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An FDA Laboratory Approach to Uncovering Potential Fraud in the Generic Drug Industry

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Abstract: The Division of Drug Analysis of the U.S. Food and Drug Administration In St. Louis, MO, has screened more than 1400 drug samples for potential generic drug fraud by a combination of physical, Instrumental, and chemical techniques. The approach to fraud centered around the analysis of excipients as opposed to the normal approach of analysis of active Ingredients. Approximately 80% of the drug formulation pairs (innovator and generic) submitted for bioequivalence testing could be differentiated by a combination of physical and Instrumental analysis, mainly thermogravimetric analysis (TGA) and Fourier-transform Infrared (FTIR) spectrometry. TGA proved to be the single most useful Instrumental technique to determine differences In formulations. Liquid chromatography, gas chromatography, chemical tests, and polarizing microscopy were found to be the most useful tools to differentiate formulations that could not be resolved by FTIR, TGA, or physical comparisons. X-ray powder diffraction and nuclear magnetic resonance spectroscopy were found not to be useful techniques to differentiate formulations. No clear-cut evidence of direct fraud was found, but inconsistencies and suspicious samples were noted. Follow-up Inspections based on the laboratory findings will probably occur. The procedures discussed In this article could be streamlined and made more efficient for examining large numbers of potential problem formulations.

In 1989, investigators of the U.S. Food and Drug Administration (FDA) uncovered fraudulent activity in the generic drug industry. As a result, FDA's Division of Drug Analysis (DDA) was asked to investigate the problem. Thomas Layloff has given an excellent overview and discussion about FDA's approach to this type of regulatory activity.[1]

This article presents DDA's approach in detecting possible fraud in specific samples collected concerning the generic drug industry. An outline of the procedures followed is given, not the specifics of the methods. DDA received 1400 samples from various sources in about a month. Most samples were received from two pharmaceutical testing laboratories that had compared the bioequivalence of submitted generic formulations to innovator formulations. Although many types of fraudulent activity are possible, DDA decided to concentrate on being able to detect and prove the following: (1) direct substitution of one product (innovator) for another (generic), (2) altered innovator dosage formulations, and (3) unapproved changes in batch formulas.

The concept of analysis of samples for fraud was completely new to our laboratory. We quickly realized that an in-depth analysis of each sample for active and inactive ingredients (excipients) and conclusions to be made about fraud could not be accomplished in a timely manner. Many months or years might be involved.

[1] Layloff, T.P., (1991) Pharm. Tech., **15**, 146-148.

In an attempt to solve this dilemma, we examined some possible fraud scenarios. If a generic company substituted an innovator's product for their own, then any physical data and any instrumental data would be identical, albeit possibly disguised. If a generic company had tampered or slightly modified an innovator's product, the data comparisons would be similar. If the generic company's and the innovator's products were truly different, then the comparisons could be different. If the generic company's and the innovator's products were truly different but contained the same excipients in about the same proportion or differed by a minor excipient, the data could be similar.

We were dealing with "similar" (sameness) or "different," and a gray area in between. Management selected an 80% or better match of the physical and instrumental data as a decision making marker. Two categories were established: (a) significantly different, no further work required, and (b) similar, needs further work. The 80% guideline was adopted to decrease the possibility of missing a fraudulent generic-innovator sample pair.

A laboratory protocol was set up for sample screening and comparison (data evaluation). The tools selected were physical measurements (size, weight, color, etc.) and instrumental techniques, including Fourier-transform infrared (FTIR) and thermogravimetric analysis (TGA). Nuclear magnetic resonance spectroscopy (NMR) and X-ray powder diffraction (XRPD) were used on a limited basis. Approximately 80% of the generic-innovator sample pairs were eliminated after the first screening. The remaining 20% required further testing.
Batch records were requested from FDA's Division of Generic Drugs for the samples that required further testing. Additional tools were used in the follow-up analysis, including liquid chromatography (LC), gas chromatography (GC), IC (ion chromatography), polarizing microscope, and chemical tests.

Experimental

Apparatus

(a) Camera.-Model CU-5 with 2x close-up attachment (Polaroid Corp., 575 Technology Square, Cambridge, MA 02139).
(b) Color guide.-PANTONE by Letraset Color Products Selector.
(c) FTIR spectrometers.-Model 1600 (Perkin-Elmer Corp., 761 Main Ave, Norwalk, CT 06859) and Nicolet Model 710 (Nicolet, 5225-1 Verona Rd, PO Box 4508, Madison, WI 53791-9598).
(d) Gas chromatograph.-Model 5890 (Hewlett-Packard Co., Route 41, PO Box 900, Avondale, PA 19311-0900).
(e) Ion chromatograph.-Model 4000i (Dionex, 1228 Titan Way, PO Box 3603, Sunnyvale, CA 94088-3603).
(f) Polarizing microscope.-Model GFL (Carl Zeiss, Inc., 1 Zeiss Dr, Thornwood, NY 10594).
(g) Microscope.-Wide field, low power (10-25x) (Bausch and Lomb).
(h) *Thermal* analyzers.-Model 9900 computer thermal analyzer, and Analyst 2000 with Model 951 thermal gravimetric analyzer (Dupont Co. Instrument Systems, Concord Plaza, Quillen Building, Wilmington, DE 19898).
(i) X-ray *powder-diffraction spectrometer.-Datamax* A (Rigaku USA, Inc., Damen Building, Suite 305, 200 W. Higgins Rd, Schaumbury, IL 60195).

(j) *Liquid* chromatograph.-Model 6000 solvent delivery system, Model 450 variable wavelength detector, Model 710B autoinjector, and Model 730 data module (Waters Chromatography Div., Millipore Corp., Milford, MA 01757).

Laboratory Format

Before laboratory analysis began, DDA set up a system for handling the samples submitted under investigators' seals. The investigators placed many samples from the testing facility in several sample cartons under one FDA seal and collection report. These samples were repackaged and individually resealed by DDA personnel.

Each generic company's bioequivalence sample was mated with the corresponding innovator's marketed product that was submitted by the generic company for comparison with the generic sample for bioequivalence study. An 8 digit numbering system was set up to mate the samples; we assigned odd numbers to indicate generic company samples and even numbers to indicate innovator company samples. These 8-digit numbers were directly related to the serial number of the investigator's collection report. The samples were then logged into our computer system. Sample cards and labels were printed for each sample.

To keep track of the information about the samples and their path through the laboratory, a 16-field database was set up on the computer system. Entries in the database consisted of drug name, sample number, serial number of the investigator's collection report, subnumber, innovator's name, study number (associated with the origin of the sample), status, generic company, sample type (generic or innovator), dosage, dosage units, dosage form, lot number, date received, date completed, and generic code for the drug name.

To prevent bias and to protect against sample mix-up, analysts were allowed to have only one sample at a time. As another safeguard, we set up a new sample storeroom that was only accessible to the sample custodian and 2 laboratory supervisors.

Data Collection

When an analyst received a sample for initial testing, a sticker label was forwarded to the team leader, who logged the sample into the database with drug name, generic company, and status. The status code used for in process samples was a dash (-).

The analyst began the testing using a laboratory protocol especially designed for this work. A physical examination was first. The units (tablets or capsules) were observed under a low-power (10-25x) Bausch and Lomb wide-field microscope for signs of tampering, such as innovator markings obliterated or painted over. Next, a unit was photographed with a Polaroid Model CU-5 camera with a 2x close-up attachment. The unit was measured and the net weight of the unit recorded. The unit was then numerically coded using an identification guide.[2] The unit was compared to a commercial printer's color guide and the color number recorded. This was more accurate than allowing the chemist to make a judgment about the color, i.e., red, peach, pink, orange, etc.

[2] Hefferren, J.J. (1962) J. Am. Med. Assoc., **182**, 1145-1302.

A portion of a finely powdered unit was then mixed with KBr to make a 2% w/w pellet, whose FTIR spectrum was recorded from 4000 to 400 cm^{-1} by either of the FTIR spectrometers. A thermogram was obtained from another portion of the finely powdered unit by either of the thermal analyzers. The thermogram was taken from 25 to 600'C at 10°C/min. This rate was used instead of the optimum 2°C/min because of the pressure of the work load. The individual analysts ran the innovator and generic samples on the same instrument. XRPD spectrometry was used to supplement the FTIR and TGA instrumental data on certain samples.

Results and Discussion

Originally, all the samples were analyzed on the thermal analyzer, but the system quickly became backlogged at the TGA instruments because of their longer running time. The protocol was modified briefly to obtain only the physical characteristics and FTIR spectra. However, 80% of the sample pairs (innovator and generic) gave FTIR spectra too similar to allow judgments, and TGA scans had to be performed.

Data Evaluation

When the analyst completed the work on the sample, the sample was resealed and returned to the sample custodian. The worksheet, physical data, and instrumental spectra were forwarded to the team leader. The team leader held the sample worksheet until its mate was received. At that time, the physical data and instrumental spectra were reviewed. The team leader then labeled the pair as Status 1 (significantly different, no further work required) or Status 2 (similar, needs further work).

If the conclusion was "significantly different, no further work required," the samples were marked NAI (No Action Indicated), and the status was changed from dash (-) to 1. Approximately 80% of the samples fell into this category. If the conclusion was "similar, needs further work," the batch formula was requested from the Division of Generic Drugs in Washington, DC, and the status was changed from dash (-) to 2. Approximately 20% of the samples fell into this category.

The decision of whether samples were Status 1 or Status 2 was made by the team leader in conjunction with 2 laboratory supervisors.

Table 1 below shows the percentage breakdown of the techniques used for making the determination "significantly different, no further work required." Approximately 80% of the samples were eliminated from further work using these techniques. Thermogravimetric analysis proved to be the most useful technique for determining differences in formulations. Approximately 60% of the samples could be eliminated from further work using only this technique. XRPD is not recommended as a technique to differentiate these samples.
NMR was also used on a limited number of samples without success.

Table 1. Percent of Sample Pairs Found Significantly Different by Techniques Used in First Screen	
Technique	Percent
TGA	58
FTIR	18
Physical Examination	3
X-ray	1
Undifferentiated by above techniques	20

We updated the database by adding the rest of the sample information to the data fields. The Wang office management system was accessible to all managers, and managers could query the system about the status or other information on any sample.

In-depth Follow-up Examination and Data Evaluation

When the batch records were received for a pair (generic and innovator) of Status 2 samples, the records and samples were assigned to an analyst for further testing. The batch records were reviewed for differences, which formed the basis for additional testing. A variety of tests were performed, ranging from simple chemical tests for sulfate ion to complex chromatographic procedures. In some cases, corn starch was the difference in the formulations, and a polarizing microscope was used to confirm the presence or absence of starch in the samples. In other cases, magnesium stearate was targeted, and IC was used to test for magnesium ion. GC was used as the qualitative/quantitative method of analysis to determine stearic acid and lactose.

Certain formulations appeared to be identical. In this case, an impurity profile by LC was used to examine the active ingredient and related substances (3). When the formulations were tested in this manner, the liquid chromatograms of the active ingredients sometimes exhibited different impurities, thus showing different sources of the active drug material.

Table 2 below shows the percentage breakdown of the techniques used for differentiating the innovator-generic samples that were initially marked Status 2, "similar, needs further work." Some formulations appeared to differ from the approved batch formula and are being investigated further.

Table 2. Percent of Samples Found Different by Additional Techniques.[a]	
LC	35
Polarizing microscope	25
Chemical tests	20
GC	15
Ion chromatography	5
[a] The 20% of samples undifferentiated by the techniques in Table 1.	

When the additional work was completed, the samples were reviewed by the team leader and the laboratory supervisors. If the conclusion was that the samples were "significantly different, no further work required," the samples were marked NAI, and the status was changed from 2 to 7.

Status Code 7 identified samples found significantly different only after additional testing and differentiated them from Status 1 samples (those found significantly different after initial FTIR and TGA examinations). Data could then be kept on how many and which samples had undergone additional testing and were found different. No samples required further testing past the Status 2 category.

Summary

In conclusion, our laboratory learned a great deal about analysis of drug formulations for excipients. The TGA and FTIR scans of powdered formulations showed many sample pairs were significantly different and quickly reduced the number of formulations requiring further work. Many simple chemical and colorimetric tests could be performed on what appeared to be a relatively complex mixture of ingredients. Chromatographic tests (GC, LC, etc.) could also be used to allow definite conclusions about the formulations. The polarizing microscope proved an invaluable tool to differentiate formulations. Before this experience, our examination of drug samples consisted of analyzing the formulations for the active ingredients; during examination for fraud, however, spectral, chromatographic, or chemical analysis of excipients predominated.

No direct evidence of fraud was found, but inconsistencies were found in batch formulas submitted to the Division of Generic Drugs. FDA is setting up programs for further investigations.

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