May 16, 2008

Andrew C. von Eschenbach
Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
5630 Fishers Lane
Rockville, MD 20852

Re: Technologies for Prescription Drug Identification, Validation, Track and Trace, or Authentication; Request for Information [Docket No. FDA-2008-N-0121]

Dear Commissioner von Eschenbach:

Cellular Bioengineering, Inc ("CBI") welcomes the opportunity to respond to the Food and Drug Administration's ("FDA") request for comments and information regarding technologies used for the identification, validation, tracking and tracing, and authentication of prescription drugs. CBI specializes in high technology applications and has developed a microtag identification and authentication technology which it believes will prove to be of high utility in combating drug counterfeiting and diversion.

The FDA issued its Request for Information pursuant to the statutory mandate in Section 913 of the Food and Drug Administration Act Amendments of 2007 ("FDAAA") that the Secretary of Health and Human Services "develop standards and identify and validate effective technologies for the purpose of securing the drug supply chain against counterfeit, diverted, subpotent, substandard, adulterated, misbranded, or expired drugs." In discharging this responsibility, the Secretary was directed to "prioritize and develop standards for the identification, validation, authentication, and tracking and tracing of prescription drugs." Congress required that the standards promulgated by the Secretary must address "promising technologies" which were defined in the statute as radio frequency identification technology, nanotechnology, encryption technologies, and other track-and-trace or authentication technologies.

As these comments will demonstrate, CBI's microtag identification and authentication technology fits squarely within the types of technologies which Congress directed the FDA to include in its standards. For this reason, CBI respectfully

requests the FDA to ensure that any standards which it develops accommodate the company's microtag technology. Furthermore, as the FDA identifies and validates "effective technologies" to prevent counterfeiting, diversion, or the introduction of unsafe or ineffective drugs into the supply chain, CBI asks that its technology be so identified and validated.

Prescription Drug Counterfeiting

It is beyond dispute that counterfeiting and diversion of prescription drugs has reached epidemic proportions worldwide. The Center for Medicine in the Public Interest estimates that counterfeit drug sales will reach $75 billion globally in 2010, an increase of more than 90% from 2005. [1] In 2006 the World Health Organization estimated that 10% of global pharmaceutical commerce will be counterfeit, and that number is expected to double by the year 2010 as international criminal organizations become more sophisticated. [2]

The Organization for Economic Cooperation and Development ("OECD") released a white paper in 2007 entitled "The Economic Impact of Counterfeiting and Piracy" which reported on a thorough examination of the worldwide counterfeit business. It concluded that illegal organizations will reap billions of dollars each year from the sale of counterfeit products, including prescription medicines.[3] The OECD study also described the increasingly sophisticated distribution channels which counterfeiters utilize:

> Counterfeit and pirated products, previously distributed through informal markets, are infiltrating legitimate supply chains, with products now appearing on the shelves of established shops. Internationally, free trade zones, which are areas where international traders can store, assemble and manufacture products that are moving across borders with minimal regulation, are of increasing concern. Passing merchandise through such zones provides opportunities for parties to "sanitize" shipping documents in ways that disguise their original point of manufacture. They also allow parties to essentially establish distribution centers for counterfeit and pirated goods, with little or no IPR-related enforcement actions taken. Within the zones, goods can be repackaged with counterfeit trademarks, prior to being exported to other economies, and place of origin can be falsified to reduce enforcement scrutiny at their destination.

The OECD report also described how the Internet has facilitated counterfeiting operations:

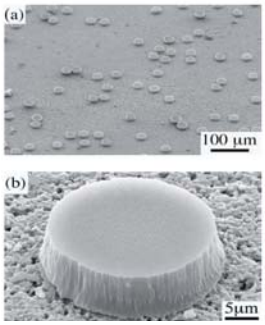
> The Internet has provided counterfeiters and pirates with a new and powerful means to sell their products via auction sites, stand alone e-commerce sites and email solicitations. The online environment is attractive to counterfeiters and pirates for a number of reasons including the relative ease of deceiving consumers and the market reach.

The risks posed by drug counterfeiting operations are not theoretical or speculative. On December 17, 2007, the New York Times [4] reported on the seizure of a large cache of counterfeit prescription drugs from a warehouse inside the free trade zone in the United Arab Emirates. The article observed that the case has a "link to a complex supply chain of fake drugs that ran from China through Hong Kong, the United Arab Emirates, Britain and the Bahamas, ultimately leading to an Internet pharmacy whose American customers believed they were buying medicine from Canada." The article also described the seizure of a half million counterfeit pills of the blood thinning drug Plavix some of which contained cement powder. Another large seizure at Heathrow Airport netted 846 pounds of counterfeit prescription drugs which contained traces of metal.

CBI's Microtag Technology

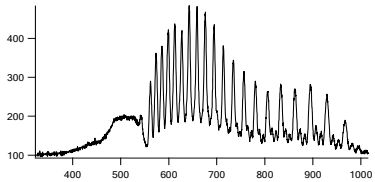
CBI understands and appreciates that there is no single "silver bullet" for alleviating the threats posed by increasingly pervasive, lucrative, and sophisticated drug counterfeiting operations. CBI submits, however, that individual drug tagging and authentication must be an essential element of prescription drug supply chain security. For this purpose, CBI has developed an edible silica microtag technology as a complement to proposed track and trace technologies such as e-pedigree. The optically-read, inexpensive tag has the potential to authenticate an individual medicine, with the option to cryptographically bind to its container for increased security. Watermarking of the silica tags is an additional security option. This is consistent with CBI's premise that a layered and renewable security solution offers the most value and highest level of security for the pharmaceutical industry -– one that can grow with the industry as international criminal organizations become more proficient in quickly defeating drug anti-counterfeiting measures.

At present, the primary means of tracking and verifying medicine is through packaging. However, current tagging and tracking technologies such as radio-frequency identifiers (RFIDs) are not amenable to tagging individual medicines. Package-based systems are inherently weak since the valued product is not the package, but the prescription medication which it contains.



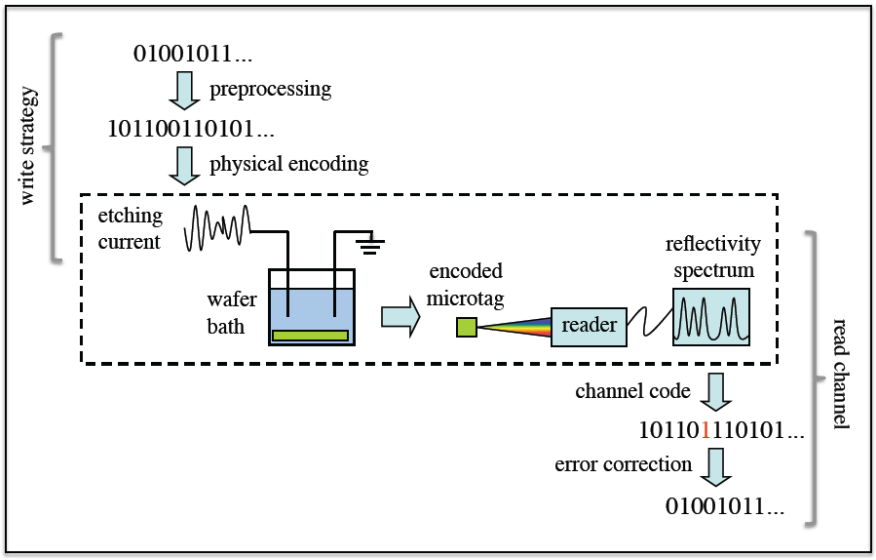
SEM images of porous silicon microtags:
a) 186 × b) 3245 × mag.

CBI's porous silicon microtags are secure, optically-encoded, micrometer-sized tags that can directly mark a medicine. Simple thermal oxidation converts them to silica, generally regarded as safe for human consumption. Use of existing silicon manufacturing techniques allows the cost per tag to be a small fraction of a cent, making widespread tracking of individual medicines feasible. Prototype manufacture has been demonstrated at the University of California San Diego in collaboration with, and under exclusive license to, CBI.



Reflection spectrum of porous silicon microtag exhibiting unique spectral ID that confirms authenticity of pill.

The proprietary technology etches unique spectral barcodes in a porous silicon wafer. The resultant tags contain a complex nanostructure that is programmed during electrochemical synthesis to display a unique reflectivity spectrum. The spectrum can be measured via a hand-held spectrometer, then quickly decoded, decrypted, and authenticated to link to secure details of the product manufacturing history. Information capacity is projected at 80 bits per tag, on par with typical UPC barcodes. The microtag is passive, inconspicuous, and potentially encrypted.



CBI's microtag–reader system encompasses the entirety of the method for embedding information into a microtag, the method for measuring the optical reflectivity of the microtag, and finally the "channel code", or method for mapping the 1's and 0's of binary data into controllable characteristics of the tag's spectral response. The above figure illustrates the basic system concepts from binary data input and encoding to the readout, decoding, and error correction of the stored information.

CBI's microtags offer a range of advantages over existing security solutions. Layered security schemes can include both a code on the packaging and a code stored in the microtag on the contents and combined in what is known as a cryptographic hash. A hash violation would result if someone tampers with either the container or its contents. There is the added possibility for development of a spectroscopic watermark that is not obvious and difficult to reproduce. Hence the security of CBI's microtags can be scaled to suit specific product needs.

Advantages of CBI's Microtag Technology

While proposed standards such as e-pedigree offer solutions for tracking and tracing drug shipments via data collection and management of serialized IDs attached to packaging, there remain sizeable opportunities for such systems to be infiltrated by counterfeiting and piracy. CBI acknowledges that e-pedigree packages with serialized IDs -- along with authenticated e-documents that track movement through the supply, (re)packaging and distribution chain –- raise some hurdles to diversion and counterfeiting. However, they are not foolproof safeguards and can be defeated. For example, under an e-pedigree schema, an unscrupulous repackager would have the opportunity to substitute counterfeit drugs into authenticated and tracked packages, while

diverting the real drugs into illicit markets that do not support e-pedigree standards.

Item-level drug tagging (e.g. a tagged pill), together with proposed e-pedigree standards, could block this potential hole. The fundamental premise is that while documents and packages may be authenticated to a high level of certainty, the most valuable part of the shipment - the drug contents – is often at risk unless each individual medicine can be uniquely tagged and cryptographically tied to its package.

CBI's optical spectrum-encoded, edible silica microtags have the potential to provide a high level of security within the drug distribution chain.

CBI's microtags can be attached to a variety of surfaces, including tablets, capsules, and vials.

The optical spectrum of a tag is its reflectivity measured as a function of wavelength. Data is encoded in spectral features that are not distinguishable by the naked eye; hence, a machine is required to measure the spectrum, which is in itself a security advantage over UPC or other barcodes. The tags are made from silica (SiO_2), which is generally regarded as safe (GRAS), and in common use as an ingredient in many consumable products. Because it can be easily derived from pure silicon, the wealth of knowledge gained in silicon processing over the past 30 years can be leveraged in the controlled production of silica. Recently, a new method of processing silicon wafers into thin, porous silicon films with a controllable density of embedded pores has been developed under license to CBI. [5] This process allows control of the optical properties of silicon films, which carry over into the optical properties of the silica films obtained through oxidation.

Porous silicon films are made by acid-etching a silicon wafer in the presence of an electric current. The etching process creates small pores in the wafer that can be controlled as a function of depth; size and density modulation is achieved by controlling electric current density with time. Although the sizes of the pores vary, over a wide range of current densities the pore size is much smaller than the wavelength of optical light. By modulating the pore density as a function of film depth, the index of refraction of a porous silicon film is similarly modulated. Thus a unique spectral 'signature', or code, can be assigned to a multitude of inexpensive silica tags derived from the parent film. The film, as thin as ten micrometers, is robust enough to require no substrate. The

combination of common processing techniques and minimal material usage allows these films to be produced at very low unit cost. The information is encoded into the depth of the film, so the film can be divided into numerous small tags (tens of micrometers in lateral dimension) without any loss of information, further reducing cost. These tags can be incorporated into a producer’s manufacturing validation process and applied as part of standard solid-drug coatings.

The tags have a demonstrated information capacity of 20 bits with the potential to grow to 80 bits - on par with standard UPC codes - as industry security needs evolve. It is not proposed these tags carry all necessary track and trace documentation, but rather sufficient information to be used in the critical step of authenticating the drug. A portion of the information capacity can be dedicated to error correction for robustness and encryption for security. Additionally, each tag can reference a label in a cryptographically-secure database, where additional information about the item can be stored as desired, such as a link to a secure e-pedigree track and trace system.

Porous silica microtags offer a range of advantages over existing security solutions; this originates in a number of ways. Because an optical spectrometer is required to observe the encoded signal, the barrier to decoding the signal, and even more so reproducing it, is much higher than with a barcode. Layered security schemes can include both a code on the packaging and a code stored in a silica microtag on the contents and combined in what is known as a cryptographic hash. [6] A hash violation would result if someone either tampered with the packaging code or swapped the contents. There is the added possibility for development of a spectroscopic watermark that is not obvious and difficult to reproduce. Hence the security of a porous silica microtag identifier can be scaled to suit specific product needs.

Since the microtags are encoded with information purely in their depth, rather than along their surface, they can be broken into pieces, with each piece still containing all of the encoded information. This makes porous silica microtags suitable for forensic applications, where the tag may be subjected to rough handling. As long as any piece of the tag can be recovered, the information is not lost. So even after the use and disposal of a product, in all but extreme situations a silica microtag may be expected to survive. This is in contrast to RFID, which requires internal electrical connectivity, and UPC codes which require that the surface of the code remain intact.

In addition, the tags may in some circumstances be mixed into an ingredient prior to manufacturing a product, so the potential exists for forensic recovery. Such a system could be useful in products with high resale value to ensure authenticity, or in the case of a product recall.

Conclusion

CBI believes that its microtag technology will be an important supplement to other techniques and technologies designed to secure the prescription drug distribution chain from counterfeit, diverted, and unsafe or ineffective products. For this reason, the technology should be included in the standards which the FDA is developing pursuant to Section 913 of FDAAA. CBI stands ready to assist the agency in anyway possible as it carries out this responsibility.

Respectfully submitted,

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