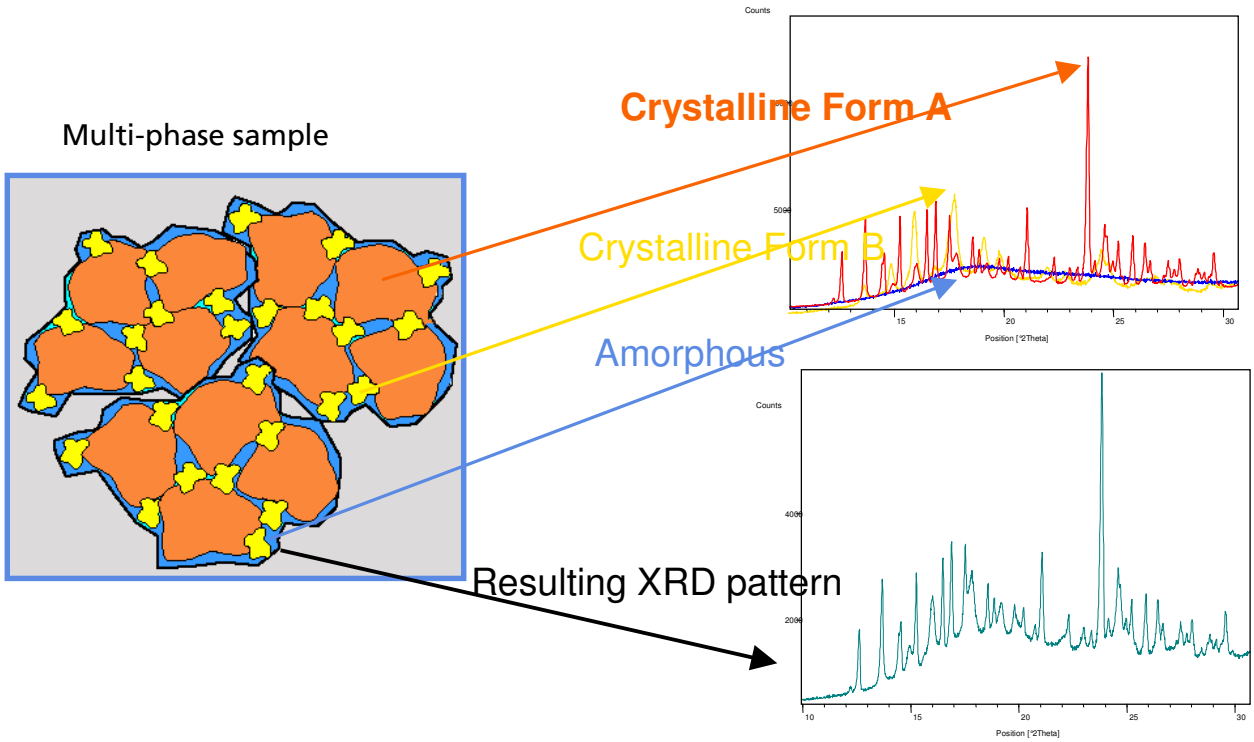


Figure 1: Schematic representation of an XRPD pattern of a multi-phase mixture. The resulting XRPD pattern is a sum of the patterns of the single phases.

Example 1a: XRD measurement of an emptied blister, with and without the aluminum lidding

Figure 2 shows the measurements of an emptied blister with and without aluminum foil. The polymer part is evidenced by a broad background, whereas two intense peaks from the aluminum are seen at higher angles (expressed as 2 Theta in degrees).

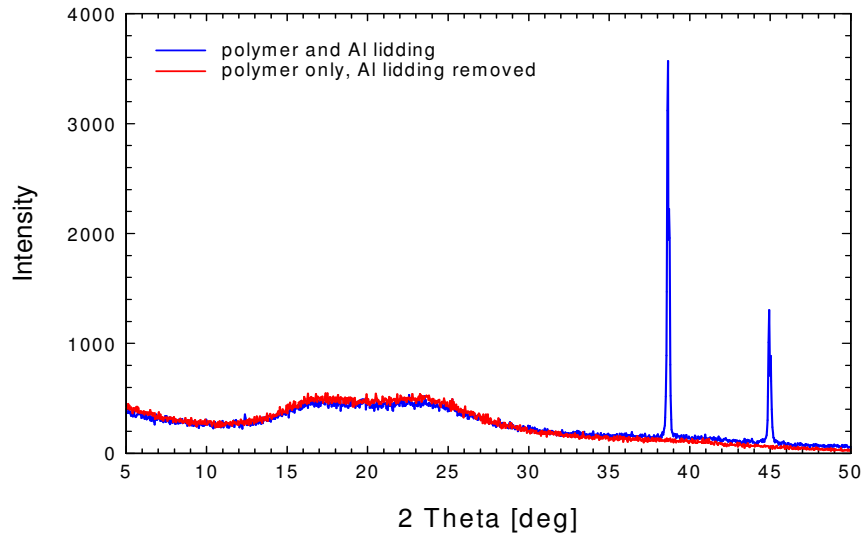


Figure 2: Measurements of an emptied blister with and without aluminum foil

Example 1b: XRD measurement of the tablet within the blister and after removal of the blister

The blister is identical to the one measured in example 1a. The scattering intensity from the polymer of the blister material is very small compared to the intensities of the X-ray pattern from the tablet and only result in a slightly increased background. The two intense peaks in green (at 39° and 45° respectively) are attributed to the aluminum lidding.

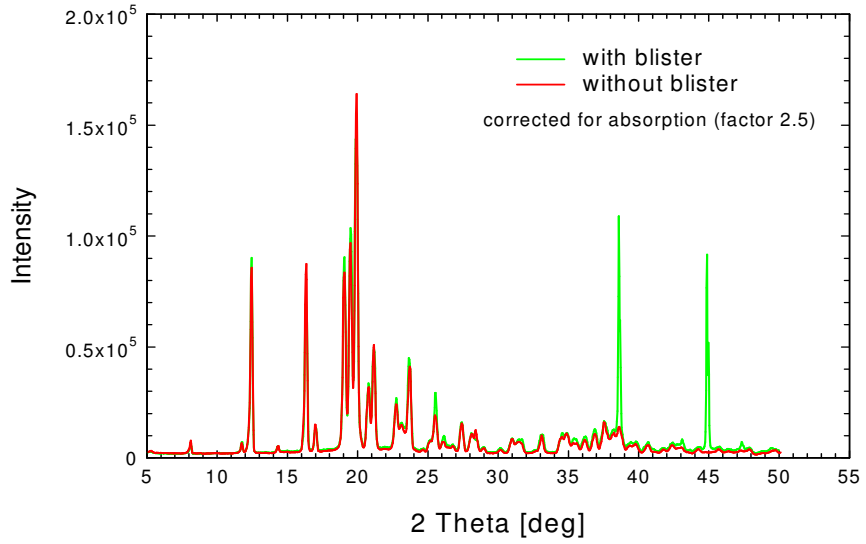
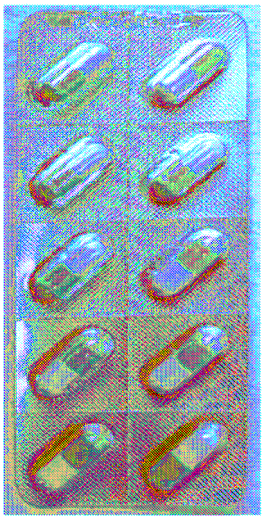


Figure 3: Comparison of an XRD pattern of a tablet in the blister package and a tablet removed from the blister (the pattern of the tablet in the blister is scaled by a factor of 2.5)

Example 2: Influence of packaging and capsule material on the results

In this example, we looked at a Tamiflu capsule in its blister.



On this material, we performed the following measurements, shown in the figure below.

1. Tamiflu capsule in blister (purple)
2. Empty blister – capsule removed (green)
3. Capsule taken out of blister and emptied (blue)
4. Tamiflu powder taken out of the capsule (red)

With this example, it is proven that XRPD can distinguish between the different constituents of a capsule in a blister. It can also be seen that not only the tablet contents itself, but also the capsule and blister materials add their unique fingerprints to the total XRPD pattern. All different constituents can easily be identified.

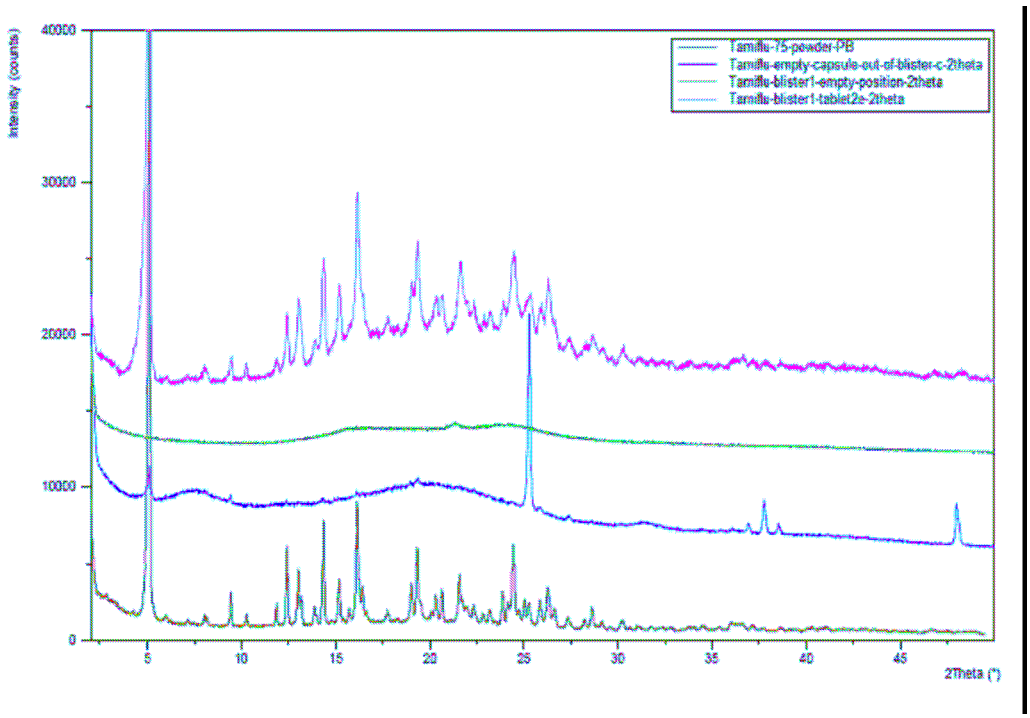


Figure 4: XRD patterns of a Tamiflu capsule in a blister, the empty blister, the empty capsule and the Tamiflu powder taken out of the capsule.

Example 3: A fully opaque blister

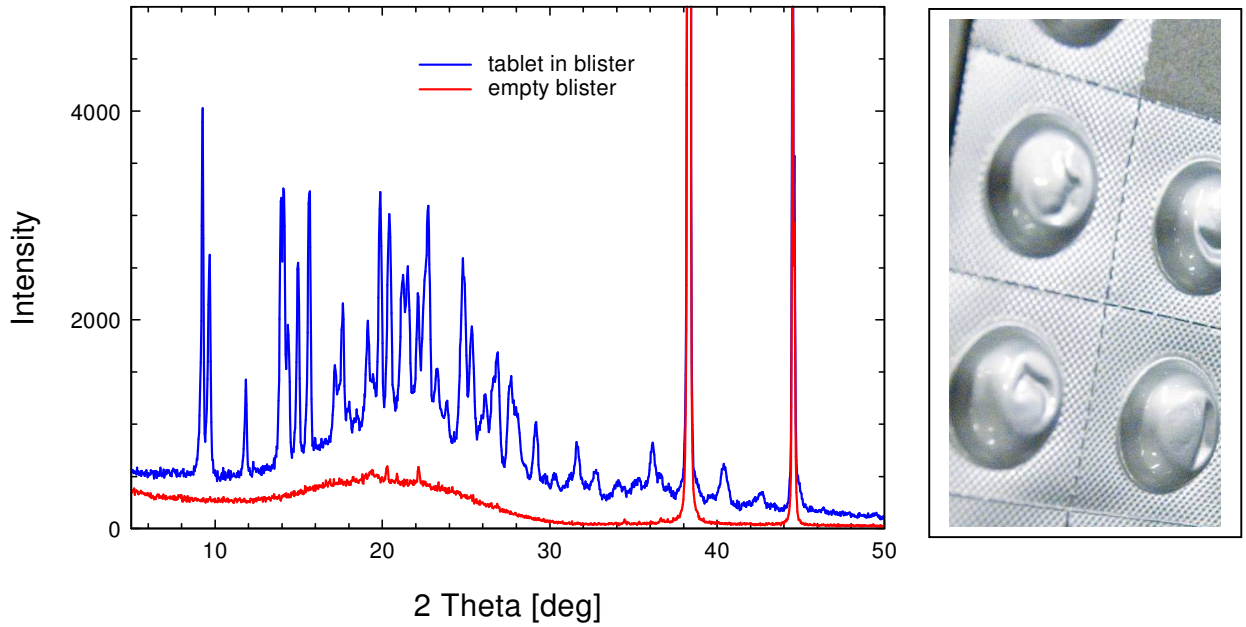


Figure 5: XRD patterns of a tablet in an opaque blister and of the empty blister

Also in this example of an opaque blister (which is transparent for X-rays), the separately measured emptied blister material (red) does not significantly interfere with the diffraction pattern of the tablet. This scan took approx. 30 minutes.

Example 4: Comparison of tablets with different API concentrations and API phases (polymorphs)

In this experiment, tablets with different compositions were prepared in blister packaging in order to simulate drugs in which tablets contain different API polymorphs or no API. This example also serves to demonstrate the ability to detect polymorphic changes during processing or storage.

Different polymorphs of Indomethacin (IMC) were used as API, namely the α- and γ-forms. In addition, one set of tablets was entirely placebo. The tablets were placed in an emptied commercial blister card, which was carefully re-closed. The difference in crystal form and/or amount of active pharmaceutical ingredient is clearly visible through the absence or presence of various XRPD information mainly shown at the diffraction angles below 25°. For easy visible approach the reflections are marked by arrows in Figure 6.

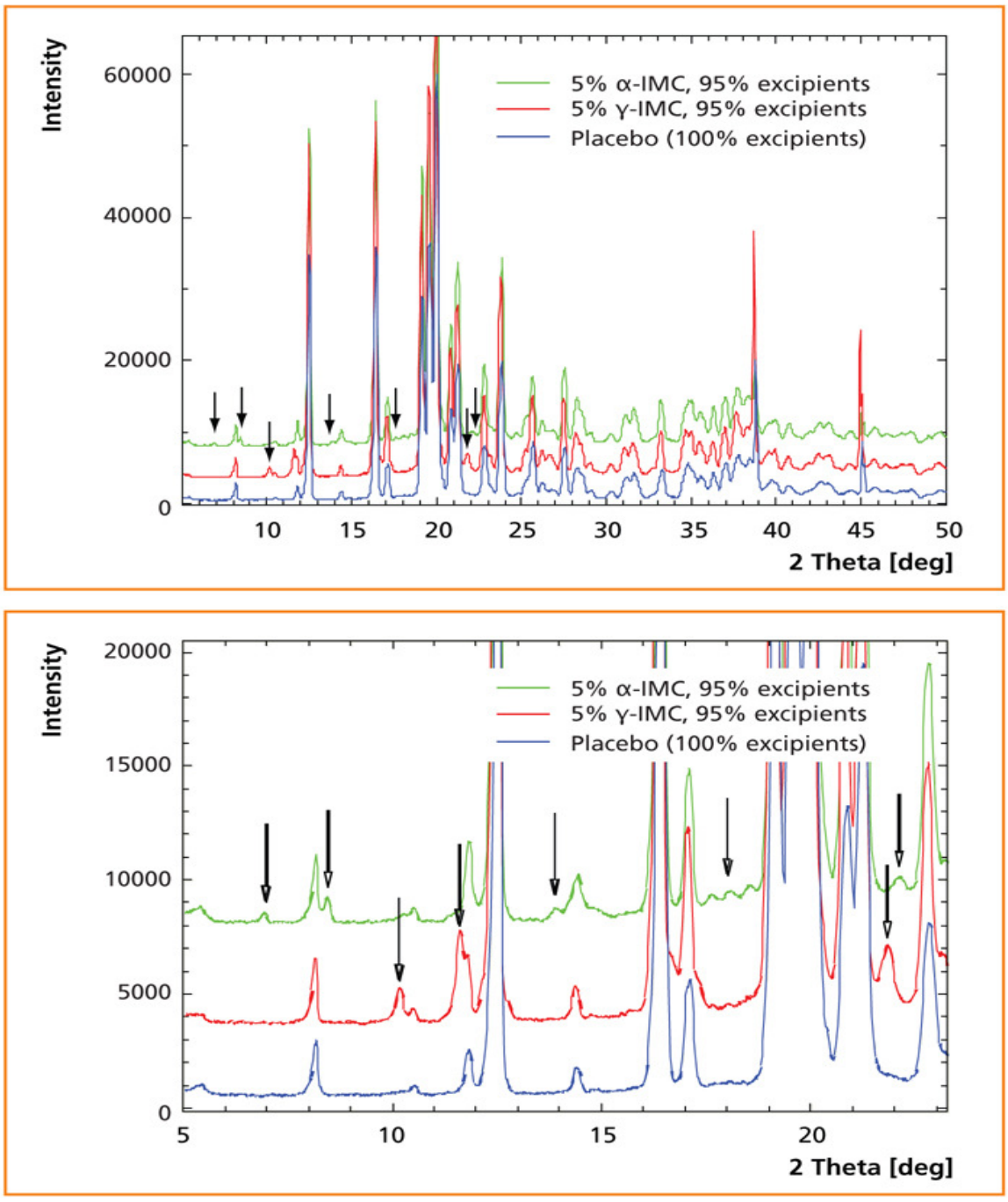


Figure 6: XRPD data measured from the test tablets with different API phases and concentrations. Measurements were performed on tablets in the blister pack. Bottom: magnification of the experimental data in the angular range where differences are most evident.

Example 5: Comparison of an original product with a fake tablet

In this example we show the comparison of an XRPD pattern measured on an original Viagra tablet (Pfizer) with the XRPD pattern of a copy product. Both tablets contain 100mg Sildenafil citrate.
From the patterns it becomes visible that a) the total composition the tablets is different, and b) also the crystallinity of the API (which may have influence on the bioavailability).

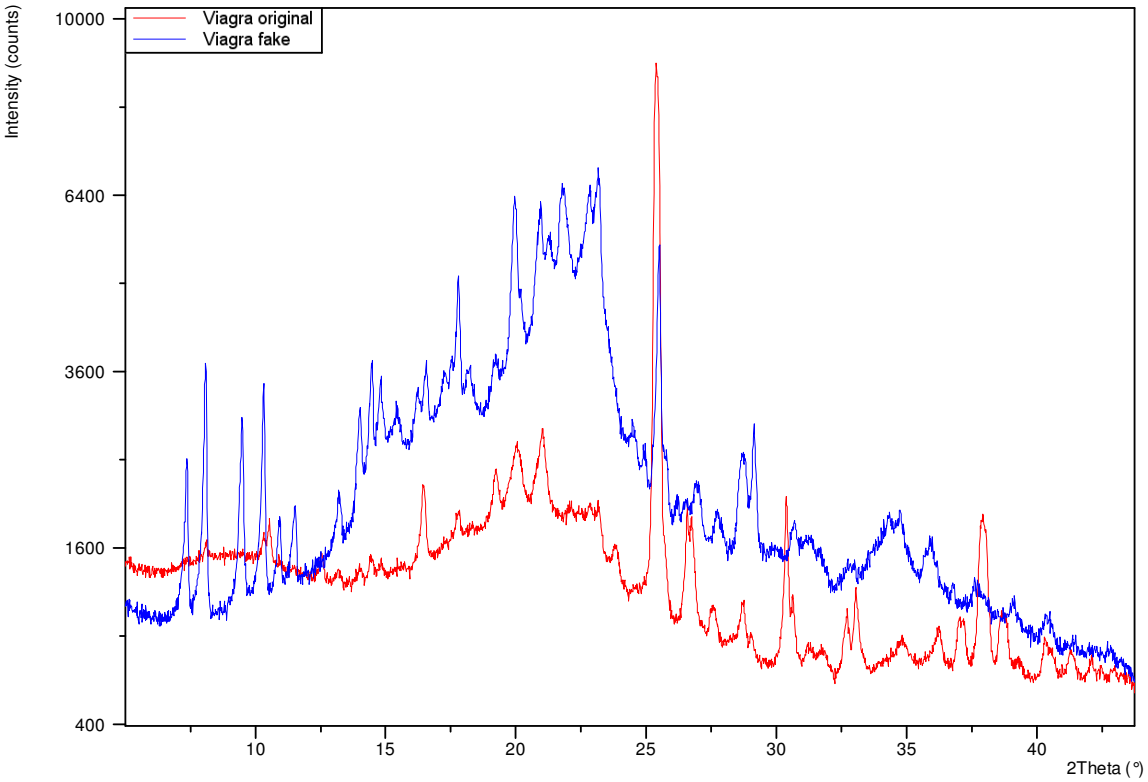


Figure 7: Comparison of the XRPD pattern measured on an original Viagra tablet (Pfizer) with the XRPD pattern of a copy product.

A comparison of three original products (from different sources) and several copy products / fake drugs show that easy differentiation is possible with a cluster analysis of the measured scans (Figure 8.) The scans of the original Viagra tablets cluster closely together in the grey cluster in Figure 8. The scans on other tablets (copy products / fake drugs) are different from the original scans and cluster into different other groups.
A report with a more detailed analysis on these samples is attached in the appendix.

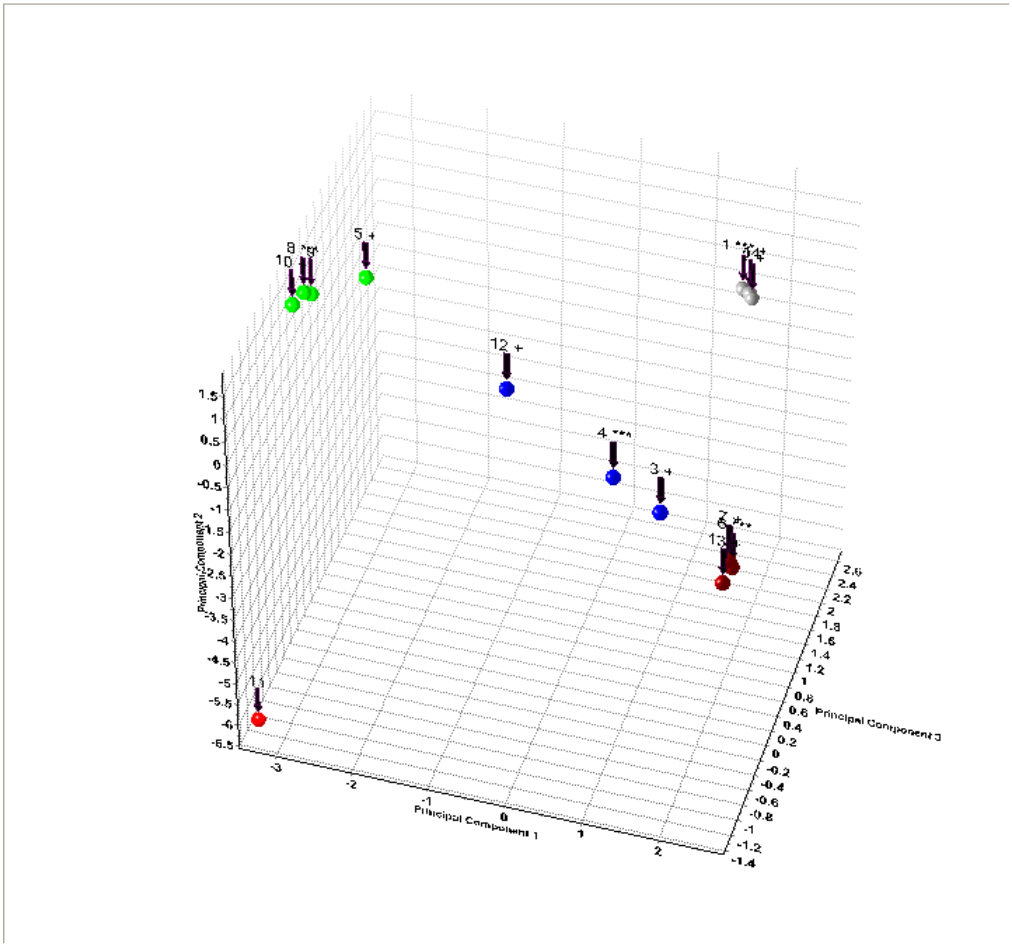


Figure 8: PCA of the cluster analysis of all samples. The grey cluster contains the original samples. Copy products were grouped into other clusters depending on their origin / composition.

4) List of currently investigated materials

Name	Dose	Producer
Actonel	35mg	Procter&Gamble, DE/ Sanofi-Aventis, DE
Casodex	50mg	AstraZeneca, DE
Celebrex	100mg	Pfizer, DE/H. Mack Nachf, DE
Cialis	20mg	Lilly, ESP
Diovan	80mg	Novartis, DE
Diovan	160mg	Novartis, DE
Fluctin	20mg	Lilly, ESP
Levitra	20mg	Bayer, DE
Lorzaar Protect	50mg	MSD, GB
Lorzaar Protect	100mg	MSD, GB
Nexium mups	40mg	AstraZeneca, DE
Nexium mups	20mg	AstraZeneca, DE
Plavix	75mg	Sanofi-Synthelabo, GB
Propecia	1mg	MSD, DE
Sortis	20mg	Pfizer, DE/Goedecke, DE
Tamiflu	75mg	Roche, DE
Valium	10mg	Roche, DE
Viagra	100mg	Pfizer, FR
Zyprexa	5mg	Lilly, ESP

5) Current situation

At the time of writing, all experiments have been performed on an instrument designed for a research environment. A dedicated 'black box' tool for e.g. border control and customs offices does not exist yet, but is very conceivable.
The experiment shown are performed with scan times varying between 5 and 30 minutes for the total analysis (depending on the absorption of the packaging material).
Based on these and also other experiments, we are building up a database of genuine and counterfeit pharmaceuticals in their packaging. In a separate, but related project, we are also successfully investigating the unambiguous identification of narcotics, synthetic drugs and other controlled substances, in close co-operation with Health Canada.

6) Summary and outlook

We are confident that X-ray powder diffraction offers unique opportunities for assisting governments and pharmaceutical companies in their fight against counterfeits. Our technique is non-destructive and does not require crushing the tablet or opening the blister. In fact, even the properties of the blister itself can be taken into account for specific discriminating purposes. Our method yields the highest possible resolution – required for the separation of different polymorphs and the accurate detection of API concentrations. Based on these experiments, we have filed a European patent under application # 08151542.1

Company profile

PANalytical is the world's leading supplier of analytical instrumentation and software for X-ray diffraction (XRD) and X-ray fluorescence spectrometry (XRF), with more than half a century of experience. The materials characterization equipment is used for scientific research and development, for industrial process control applications and for semiconductor metrology.

PANalytical, founded in 1948 as part of Philips, employs around 900 people worldwide. Its headquarters are in Almelo, the Netherlands. Fully equipped application laboratories are established in Japan, China, the USA, and the Netherlands. PANalytical's research activities are

based in Almelo (NL) and on the campus of the University of Sussex in Brighton (UK). Supply and competence centers are located on two sites in the Netherlands: Almelo (development and production of X-ray instruments) and Eindhoven (development and production of X-ray tubes). A sales and service network in more than 60 countries ensures unrivalled levels of customer support.

The company is certified in accordance with ISO 9001:2000 and ISO 14001.

The product portfolio includes a broad range of XRD and XRF systems and software widely used for the analysis and materials characterization of products such as cement, metals and steel, nano materials, plastics, polymers and petrochemicals, industrial minerals, glass, catalysts, semiconductors, thin films and advanced materials, pharmaceutical solids, recycled materials and environmental samples.

PANalytical's range of systems for X-ray analysis within the pharmaceutical industry are all designed to meet regulatory requirements, including suitability for use in a 21 CFR Part 11 compliant laboratory environment.

PANalytical is part of Spectris plc (UK), the precision instrumentation and controls company.