The evolution of on-dose product identification

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On-dose identification enhances patient safety and differentiates your product. This article reviews traditional methods of adding identifiers to tablets and capsules and discusses new technologies that will increase safety, protect the supply chain, and meet manufacturers’ business needs.

Imagine a world where all tablets and capsules are imprinted, allowing every tablet and capsule in a prescription to be digitally verified as they’re dispensed to patients. With a smart phone, patients anywhere in the world could instantly and at any time confirm they have the correct medicine and dose. A phone app could also help patients manage their regimen, ensuring each medicine is taken at the right time of day and reducing dose duplication.

For pharmaceutical manufacturers, digital printing holds the promise of better brand protection and another layer of deterrence against counterfeiting. In fact, this is all happening right now as new thermal inkjet cartridge systems allow on-demand digital printing of codes onto tablets and capsules that can identify the manufacturing lot, expiration date, and country of origin.

On-dose markings can show—alone or in combination—trademarks, product names, dose strengths, manufacturer name, and data matrix codes. This information helps prevent patients from taking the wrong medication. It also helps prevent dispensing errors at the pharmacy or by caregivers and could reveal counterfeit and expired drug products.

Background

Since the early 20th century, rotary tablet presses have enabled manufacturers to identify their products with debossing. This wasn’t possible with hard shell capsules, and the only option for differentiating them was to use different color combinations for the bodies and caps.

My research indicates that the first use of imprinting to identify a tablet occurred in the early 1950s, even though the technique of printing with pads and rolls was widely used in other industries. Just after World War II, for instance, Ford Gum began using inked rubber rolls to print its name on candy-coated chewing gum to distinguish it from inferior products.

Soon, many pharmaceutical manufacturers began branding their coated tablets with ink. At the time, tablets were coated in pans like those used for candy. In that process, heavy syrup and powder are layered on the tablets to build up a thick, elegant coating. The coating made any tablet debossing illegible or invisible. Printing on the surface of coated tablets thus became a new means of identifying tablets. Imprinted capsules soon followed.

Regulations

Today, it’s hard to imagine that manufacturers of solid oral dosage forms (SODFs) could operate without identifying their products with unique markings. But prior to 1995, there were no regulations. In fact, it was only in 1986 that the FDA began gathering identification data from manufacturers, which they provided voluntarily. FDA’s CDER then made the data available to pharmacists. In that pre-internet age, inquiries were time-consuming, and for some drug products no data could be found. By 2006, more than 30,000 imprints were available online in CDER’s searchable database.

In 1995, the FDA implemented the regulations in 21 CFR Part 206, “Imprinting of solid oral dosage form drug products for human use.” Section 206.10 states, in part, that:

[N]o drug product in solid oral dosage form may be introduced or delivered for introduction into interstate commerce unless it is clearly marked or imprinted with a code imprint that, in conjunction with the product’s size, shape, and color, permits the unique identification of the drug product and the manufacturer or distributor of the product.

Only a few exemptions were allowed, and those are described in Section 206.7. The FDA allows manufacturers some latitude in what imprinting technology they use, and defines imprinted as “marked with an identification code by means of embossing, debossing, engraving, or
Counterfeiting

There are many routes and schemes for falsifying and adulterating medicines and then (re-)introducing them into the supply chain. On-dose identification programs may never halt these crimes, but clearly identifying tablets and capsules independent of their packaging is a big help.

According to a March 2013 report from The Thomsen Group, “The average U.S. retail pharmacy dispenses 78% to 82% of its daily prescription volume from bulk tablets and capsules.” Once the dosage leaves its package and lands on a pharmacist’s counting tray, any traceable link to its lot number, expiration date and, possibly, the name of the manufacturer is severed. Furthermore, some distributors accept returns of drug products that were dispensed from bulk. That raises the risk of expired, substituted, or counterfeit medications entering the supply chain.

Anti-counterfeiting strategies can now go well beyond what debossing and basic printing can provide. Advances in covert identifiers, such as microtags, and the introduction of thermal inkjet printing technologies are helping drug makers improve how they secure their brands and enhance patient safety. Ink manufacturers are developing edible color-shifting inks and UV-visible pigments that require a “black light” to see (photo). Other inks become visible only after exposure to an inert gas. There are also cartridge-based thermal inkjet printers that print not only on the faces of tablets, but also into bisects and detailed debossing. This more complex marking makes counterfeiting more difficult, and legitimacy be can be verified optically at the point of use.

Business drivers

Apart from the regulatory requirements, which identification scheme manufacturers select depends on their goals for branding, marketing, artwork, and even the dosing strategy. In a recent Freund-Vector survey, respondents were equally divided in designating where decisions about on-dose identification are made: Half said the staff in the corporate marketing and half said the staff in formulation development. Certainly, marketing would create the most appealing designs, but every proposal must account for the formulation’s characteristics and manufacturability, including debossing on a tablet press.

The primary reason identifiers are added to SODFs is to prevent people from taking the wrong medication, which can cause injury or death. With the stakes that high, best practice is to consider identification schemes when you start developing the product and that you continue doing so until the product is finalized and the NDA or ANDA is filed.

SODF markings should include text and numerals that are legible and easy to recognize and describe. Keep in mind that patients and others may separate tablets and capsules from their original packaging, perhaps for storage in a daily-reminder pillbox. In such cases, the only means to identify the product is on the dose.

While brand identifiers (logos, symbols, unusual characters, etc.) may be unique and deter counterfeiting, they may also be ambiguous. Imagine a patient, caregiver, or first-responder in an emergency trying to describe the # symbol over the phone, perhaps to someone at a hospital or poison control center. Is it a pound sign, hashtag, number sign, or crosshatch? How about a company logo that “kind of looks like” something different to different people? Ambiguity hampers communication and endangers people’s health.

Removing tablets and capsules from their original packaging—which is common—severs any link to the label and inserts. Only the marking on the dosage form itself enables you or others to identify it.

Digital thermal inkjet printing enables manufacturers to apply machine-readable QR codes onto tablets and capsules. Covert inks activated by UV light are in development and could provide another means to deter counterfeiting.

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Branding: Dress for success!

Pharmaceutical companies strive to differentiate their products from competing products. Innovator brands must also differentiate themselves from the expanding field of generic rivals. A product’s “trade dress”—its physical characteristics, such as shape, size, color, bisects, engraving, debossing, and printing—is a unique combination of features that qualifies as intellectual property protected by law in many countries. These combinations
Identification schemes that involve shape, color, finish, and imprinting help brand and differentiate your product. Unique combinations of features, the product’s trade dress, is usually protected by law.

of characteristics provide tablets and capsules with their own “personalities,” even outside their original packaging. A great example is Nexium, known as “The Purple Pill.”

Methods of identifying SODFs

Which identification technology you choose for your SODF is driven by the content, format, and complexity of the identifiers desired/required to achieve your business needs. There are pros and cons to each option, which include tablet debossing, traditional printing, continuous inkjet printing, thermal inkjet printing, and ultraviolet (UV) laser marking.

Tablet debossing. Traditionally, and even today, debossing tablets at the tablet press remains the dominant and most cost-effective means of fulfilling the basic requirements of tablet identification. It eliminates the need for secondary equipment, which entails additional material handling, validation, batch documentation, and quality control. Designs can combine embossing with debossing, and they can even include a shaped hollow core to provide unique branding. Valium tablets, for example, include a V-shaped void at their center.

Naturally, there are limits to the size and type of debossing that a tablet press punch can provide. Factors include the tablet’s size, the amount of compression force applied, the propensity for defects when certain numbers, letters, or fonts are used, character spacing, tablet shape, the punch cup depth, etc. Many of the issues involved in selecting debossing are discussed in the Tableting Specification Manual, or “TSM,” published by the American Pharmacists Association. Reputable tooling suppliers also offer design services and can evaluate how the proposed punch cup will perform under compression.

Traditional printing. Printing onto finished tablets and capsules with ink enables you to include detailed logos and symbols and to print in multiple colors, increasing the number of possible identification schemes. It’s a mature technology—in use for more than 60 years—and many companies offer machines that print using rubber rolls or inkpads. These printing machines are well supported by ink manufacturers with products that satisfy the various regulatory requirements of different regions around the world.

The basic approach is to transfer ink from an engraved pattern onto a rubber roll or pad and then onto the tablet/capsule. In rotogravure printing, a rubber roll or drum transfers ink from an etched metal cylinder onto the surface of the product. Another technique, commonly known as “Tampo,” transfers ink from a stationary engraved plate onto a rubber pad that “tamps” the surface of the SODF. The two techniques offer similar capabilities and differ mainly in their throughput, which is determined by how the machine handles the product and how quickly the ink dries.

Rotogravure printing was well-known in other industries before pharmaceutical manufacturers adapted it for on-dose identification. It begins with a design roll whose metal surface is chemically etched or machine-engraved to create recessed cells in the desired pattern. The metal surface is either a thin sheet wrapped around a cylinder or is part of the cylinder itself. In operation, the etched cells fill with ink as the design roll rotates through a pan of ink. A stationary “doctor blade” rides on the surface of the roll to remove excess ink, leaving fluid only in the cells. When the design roll contacts a rubber “offset” or “transfer” roll, ink moves from the cells to the surface of the roll, which then transfers the ink pattern onto the product by direct contact.

Tampo printing is essentially a linear stamping process that begins with a stationary etched or engraved metal plate. The plate receives ink from a supply bag or pot and a doctor blade passes over the plate to remove any excess ink. Next, a rubber pad contacts the plate, picking up the ink pattern. The pad then moves into position over an array of oriented SODFs and tamps the ink onto their surfaces.

Inkjet printing. This technology is the most recent method to gain acceptance in the pharmaceutical industry. There are two approaches: continuous inkjet (CIJ) and thermal inkjet (TIJ), both of which are digital “drop-on-demand” techniques. They offer the greatest versatility in terms of printing schemes and colors, complex logos, and machine-readable codes. The only limitations are the print head’s resolution and choice of inks. With either method, you can easily change the print format and/or data sequencing using software. Because both apply ink without contacting the tablet or capsule, inkjet printing offers an alternate to debossing uncoated tablets, some of which are too soft for debossing. Certain orally disintegrating tablets, or ODTs, are one example.

CIJ. With CIJ printing, a recirculating stream of ink is supplied to a nozzle that applies it to the tablet or capsule. Any ink that isn’t used for printing enters a return gutter and flows back to the ink reservoir. To produce the ink droplets, the print head vibrates using a piezoelectric crystal. These are deflected by energized electrodes and impinge on the product’s surface. This happens extremely fast and produces precise, sharp imprints with good resolution. The bulk of the ink used in CIJ
OTC package before purchase to ensure the product won't have harmful interactions with the patient's other medications. Serialization. Seen as the first step toward achieving traceability down to the last saleable unit, serialization of individual doses could be next. After all, if a tablet or capsule is dispensed from a bulk bottle at the pharmacy, isn't that so the last saleable unit? Using the digital, on-demand printing that TIJ offers, it may be possible to achieve that level of traceability.

Beyond the basics of identification

Advances in identification technology, coupled with smart phones and other personal electronics, promise to bring the internet-of-things to pharmaceutical tablets and capsules. That means new possibilities for supporting patient care.

Clinical trials. Printing data matrix codes onto tablets and capsules at the point of dispensing would help identify and track the experimental drug products, comparators, and placebos in double-blind clinical studies. Codes could be read optically by smart phones or other devices and the dispensing data could be transmitted to clinical trial managers in real time. It would even be possible to authenticate that the correct product is being administered to individual patients/subjects.

Drug interaction warnings. Today, warnings about how drug products can interact are provided in lengthy, very fine print on inserts and pharmacists' printouts. The few people who actually read them probably find them difficult to comprehend. With a smart phone, patients could simply scan tablets and capsules to verify their identity and then get data from an online database about potentially dangerous combinations. If a patient's regimen information has been uploaded to a database, it would be possible for him or her to scan codes on an

TIJ. This is the newest approach to printing on tablets and capsules. TIJ printing uses a compact cartridge that operates on a principle similar to that of the cartridges home and office printers use. The cartridges feature an array of miniscule chambers, each with its own electrical heating element. When an electric pulse passes through an element, heat instantly vaporizes ink in the chamber, causing expansion and a rise in pressure, which propels ink droplets onto the product. The ink remains in solution inside the cartridges, which have no moving parts and require no external supply of ink. This greatly reduces volatile organic compounds at the point of use.

UV laser marking. As a digital technology, UV laser marking also allows you to create images using software. The software interfaces with a control system to operate a series of high-speed mirror galvanometers that redirect the laser beam into the desired pattern. Lasers operating in the UV spectrum create their mark by oxidizing an excipient, titanium dioxide, which effects a change in the oxidation state of the titanium. This releases oxygen atoms and changes the excipient's color from white to gray.

UV laser marking provides well-defined, indelible marking, depending on the nature of the SODF surface. Some lasers can mark SODFs after they are sealed in clear blister packaging. One drawback to UV laser marking is that it can only leave a medium-to-dark gray marking. Nonetheless, these markings contrast well with most colors found on tablets, capsules, and softgels.

OTC package before purchase to ensure the product won't have harmful interactions with the patient's other medications.

Serialization. Seen as the first step toward achieving traceability down to the last saleable unit, serialization of individual doses could be next. After all, if a tablet or capsule is dispensed from a bulk bottle at the pharmacy, isn't that SO the last saleable unit? Using the digital, on-demand printing that TIJ offers, it may be possible to achieve that level of traceability.

Doing so would require that the TIJ equipment 1) interface with software that could generate dynamic data matrix codes, 2) interact with the manufacturing site's IT platform, and 3) have the capability to verify each printed code. That would enable the TIJ equipment to print “bottle-level” codes onto tablets or capsules during packaging and aggregate them to the serialized bottle into which they're filled. So long as the products are authenticated along the way, the supply chain is protected, and there is traceability to production lots and expiration dates.
Using data matrix codes, it will be possible to authenticate single tablets and capsules. The codes also enable manufacturers to provide patients, pharmacists, and others complete information about the manufacturer and the expiration date. It may even be possible to uniquely identify each tablet and capsule.

**Figure 1**

Digital printing eliminates ambiguity

a. This tablet is embossed with “463” on the front. The embossing on the reverse can be interpreted as “93” or “E6”.

b. If patients break the tablet at the score, the confusion grows because the “6” in “463” is obliterated. On the reverse, is that a “9” or a “6”? Is it a “3” or an “E”?

c. Using digital thermal inkjet printing, “93” appears on either side of the score on the tablet’s front, and “463” appears twice on the reverse to avoid guesswork. The printing is also easier to read than the embossing.

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