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Scientific Fingerprinting: A Pharmaceutical Regulatory Tool .

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During the summer of 1989, investigators from FDA's San Juan District discovered extensive fraudulent manufacturing practices at a generic pharmaceuticals manufacturer. During these investigations, it was discovered that the manufacturer had fraudulently submitted two portions of the innovator's product for bioequivalence testing; one portion had been disguised to represent the generic product by coating it with a different color to avoid detection. Subsequent investigations with another generics manufacturer detected that the firm had filled its own capsule shells with the innovator's product and then submitted the fraudulent capsules along with samples of the innovator's product for a bioequivalence study.

As a result of these fraudulent practices, FDA undertook large-scale investigations into the generic pharmaceuticals industry and collected reserve bioequivalence test samples that had been submitted to several laboratories for testing. Approximately 1400 samples representing almost 700 purportedly paired innovators' and applicants' product submissions were forwarded to the FDA Division of Drug Analysis (DDA) with instructions to determine whether any fraudulent submissions had occurred with these samples.

DDA chemists determined that this assignment would require an extraordinary amount of time in obtaining the batch formulas for all of the products and developing or validating methods that could be used to analyze all components of the products. They also noted that although FDA approves formulations of products, there are no legally established validated methods of analysis to determine whether the products were in fact formulated as they had been approved. Therefore, the total analyses of these finished dosage forms to determine the individual components and their allowable impurities could not quickly reveal whether fraudulent submissions had occurred. After this review, FDA determined that total analyses were not required because instances of fraud could be addressed by determining the "sameness" or "differences" of the various samples. It had been previously suggested that FDA use some form of "scientific fingerprinting" for excipients to determine whether products were what they were purported to be.² DDA chemists concurred with that suggestion and began to establish protocols to build libraries of analytical fingerprints or databases that could be used to compare the sameness of products.

In addition to these analytical fingerprints, products also are characterized by physical properties such as color, weight, shape, imprints, bevels, texture, etc.; this array can be thought of as a physical fingerprint. In addition to these fingerprint attributes, one may acquire the usual attributes of the active drug substance, including content uniformity, dissolution rate, assay, etc. Our initial efforts in this fingerprinting have focused on physical attributes such as dimensions, color, weight, etc., and spectroscopic techniques that can be readily calibrated and provide data that are highly reproducible and available in a computer-readable form such as Fourier-transform

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² W. Haddad in a 7 August 1989 letter to FDA as quoted in *F-D-C Reports*, "The Pink Sheet" (F-D-C Reports, Inc., Chevy Chase, Maryland, 14 August 1989). p. T&G 6.

infrared (FTIR) and X-ray powder diffraction (XRPD). In addition, we have used thermal gravimetric analysis (TGA) as another fingerprint source. Data sets from these instruments are fixed on one dimension (e.g., wavelength, diffraction angle, or temperature) that can be accurately calibrated and thus provide well defined data on that dimension. The allowable absorbance, intensity, or decomposition-curve ranges depend on the allowable formulation ranges and impurity levels in the components and their subsequent reactions in the formulation. As noted previously, the absolute analyses of the formulations and their included impurities at this time would require an extreme effort.

Although the NMR, TGA, and XRPD analytical techniques are robust, they suffer from a lack of sensitivity. We estimate that these techniques can detect differences in the formulations that are greater than ca. 10% of the total sample matrix. Even with this limitation, these fingerprinting techniques allowed us to demonstrate that ca. 80% of the submitted sample pairs were different. A summary of our efforts to resolve the differences or sameness for these samples will be published elsewhere.³

These successful efforts have focused our attention on the feasibility of using these techniques and an array of others that are currently under investigation in order to extend analytical fingerprinting to much lower concentrations of formulation components. The need for greater sensitivity can be illustrated with Digoxin tablets, which weigh ca. 100 mg but contain only 125-250 micrograms of active drug; thus, we are dealing with a matrix in which the Digoxin is present in the parts-per-thousand range. At this level, Digoxin would not be detectable with our current fingerprinting techniques. To compound the problem further, a 2% impurity in bulk Digoxin would be present in the tablet matrix in the parts-per-million range. When these lower fingerprinting levels are achieved, they may be used in a sameness test to determine if a product had been formulated as FDA had approved it.

Our initial efforts to lower the operating limits have involved the use of chromatographic techniques. Although these are extremely useful in testing bulk pharmaceutical products for impurities, they are not a panacea for our fingerprinting efforts because chromatographic data are fuzzy or not repeatable within the context of our spectroscopic analytical acceptance criteria. This fuzziness occurs especially with high performance liquid chromatography because of lot-to-lot changes in the column packing and coatings, in addition to the degradation of the column's operating characteristics during its lifetime. These variations in chromatographic data make absolute or statistically based comparisons difficult. However, when enough sample is injected to give an off-scale signal for the main drug component, experienced analysts can visually compare the chromatographic pattern of impurities and estimate with a high level of certainty whether samples are the same or are different.⁴ Comparisons of such chromatographic data have tentatively allowed the association of two recent cases of pharmacogenic diseases (isoxicam with Lyell's syndrome⁵ and L-tryptophan with eosinophilia-myalgia syndromes⁶) with changes in the synthetic route or yield pattern in the preparation of the bulk pharmaceutical product.

³ R.D. Kirchhoefer, submitted for publication.

⁴ E.L. Inman and H.J. Tenbarge. *J. Chrom. Sci.* 26, 89-94 (1988).

⁵ The Wall Street Journal. 19 February 1987, p. 51.

⁶ MMWR 39, 589-591 (1990), as reported in JAMA 264, 1656 and 1698 (1990).

As the sensitivities of these fingerprinting techniques become sufficient to enable detection of differences in the synthetic routes of bulk pharmaceuticals used in finished dosage forms, we will apply them more rigorously in our regulatory efforts. We plan to obtain, either in our laboratories or from the manufacturer, fingerprint data sets from a portion of the pivotal lot - the lot used to establish bioequivalence of commercial production lots with the material used in clinical studies. This initial data array for an approved product will include the chemical and physical fingerprints, as well as the required active drug substance data, such as content uniformity, assay, release rate, etc. These data will be stored in computer-searchable files.

Data arrays obtained in the same fashion on subsequent lots could then be compared to the data arrays obtained on the approval lot to determine sameness. If differences are observed, we will determine if the variations are within allowable formulation ranges through the use of convolution-deconvolution techniques with data arrays obtained on excipient and drug substances or by comparison techniques for fuzzy data sets⁷ on data arrays obtained from pivotal lots formulated at the lower, optimum, and upper acceptance limits.

We anticipate that formulations containing proteinaceous active drug substances will also be amenable to fingerprinting control strategies with the inclusion of data arrays obtained from electrophoretic, chromatographic, and other mapping or analytical techniques. For these materials, it probably will be desirable to push usable sensitivities until the methodologies and systems are able to deal with materials present at the parts-per-billion level or less; such sensitivities would, we hope, allow the determination of significant decomposition of active substances or their reactions with matrix components.

In summary, we have undertaken an effort to establish computer-based fingerprint data arrays that can be used for fuzzy data comparisons to determine if a product was manufactured in accordance with its FDA-approved formulation and was made from approved components that individually meet quality standards. We and others have observed that high-sensitivity chromatographic techniques applied to bulk drug substances will allow us to determine the precursor and degradation profiles in the bulk drug matrix by visual comparisons.⁸ We anticipate that it soon will be possible to load these data libraries into a suitable computer-readable form, making these comparisons easier and more reliable. We have established computer-based standard data files for FTIR, TGA, and XRPD techniques, and we plan to expand these files to include other characteristics and attributes that will further serve to identify and define the products. This will require the determination in some instances of whether two products are the same or different at a level of sensitivity of parts-per-million or lower. With these levels of sensitivity, such occurrences as unapproved changes in components or formulations will be more easily and accurately determined. With such information, the investigational resources of the agency may be better focused on potential problem areas, leading to higher levels of compliance with the law.

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⁷ For example. see M. Otto. *Anal. Client.* 62, 797A-802A (1990).

⁸ For example. see L.J. Crofford et al.. *J. Clin. Invest.* 86, 1757-1763 (1990).

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