

This article presents an approach that incorporates real time monitoring that can be used as a quality and security measure, by establishing and monitoring a quality threshold.

Risk and Reputation: A Science and Risk-Based Approach to Brand Protection

by Gary E. Ritchie, Emil W. Ciurczak, Sharon Flank, Stephen W. Hoag, and James E. Polli

Introduction

Economically motivated adulteration threatens the drug supply through counterfeiting, diversion, and tampering. Current approaches tend toward external protection mechanisms. This article shows an approach that incorporates real time monitoring that can be used as a quality and security measure, by establishing and monitoring a quality threshold. New data on the ease of incorporating a low cost, rapid, non-invasive, and non-destructive quality measurement system in real time, in the field at a pharmacy point of dispensing, is presented. A side benefit of the proposed science and risk-based approach is that brand protection expenditures may then be refocused on maintaining high product quality as a brand distinguishing feature.

Quality Beyond Manufacturing

There is increasing pressure on companies to answer questions about quality anywhere in the supply chain. Areas of concern also include contaminated and non-conforming raw materials. Optimally, existing quality processes could

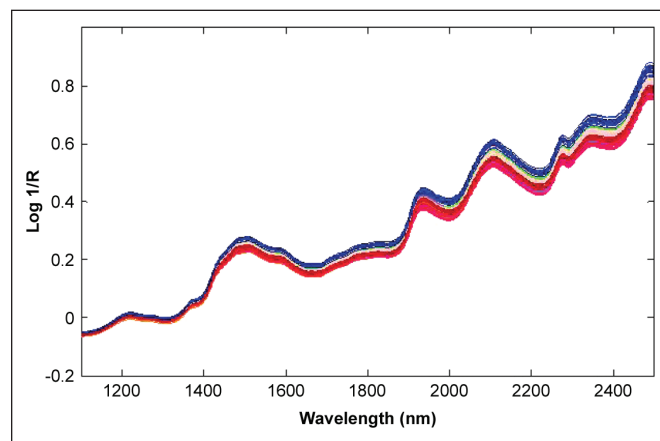
be leveraged as a predictor, monitor, and brand protection system.

Quality approaches focus on limiting cost and reducing waste by improving processes. These principles are not limited to the pharmaceutical industry; lean manufacturing and Six Sigma are now ubiquitous. Catching flaws as early as possible, preferably in the design stage, makes them inexpensive to fix. The simplest recitation of this rule is, perhaps, measure twice, cut once. In practice, this is taken to mean establishing a design space that embraces formulation composition.

Manufacturers who adopt quality-based brand protection gain better control of the supply and advance in competitiveness and quality, not only over their competitors, but over counterfeiters as well. Quality at delivery is what matters. If there are no defects in the product from the manufacturing site, but the customer receives a counterfeit or adulterated version, the quality process has failed, and the company may follow. Not only can quality be built in, but security can be built in too.

First, data are presented on existing variation in a commercial product, Norvasc. It is established that the current variability is low enough to permit exploration of intentional variation as a marking mechanism. Next, an efficient marking method is presented that allows for product, brand, and dose identification that can evolve in case of threat from counterfeiters and diverters. It uses data from the design space and shows how to exploit controlled intentional variation within the US Food and Drug Administration (FDA) Scale-Up and

Figure 1. The Norvasc raw spectral plots (N = 150) show tight uniform spectra, indicative of very low variability of the commercial product.



Post-Approval Change (SUPAC) parameters. Finally, data from experiments in a retail pharmacy is presented, showing the practicality of real-time testing by non-experts, at the point of dispensing, using a portable spectrometer.

Spectral Fingerprinting

In order to use point-of-dispensing quality monitoring, a baseline must be established. The baseline is established by modeling the spectra from the existing product. Spectroscopy can be used to record a spectral fingerprint of that product and then check for identical spectral matches at the point of dispensing.

The first question to be addressed is that of commercial variation: is the quality control sufficient in the standard commercial product? How much variation across batches is seen in spectroscopic testing? For this study, 12 lots of Norvasc 10 mg were used, with 15 samples taken from each lot. This plot in Figure 1 shows five different lots of Norvasc, tested on Foss NIRSystems Rapid Content Analyzer. Samples were placed into sealed glass scintillation vials and scanned in reflectance mode; each sample was scanned 62 times and averaged into one spectrum; the wavelength range was 400 nm to 2500 nm with 2 nm spectral resolution. The raw spectral data were converted to log 1/R followed by 2nd derivative pretreatment using Foss's Vision software package.

Intentional Variation Experiments: Scale-Up and Post-approval Changes (SUPAC)

The FDA allows for a range of component and composition changes in the manufacturing of products, without onerous regulatory requirements. The Center for Drug Evaluation and Research (CDER) publishes a series of monographs in its "Guidance for Industry" series.¹ Its monographs "Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls: In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation" (SUPAC) deal with allowable changes in various dosage forms and reporting requirements.² Level 1 changes to excipients are those that are unlikely to have any detectable impact on formulation quality and performance; regulatory filing documentation of a Level 1 change is limited to the Annual Report. Level 1 changes are capped at 5%. Comparable European limitations on excipient changes (Type 1A) are 10%.³

In case of severe counterfeiting or diversion activity, or highly valuable product, an intentional variation fingerprint may be introduced for definitive identification. This fingerprinting method is optimized for today's contract manufacturing environment: it is possible to introduce a separate fingerprint or set of fingerprints for each contract location, making diversion easier to spot.

In the intentional fingerprinting experiments described, SUPAC Level 1 changes are used as a potential approach for tagging authentic product, in order to avoid counterfeiting and facilitate the detection of counterfeiting through spectroscopy. This approach avoids the use of a taggant that is fixed or one included in the formulation for the sole purpose as a taggant. The formulation-as-tag approach is less detectable, more nimble, and more cost-effective; it also avoids potential consumer concerns about ingesting nanoparticles or allergens.

Materials

The following drug substances and excipients were used as received: aspirin (Spectrum; Gardena, CA), prednisone (Sigma; St. Louis, MO), indomethacin (Spectrum; Gardena, CA), acyclovir (Spectrum; Gardena, CA), microcrystalline cellulose (Emocel 90M, Mendell; Patterson, NY), magnesium stearate (Spectrum; Gardena, CA), croscarmellose sodium (FMC Biopolymer; Princeton, NJ), starch (Lycatab C, Roquette; Lestrem, France), and lactose monohydrate (Super-tab, The Lactose Company; Hawera, New Zealand).

Component	Formulation A1 (mg/tab)	Formulation A2 (mg/tab)	Formulation A3 (mg/tab)
Aspirin	325	325	325
Microcrystalline cellulose	73	83	63
Magnesium stearate	2	2	2
Total Weight	400	410	390

Table A. Composition of Aspirin formulations.

Component	Formulation B1 (mg/tab)	Formulation B2 (mg/tab)	Formulation B3 (mg/tab)
Prednisone	5	5	5
Microcrystalline cellulose	94.5	94.5	94.5
Magnesium stearate	0.5	0.75	0.25
Total Weight	100	100.25	99.75

Table B. Composition of Prednisone formulations.

Component	Formulation C1 (mg/tab)	Formulation C2 (mg/tab)	Formulation C3 (mg/tab)
Indomethacin	25	25	25
Microcrystalline cellulose	71.5	74	69
Croscarmellose sodium	3	2	4
Magnesium stearate	0.5	0.5	0.5
Total Weight	100	101.5	98.5

Table C. Composition of Indomethacin formulations.

Component	Formulation D1 (mg/tab)	Formulation D2 (mg/tab)	Formulation D3 (mg/tab)
Acyclovir	200	200	200
Microcrystalline cellulose	113.26	120.26	106.26
Starch	35	27.99	41.99
Magnesium stearate	1.75	1.75	1.75
Total Weight	350	350	350

Table D. Composition of Acyclovir formulations.

Formulation Methods

Three tablet formulations were designed and evaluated for each of four drugs, such that 12 formulations were made. The four drugs were aspirin, prednisone, indomethacin, and acyclovir, and are denoted as drug A, B, C, and D, respectively. The drugs differ in their therapeutic uses, physicochemical properties, spectral properties, and dose ranges. For each drug, three tablet formulations were fabricated. Tables A to D describe the composition of the 12 formulations and refer to formulations A1, A2, A3, B1, etc. In each table, the first formulation is denoted the reference formulation (i.e., A1, B1, C1, and D1 are reference formulations). For each drug, the formulations were varied within the SUPAC Level 1 tolerance by varying one or more excipients, relative to the reference formulation, resulting in the second and third formulations (i.e., formulations A2 and A3 were variants for formulation A1; formulations B2 and B3 were variants for formulation

B1). Second derivatives were plotted for Figures 2 to 5 to highlight the NIR differences in the formulations.

Variant formulations were attained through the following changes, relative to the reference. For aspirin, microcrystalline cellulose was increased and decreased. For prednisone, magnesium stearate was increased and decreased. For indomethacin, microcrystalline cellulose and croscarmellose sodium were simultaneously varied. For acyclovir, microcrystalline cellulose and lactose monohydrate were simultaneously varied. In some cases, the tablet weight changed.

Near-Infrared (NIR) Spectroscopy Methods

The formulations were scanned and analyzed by the Rapid Content Analyzer. The following test conditions were used. Samples were placed into sealed glass scintillation vials and scanned in reflectance mode; each sample was scanned 62 times and averaged into one spectrum; the wavelength range was

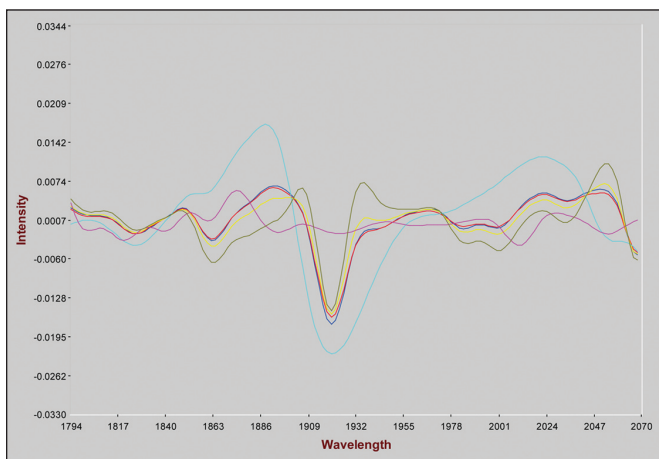


Figure 2. Second Derivative of Aspirin formulations where formulations A3 (yellow), A1 (blue), and A2 (red) contained increasing amounts of microcrystalline cellulose; the intensities around 1995 nm and 2055 nm reflect NIR differences of the formulations.

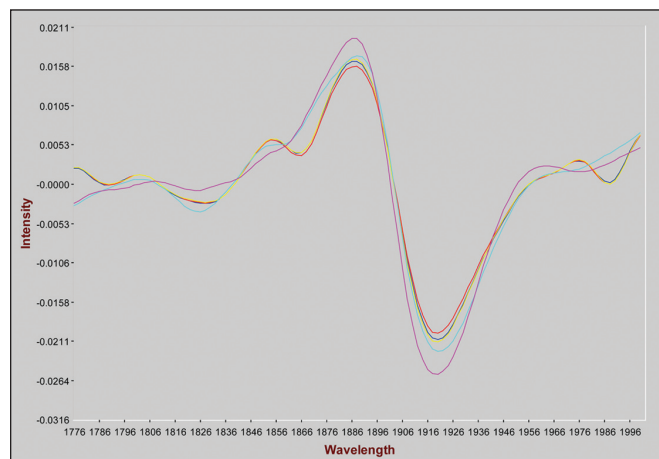


Figure 4. Second Derivative of Indomethacin formulations where formulations C3 (yellow), C1 (blue), and C2 (red) contained increasing amounts of microcrystalline cellulose; the intensities around 1890 nm and 1920 nm reflect NIR differences of the formulations.

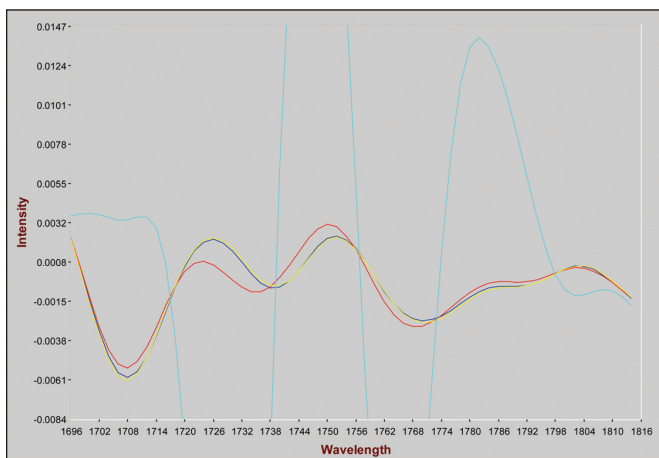


Figure 3. Second Derivative of Prednisone formulations where formulations B3 (yellow), B1 (blue), and B2 (red) contained increasing amounts of magnesium stearate; the intensities around 1705 nm as well as the regions between 1725 to 1735 and 1735 to 1790 nm reflect NIR differences of the formulations.

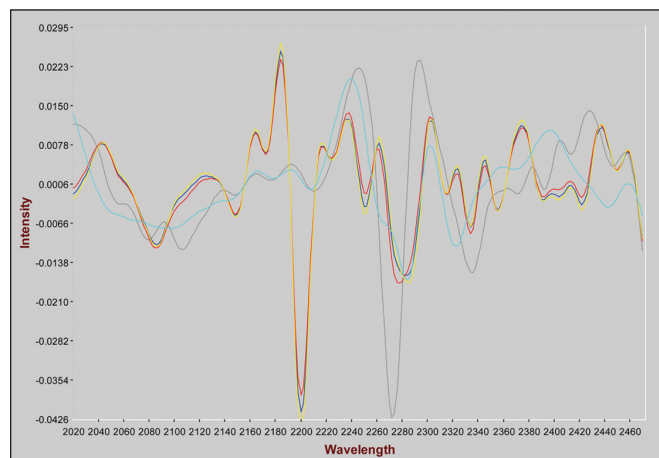


Figure 5. Second Derivative of Acyclovir formulations where formulations D3 (yellow), D1 (blue), and D2 (red) contained increasing amounts of microcrystalline cellulose as well as decreasing amounts of starch; the intensities around 2175 nm, 2205, and 2225 nm reflect NIR differences of the formulations.

400 nm to 2500 nm with 2 nm spectral resolution. The raw spectral data were converted to log 1/R followed by 2nd derivative pretreatment using Foss's Vision software package.

Testing at the Point of Dispensing

Most manufacturers do not worry about counterfeits during the production process; however, the growth of contract manufacturing and other outsourcing suggests that it is prudent to verify incoming raw materials. Labeling errors highlight the importance of verifying the drug itself, not just the label: Pfizer's prostate cancer drug, Finasteride, was identified on some bottles as the anti-depressant Citalopram. Upsher-Smith's mislabeled Jantoven warfarin sodium was discovered by a retail pharmacist, who identified 10 mg tablets in a bottle labeled with the 3 mg dosage. Qualitest's hydrocodone bitartrate and acetaminophen tablets were found labeled as phenobarbital.⁴

There are several handoffs between production and the patient, and each of them provides an opportunity for counterfeiting and diversion. Even e-pedigree protects only the packaging, and it may be subject to bribery or blackmail. China Daily recently reported the sale of empty packages, complete with anti-counterfeiting, from hospitals, to be refilled with fakes.⁵ There is an emerging consensus that the best protections are those that are closest to the consumer, preferably in the hands of a pharmaceutical professional. In a market with major counterfeiting issues, consumer verification (such as SMS codes to text to a central authority) may be useful. In the U.S., several major pharmacies (e.g. Target, Walmart, CVS) include a description of the dose form on the vial. In informal tests, less than 10% of the population is even aware those descriptions are there. Thus, American consumers are better protected by pharmacists than by even simple mechanisms that require their attention.

Experimental: Testing at the Point of Dispensing in a U.S. Pharmacy

As a policy matter, a national joint library of spectra would be useful, but would require a degree of coordination and disclosure that might be difficult to achieve in the short run. Spectra do not reveal quantitative formulation details, but manufacturers may be reluctant to endorse their release nonetheless. Other options include manufacturer-by-manufacturer tests, in which, say, Pfizer's field testers spot-check only their own products, including optional fingerprinting as described above. Alternatively, a single pharmacy, pharmacy chain, repackager, or hospital may test samples against its own library.

Method

At RiverRx, an independent pharmacy in Bethesda, Maryland, following the procedure standard in U.S. pharmacies, a pharmaceutical technician takes the prescribed drug from a supply shelf and fills a vial with the appropriate number of tablets or capsules. Filled prescriptions (the original large container, the prescription, and the vial to be dispensed) sit in a plastic basket for several minutes, waiting for verification

by the supervising pharmacist. Those minutes constitute a theoretical time window for low-impact in-pharmacy testing. In that time, either the whole vial can be tested or as performed in this study, individual tablets/capsules can be retrieved from the vial. Sample presentation was studied by sampling directly or by the use of a variety of tablet holding mechanisms attached to the spectrophotometer, and it was concluded that a tablet holder enhanced results by reducing sampling variability.

The following test conditions were used: samples were tested using a sample holder and scanned in diffuse reflectance mode. The wavelength range was 1600 nm to 2400 nm, with pixel spacing of 8 nm and optical resolution of 11 nm. Thermo Scientific microPHAZIR software, version 1.0.3, was used to scan and monitor collection of the spectra. For chemometric analysis, Thermo Scientific Method Generator, version 3.101 R2, was used to model and predict spectra; Umetrics SIMCA-P+ 12, version 12.0.1.0, was used to investigate preprocessing of the spectra and create plots in conjunction with Method Generator.

	Dosage Amt (mg)	Manufacturer	Lot	Expiry Date
Ambien CR	12.5	Sanofi (France)	0T025	(Exp 09_2013)
Ambien	5	Sanofi (Hungary)	BC16H	(Exp 12_2012)
Atenolol	50	ZyGenerics	MK4431	(Exp 04_2012)
Ciprofloxacin	500	Ivax for Teva	BFB22A	(Exp 02_2012)
Lipitor	10	Pfizer (Puerto Rico)	V101739	(Exp 10_2013)
Lipitor	40	Pfizer	646090	(Exp 08_2013)
Lipitor	80	Pfizer (Puerto Rico)	V101145	(Exp 07_2013)
Lipitor	80	Pfizer (Puerto Rico)	V101719	(Exp 10/2013)
Methadone	10	Mallinckrodt	5771P77026	(Exp 08_2012)
Methadone	10	Mallinckrodt	5771P77093	(Exp 08_2012)
Methadone	10	Roxanne	064009A	(Exp 02_2013)
Omeprazole	20	Dr. Reddy	C006738	(Exp 09_2012)
Synthroid	100	Abbott	96010A8	(Exp 02_2012)
Synthroid	175	Abbott	92173A8	(Exp 11_2011)
Synthroid	200	Abbott	95222A8	(Exp 02_2012)
Synthroid	25	Abbott	81070A8A	(Exp 11_2010)
Synthroid	75	Abbott	96003A8	(Exp 02_2012)

Table E. Drugs tested at the retail pharmacy.

Instrument

The initial round of tests used a portable near-infrared spectrometer, the microPHAZIR from Thermo Scientific. Follow-on experiments are under way using a portable Raman spectrometer from Real-Time Analyzers as well, and preliminary results suggest high ease of use and good quality, with the exception of some laser damage on gelatin capsules. This can be ameliorated by investigating shorter acquisition times. Care must be taken in obtaining spectra, particularly with portable units, in order to minimize sampling variance and noisy spectra.

Samples

For testing at the pharmacy, tablets and capsules that RiverRx commonly dispensed were selected, with the focus on those which come in more than one dose or from more than

one supplier. As shown in Table E, seven formulations were tested, covering 12 dosage levels and seven manufacturers. Three spectra were taken from each of 18 containers for a total of 54 observations; three outliers were discarded, yielding 51 observations. Figure 6 shows Savitsky-Golay Second Derivative Plots generated from those observations, and Figure 7 shows the overall success of the spectroscopic verification test.

Results

If quality is not confirmed near the customer, quality may not be delivered. The feasibility of point-of-dispensing testing is demonstrated by the RiverRx pharmacy study.

The testing should be a full profile, not a single-ingredient test that could be adulterated, as the scandals with diethylene glycol, melamine, and heparin remind us. It is believed that

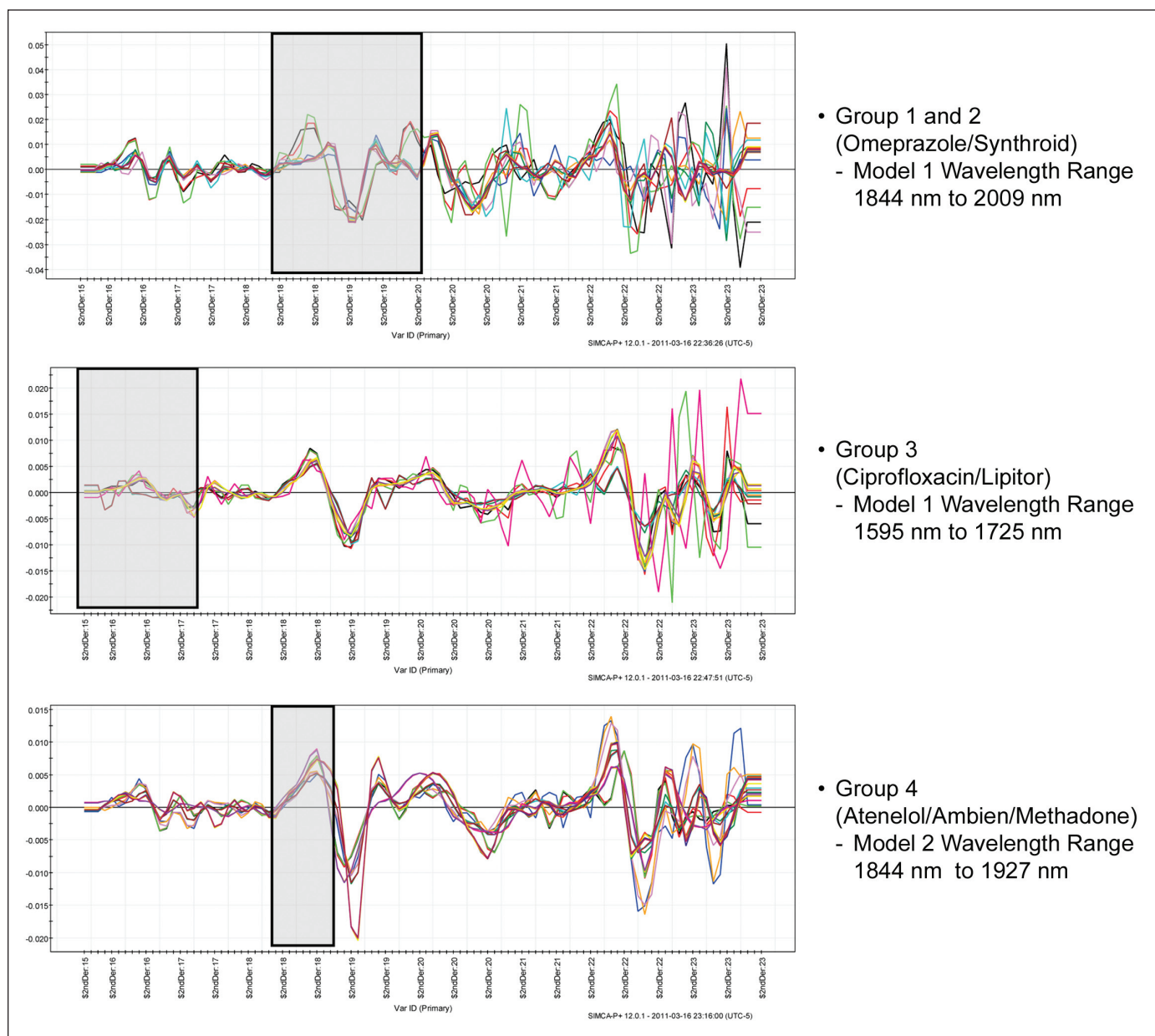


Figure 6. Savitsky-Golay Second Derivative Plots were generated, using nine point and five point second order polynomial and wavelength selection to preprocess the data for models 1 and 2 respectively.

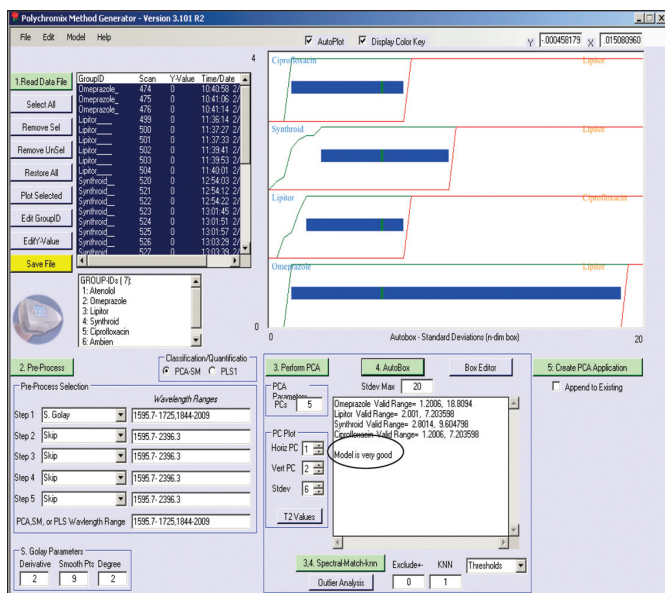


Figure 7. The pharmacy data illustrate that it is possible to distinguish right drug, right dose, with unintrusive spectroscopic tests performed within the workflow of a retail pharmacy.

the most secure method in the long run is unit dose testing at the point of dispensing via spectroscopic analysis. It offers the best protection to the patient for its ease of operation, speed and low cost, and for delivering a rapid, non-invasive, non-destructive chemical analysis of pharmaceuticals. The feasibility of intentional spectroscopic fingerprinting and analysis is demonstrated in the studies presented above.

Discussion

The situation with anti-counterfeiting and quality in 2012 appears to parallel the general manufacturing problems of a decade ago, outlined in Rathore and Winkle's exploration of science- and risk-based approaches and biologics:

"In 2000, the suboptimal state of drug manufacture and the FDA's outmoded review process had several undesirable consequences for drug regulation. As far as industry was concerned, although the quality of the products was adequate, there was a hesitation to implement new technologies because it was unknown how regulators would perceive such innovations. Many pharmaceutical companies also seemed to place little emphasis on manufacturing and its problems although the amount of product waste as a result of mistakes in manufacturing was high. In some cases, the waste was reported to be as much as 50% of the product manufactured. Also, much of the information developed or at least shared with the FDA was empirical. There appeared to be an inability to predict effects of scale-up on the final product as well as an inability to analyze or understand root causes for manufacturing failures. Furthermore, the industry had become much more global and the differences in how products were regulated from region to region lengthened preparation time and created additional paperwork to meet regulatory requirements."⁶

In fact, the approach presented in this article may be applicable to biologics as well. Counterfeit biologics have

appeared in the marketplace, and doubtless we can expect more in the future. With biologics, the variability may come from the drug substance itself, not the formulation. Process control is harder to define, and quality attributes are defined later in the process.⁷ Nonetheless, an end-to-end approach to quality may still offer rewards. Genentech, for example, recently noted that science- and risk-based approaches can help with approval time and inspections.⁸

Most manufacturers have already seen the advantages of spectroscopic testing for incoming raw materials since testing through the bin liner allows much faster results and avoids the need for a clean room process. As an aside, it should be noted that there is nothing inherent in spectroscopic quality monitoring that limits it to batch processing rather than continuous manufacturing. In-line use of spectroscopy for PAT helps reduce waste.

Quality production and point-of-sale verification are linked. However, the link has not extended from "We manufacture quality products," all the way to "We deliver quality products," focusing instead on separate, packaging-based anti-counterfeiting measures with separate costs.

Conclusion

If what the customer receives is inauthentic or mistreated product, it does not matter how good the manufacturer's quality processes are.

The last-mile problem affects every part of the supply chain. Manufacturers want control over distribution, but wholesalers and retailers stand between the manufacturer and the customer. The dispensing pharmacist is truly the guardian of the last mile. These experiments show that control can be provided to the pharmacist with a unique spectroscopic analytical model.

The pharmacist believes the label, believes in its quality promise. Our field results show added value to the pharmacy – no mixups, no tampering, no counterfeiting. The use of a rapid, non-destructive test has applications throughout the supply chain. Quality assurance procedures incorporate tested ingredients, verified suppliers, and the last mile. These results show the link between the manufacturer and quality: instant verification, linked back to the manufacturing database.

Quality optimization conflates two worthy goals: delivering the best possible product at the least cost with the least waste, and getting safe product all the way to the customer without problems or imposters in the supply chain. This conflation of benefits helps make the business case for science- and risk-based approaches to brand protection. Intentional variation as a marking mechanism can generate a quality fingerprint that is easily monitored throughout the supply chain. Furthermore, the science- and risk-based approach aligns anti-counterfeiting expenditures with current Good Manufacturing Practice (cGMP), enhancing return on investment.

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About the Authors



Gary Ritchie, M.S. is Director of Scientific Affairs for InfraTrac, providing leadership in the creation, coordination and delivery of anti-counterfeiting solutions, hospital verification system setup, analytical instruments, and consultation, training, and support programs and services. He has substantial expertise in developing, directing, and coordinating

innovative analytical solutions in pharmaceutical analysis. He is the former Scientific Fellow for Process Analytical Technology (PAT) for the United States Pharmacopeia, Documentary Standards Division. In that capacity, he assisted in the development of process analytical policy for the USP. For General Chapters, Pharmaceutical Waters, and Statistics Expert Committees, he had oversight over the development, revision, and maintenance of more than 30 general chapters and monographs that these expert committees support. He coordinated with government and industry stakeholders on compendial analytical, pharmaceutical waters, and statistical policies. As a lead investigator in the Applied Compendial Research Group, he developed and implemented experimental protocols for spectroscopy, pharmaceutical water, and statistical experiments, especially using multivariate analysis. He conducted multi-laboratory studies with US FDA and private laboratories to develop reference standards, conducted inter-laboratory studies in Near Infrared (NIR) Spectroscopy on the construction of NIR spectral libraries on multiple NIR spectrophotometers across multiple laboratories for the

detection and identification of counterfeit pharmaceuticals. He chaired the ASTM E13.11 subcommittee on Multivariate Analysis and is a former member of ASTM Committee E55 on Pharmaceutical Application of Process Analytical Technology. He serves on the Editorial Advisory Boards of *Pharmaceutical Manufacturing* and *American Pharmaceutical Review*. He was co-developer and co-author of several pharmaceutical analysis process measurement patents using spectroscopy. His multi-disciplinary expertise includes current good manufacturing practices, all facets of FDA product and process regulatory compliance documentation, validation, and data submission. He received his BS and MS from the University of Bridgeport, Connecticut. He can be reached by telephone: +1-240-367-7125 or by email: gritchie@infratrac.com.

InfraTrac, 425 Old Oak Place, Thurmont, Maryland 21788, USA.



Emil W. Ciurczak has advanced degrees in chemistry from Rutgers and Seton Hall Universities. He's worked in the pharmaceutical industry since 1970. In 1983, he introduced NIR spectroscopy consulting for Technicon (Bran & Leubbe), NIRSystems (FOSS), CDI Pharma, Infrared Fiber Systems, Brimrose, and Buchi. Most research was on pharma-

ceutical applications of NIR where he has published more than three dozen articles in refereed journals, more than 150 magazine columns, and presented more than two hundred technical papers. Ciurczak is Contributing Editor for *Pharmaceutical Manufacturing*. He has written and edited in "Handbook of NIR Analysis," "Pharmaceutical and Medical Applications of NIRS," "Molecular Spectroscopy Workbench," and chapters on NIR applications to life sciences. Ciurczak sits on several magazine editorial boards, is active in SAS, is a founder of the Council for NIRS, and was the 2002 chair for IDRC (Chambersburg Conference), and won the Achievements in NIR award for EAS (2007). He consults for various companies, was a member of the PAT committee for FDA, and is a member of the PAT Advisory Committee to the USP. He has taught at numerous colleges.



Dr. Sharon Flank founded InfraTrac in March, 2006. Her management expertise reaches back to 1981, managing scientists, academics, and software engineers. She has led technical efforts for successful commercial products. She spent 10 years at SRA International, where she wrote the company's first patent and helped create companies later sold

to AOL and Kodak. As Chief Technology Officer of eMotion, Inc., she turned around a team of 44 developers and guided them to their first of many on-time software releases for an Internet-based commercial product. Flank is a frequent speaker on anti-counterfeiting and medication safety. She received her PhD from Harvard and her AB from Cornell. She can be contacted by telephone: +1-202-251-4648 or email: sflank@infratrac.com.

InfraTrac, SSIC, 8070 Georgia Ave., Ste. 415, Silver Spring, Maryland 20910, USA.



Dr. Stephen W. Hoag is a tenured Professor at the University of Maryland School of Pharmacy. He has written dozens of papers and holds several patents in pharmacy science, focusing on formulation. He has been working with near-infrared spectroscopy for several years. Research areas include sustained release tablet formulation, dissolution testing,

mathematical modeling of tablet compaction, design of tablet machine instrumentation, PC-based data acquisition systems, computer-aided manufacture, and formulation and testing of nutritional supplements; use of mass transport theories to mathematically model calcium alginate gel formation and diffusion of bioactive molecules from alginate gels; prenatal vitamin formulation; and thermal analysis of polymers used in film coating. He received his BS in biochemistry in 1982 from the University of Wisconsin Madison, and his PhD in pharmaceuticals in 1990 from the University of Minnesota, Twin Cities. He can be contacted by telephone: +1-410-706-6865 or by email: shoag@rx.umaryland.edu.

University of Maryland School of Pharmacy, 20 N. Pine St., Baltimore, Maryland 21201, USA.



Dr. James E. Polli holds the Ralph F. Shangraw/Noxell Endowed Chair in Industrial Pharmacy and Pharmaceuticals at the University of Maryland School of Pharmacy. He received a BS in pharmacy from the Philadelphia College of Pharmacy and Science and a PhD in pharmaceuticals from the University of Michigan. Dr. Polli's research interest revolves

around the performance and pharmaceutical quality of orally administered medicines. His two main research interests are maximizing oral bioavailability and developing public quality standards for oral dosage forms. He has published in the areas of dissolution and formulation, drug intestinal permeability, oral bioavailability, in vitro - in vivo correlation, and bioequivalence. He serves as AAPS PDD Chair-Elect, Co-Chair of the FIP BCS Working Group, member of the WHO Special Interest Group on BA/BE, and the USP Expert Committee on Biopharmaceutics. He is an Editorial Board member of *Journal of Pharmaceutical Sciences*, *Molecular Pharmaceutics*, *Pharmaceutical Research*, *European Journal of Pharmaceutical Sciences*, *AAPS PharmSci*, and *Pharmaceutical Technology*. Polli has received the AAPS New Investigator Award in Pharmaceutics and Pharmaceutical Technology. He is a licensed pharmacist and teaches professional pharmacy students and graduate students. He can be reached by telephone: +1-410-706-8292 or by email: jpolli@rx.umaryland.edu.

Ralph F. Shangraw/Noxell Endowed Chair in Industrial Pharmacy and Pharmaceuticals, Health Sciences Facility II, Room 623, 601 W. Lombard St., Baltimore, Maryland 21201, USA. 