CONNECTED COMBINATION PRODUCTS: US ANALYSIS WITH POTENTIAL IMPLICATIONS WORLDWIDE

Here, Napoleon Monroe, Managing Director, New Directions Technology Consulting, from the US perspective and with an emphasis on human factors, automated identity and regulation, provides an overview of the current status of connected combination products, including points from recent conferences focusing on the topics.

Combination products have become a major feature of pharmaceutical treatment as biotech and other specialty pharma make up an ever larger share of healthcare treatments. Specialty products, which now represent a huge portion of the pharma market, require special care by definition.

Securing the benefits of specialty products by ensuring compliance with treatment regimens, and controlling costs, demands the use of combination products by patients and other non-professionals. Yet use of combination products by the laity brings a high degree of complexity to the approval process. The complexities are largely related to human factors.

Combination products connected to smart phone apps are now reaching the market in the US and abroad. Also, clinical trial approval is no longer enough. Stakeholders are demanding real-world evidence. Service is becoming part of the product value offered by biopharma companies, and the potential for connectivity to play a part in this is clear. Gathering evidence and providing service can be difficult but both present opportunities to assist patients and address some difficult regulatory questions.

There have recently been waves of partnering in the area of connecting combination products, including investment in services, devices and intellectual property. Many different designs are being developed, and numerous business models adopted. More venture capitalists are investing in connected adherence devices too. Global population health management as an industry is expected to grow to US$31.6 billion (£24.7 billion) by 2020,[1] and nearly $200 million was invested in related start-ups last year.

We should expect to see many more wearables and "carryables," including injectors, pens, inhalers, pumps and patches being connected to the Internet of Things (Figure 1). Telemanagement can offer numerous advantages including, for instance, guiding the patient through the placement, refill and use of such delivery systems through their smartphone.

However, the real world is a wild, uncontrollable place. Some regulatory questions about the real world are not easily addressed. Human factors questions arise regarding design, labelling, validations, risk assessment, risk management, change management, training, algorithms built into devices, gamification and even disposal.

The Parenteral Drug Association (PDA) and the Automated (product) Identity and Data Capture (AIDC) community regularly convene with the US FDA to help stakeholders work on regulations and standards for healthcare products. The recent PDA Combination Products Interest Group (CPIG) Conference (May 2017, Bethesda, MD, US) featured a session on connected combination products.

While other conferences include discussion of regulations and some include content on the regulation of connected combination products, the CPIG meeting was an entire day of wide-ranging discussions on combination products – including several hours devoted to

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connectivity. The event was oversubscribed. Senior FDA staff presented and engaged in a lively Q&A. There are still many open questions, and guidances and standards in the works. Connectivity was characterised several times as being a hot topic within both the agency and the industry.

Additionally, presenters at another event, the FDA Unique Device Identification Conference (June 2017, Baltimore, MD, US) provided fascinating insights on unique device identifiers (UDIs) for devices, and automated identity for drug and combination products. Many FDA automated identity initiatives remain works in progress. The FDA UDI conference this year went beyond compliance to the many potential opportunities and rewards related to gathering real world evidence using AIDC (including UDI) as the language for the "source of truth" in healthcare. While the conference title was "UDI" there was discussion on automated identity for drug products. There were suggestions for broadening the scope of the conference and more co-operation between interested organisations.

This article attempts to share some personal observations and analyses from my perspective as a participant in the conferences. I will briefly highlight some of the complex regulatory requirements for combination products and some implications for stakeholders.

As discussed below, while connectivity adds to regulatory complexity in some senses, connectivity may also be the solution for *eliminating* some of the complexity in the real, wild world. Perhaps connectivity and automated identity will have to suffice until automated intelligence matures to address all the ever-changing, real world combinations and permutations.

REGULATORY FUNDAMENTALS

There are developers who do not believe that apps and products such as connected pill boxes are medical devices. Depending on their claims, labelling, and the market and FDA's interpretations, these developers may be correct. However, great care should still be taken with understanding risks and managing the human factors. This is the case even if the app or dispenser is not a medical device. Even low-risk devices such as pill boxes should be well designed and validated to avoid risks.

Some of the regulations, FDA definitions and existing and forthcoming standards relevant to the regulation of connected combination products, including drug delivery systems, are summarised in the boxed text on Page 30.

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Figure 1: Many more wearables and "carryables," including injectors, pens, inhalers, pumps and patches will be connected to the Internet of Things.

Dosing Products, Human Factors, Automated Identity & Regulation

Dosing products used by practitioners may be regulated simply as medical devices or container closure systems. Syringes, sold unfilled, for example, are generally (legitimately) used by healthcare practitioners. Practitioners are trained to use syringes correctly, and use them frequently.

Dosing products, sold filled with drug or biologic products, used by patients, non-professional caregivers or practitioners usually will be regulated as combination products. Most pens and auto-injectors

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SUMMARY: REGULATIONS, DEFINITIONS & STANDARDS

What is a medical device? The FDA states that a medical device is an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including a component part, or accessory which is:

- recognised in the official National Formulary, or the US Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals
- and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolised for the achievement of any of its primary intended purposes.

Note that software can be a medical device.

Now, what is a combination product? FDA defines a combination product as a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product. Under 21 CFR 3.2 (e), a combination product is defined to include:

1. A product comprised of two or more regulated components (i.e. drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labelling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labelling of the approved product would need to be changed (e.g. to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose); or

4. Any investigational drug, device, or biological product packaged separately that according to its proposed labelling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

There is no formal FDA definition of a connected combination product.

What is the US Unique Device Identifier Regulation? In September 2013, FDA issued a final rule to establish a system to identify devices through distribution and use. This rule requires the label of medical devices to include a unique device identifier (UDI), except where the rule provides for an exception or alternative placement. The labeller must submit product information concerning devices to FDA's Global Unique Device Identification Database (GUDID). The primary data carrier is a GS-1 2D barcode. Serialisation is an option.

What are the Drug Supply Chain Security Act (DSCSA), and the requirements for Rx product serialisation? The Drug Quality and Security Act (DQSA), was signed into law on November 27, 2013. The DSCSA is Title II of the DQSA, under which, manufacturers must put a unique product identifier on certain prescription drug packages. Specifically, they must serialise products using a data carrier – a 2D bar code by November 2017 unless FDA delays implementation. The rest of the supply chain has more time before they need to use of the serial numbers. The serial number will be used for product returns and suspect product investigations.

Once products are serialised, manufacturers and other stakeholders can more easily know what product is in which patient's hands. Some manufacturers believe that these regulatory requirements for automated identity (serialisation) can enable improved patient support and supply chain programs. With the expense mandatory, they are positioning to use the big data generated.

What is the UPC code? This is the well-known retail barcode. While UDI and DSCSA are used for tracking, they do not contain cost information, UPC codes are used in National Council for Prescription Drug Programs (NCPDP) standards for claims/reimbursement, rebates and e-prescribing. All of these automated identity initiatives are works in progress at FDA and at the payers. The old National Drug Code (NDC) will eventually disappear.

What is coming in the interrelated new Quality Management Standard, ISO 13485:2016 and the new EU medical device regulation (Regulation (EU) 2017/745, April 5, 2017)? In short more alignment of ISO13485 with FDA regulations and requirements for automated identity. Some UK NHS Trusts appear to intend to introduce automated identity well before the EU implementation dates. There are initiatives in other countries as well.

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are generally used by patients or relatively untrained individuals acting as caregivers. The lack of training for the laity as distinguished from the professional population leads to greater potential for errors in the use of products. The human factors issues become evident when one considers all the variables in the real, wild world.

Patients and caregivers are trained initially, and supplied with instruction sheets, but use their dosing products less frequently, and may not understand or may forget the instructions. FDA could be somewhat less concerned about human factors with syringes for professional use than they are with human factors related to dosing products patient or caregiver use.

These, plus the key fact that the FDA does not regulate the practice of medicine, are the main factors determining the regulatory schemes into which dosing products will be placed. The specifics of the product, the claims made, labelling, content of the submission and the risks associated with use will also determine how strictly the product is regulated.

If used or refilled by the patient or other non-professionals, syringes, pens, auto-injectors, inhalers, transmucosal nasal administration devices, transdermal patches and pumps (refilled by patients) should be considered initially as combination products. Even droppers and spoons which can impact patient outcomes may be regulated as combination products. Filling the reservoir of a pump can be complex. This is borne out by some pump recalls and reported deaths.

These facts argue for better training, instruction and product support for combination products, and connectivity can provide support to help ensure proper use. As with consumer products, instruction at the time of combination product use can be essential to successful use.

Consumer health aids such as most consumer apps and products which the FDA does not now regulate will not be discussed here, except to say that any product on which FDA has decided to exercise regulatory discretion (not to regulate) will not be regulated, unless and until FDA decides not to exercise regulatory discretion.

Political Change

Before last year's US presidential election, Congress passed the 21st Century Cures Act with bi-partisan support. Some sections of the Act may help simplify approvals. There is also further discussion in the new administration that regulations should be simplified. Whatever is decided about simplification, FDA will still be charged with regulating to ensure safety and efficacy. The mandate that a product be safe and effective before introduction leads to many questions in a regulatory review. Regulating algorithms designed to answer all possible situations in the real world becomes very difficult. Many regulatory interpretations and guidances are likely coming in the future. The timing however is unsure.

ROLE OF CONNECTIVITY POST MARKET

As we are waiting for clarity, the importance of addressing the real, messy post-market world grows, as exemplified in a study published in JAMA earlier this year.[2] It found that among 222 novel therapeutics approved by the FDA from 2001 to 2010, 71 (32.0%) were affected by a post-market safety event. Post-market safety events were more frequent among biologics, therapeutics indicated for the treatment of psychiatric disease, those receiving accelerated approval, and those with near-regulatory deadline approval. That post market safety events are common after FDA approval, highlights the importance of continuous monitoring of the safety of novel therapeutics throughout their lifecycle.

A plethora of factors seem to be converging to support the case for, and highlight the potential benefits of, connectivity post market. These include:

- The rise of the specialty sector
- Issues related to laity injection
- The cost of developing specialty products such as biologics (generally 22 times more than small molecules) and their profitability[3]
- Recent approvals of competitive specialty products (for example the epinephrine pen from Adamis Pharmaceuticals (San Diego, CA, US)
- The emergence of biosimilars.

At the PDA CPIG meeting, a question was raised from the floor about the impact of social media on the post-market regulation of combination products. Patients share information with each other in open forums. FDA may receive information directly from patients and FDA programs previously called Signals, Sentinel; now called NEST (National Evaluation System (for health) Technology) will probably mine data. NEST was also a topic at the FDA UDI Conference.

Besides being a tool for classic FDA pharmacovigilance, the serialisation required of pharma by the US Drug Supply Chain Security Act will be used to record combination product use. This will provide data for adjudging comparative efficacy, which will provide information for analysis upon which to base decisions on reimbursement and value based purchasing decisions. It will not be surprising, therefore, if we find pharma serialisation being used in pharma marketing soon, and in patient social media as well.

At the PDA CPIG conference, a discussion of the levels of support for combination products was received with great interest and triggered some thoughts about why telemedicine and medication telemanagement have failed. The human element in human factors can't be eliminated.

Also reported in JAMA, a randomised clinical trial in 53,480 enrolees of a pharmacy benefit manager (PBM), showed basic reminder technologies such as a pill bottle strip with toggles or digital timer cap, to be ineffective compared with a standard pill box.[4] The investigators asked, to what extent three low-cost reminder devices could improve medication adherence among individuals who are

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receiving therapy but are poorly adherent, and found no statistically significant difference in adherence between those in the control group and those who received a reminder device.

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Other factors that should be considered are:

- Hot competition for ownership of the patient relationship and the patient's data
- Fear about providing and possible misuse of data
- Many bright shiny healthcare toys are time consuming, not intuitive, and don't provide perceived value or actionable information
- All sensor-based systems can be fooled. Even with direct observation or a chip on a pill a determined patient can probably fool the system.
- Judgements and the many types of information on patients which can be available in a central monitoring facility are hard to integrate into algorithms.

Future research should therefore focus on effective targeting of interventions and strategies that ensure sustained medication use.

High-support connected options with limited algorithms providing guidance to professionals for their interventions could be the model of the future for high-risk situations. This model allows professional intervention using judgements and other available information on patient situations in real time, as they materialise.

Such judgements, made by licensed professionals practicing medicine, are not FDA regulated. This is the equivalent of a "Genius Bar" (one of Apple's many trademarks) for medication adherence. Service may be costly, but less so than working as we do now in the current uncontrolled, wild, messy world. Even if regulated, this type of information system may be classed as a Medical Device Data system (MDDS) which is FDA Class I and FDA 510(k) exempt.[5] Nonetheless, quality System regulations should still be followed to ensure an accurate system

In the long run, a high-support system may be less expensive and more effective. High support s ystems could even be better for engendering loyalty than direct-to-consumer (DTC) advertisements. Indeed a Wharton expert's research report showed pharma's DTC advertisements: work for "initiates," who, however, on average, are less compliant with treatment; and expand utilisation for entire classes of drugs.[6]

But what about the implications in a value-based, real world evidence environment?

WHAT ARE HCPS SAYING ABOUT CONNECTED HEALTH?

Some medical and pharma practitioners remain sceptical, saying things like:

- We don't/can't get paid for this
- My time is limited, better spent diagnosing/marketing
- I'm already overwhelmed and can't deal with innovations
- I can't be pinged whenever a patient/customer fails to act or wants to chat
- It's EMRs/EHRs all over again. The systems aren't built for our workflow
- How does all this fit into HIPPA? What about privacy?
- Hacking is all over the news. This has to be a security threat
- I've seen some of these toys; they are all worthless
- Patients abandon apps because they are a pain
- The Affordable Care Act is being repealed.

However, most of these points are of course in contention.

Others in growing numbers, are saying: "Connected healthcare is an opportunity!" It could be an opportunity in Medicare/Medicaid (CMS), hospitals, PBMs, payers (including third-party admins), plan sponsors, wellness/PERS providers, community health centres, pharma companies, individuals and patient advocacy groups.

Pharmacy chains are numerous, they're local and are in regular contact with patients. Pharmacists can sell devices and service to other stakeholders. All stakeholders, by definition have an interest in – and many can be paid for – medication therapy management.

CONCLUSION

The evidence that poor adherence and compliance with pharmaceutical therapies are problems worth addressing is now abundant. Numerous examples are cited elsewhere in this issue of *ONdrugDelivery Magazine*. To provide two further examples from the many available, firstly, an Express Scripts 2015 Drug Trend Report updates the estimated US cost of medication non-adherence to $337 billion per year, up from the customarily cited $290 billion annual figure.[7] This increased amount still does not capture all societal costs. Secondly, a November 2016 CapGemini / HealthPrize Technologies report raises estimated global pharma revenue losses due to non-adherence to $637 billion, up from $564 billion in 2012.[8]

Connectivity can provide the solutions the healthcare profession needs, for example:

- Improved outcomes through enhanced compliance
- Information to meet requirements for real world evidence (RWE), demonstration of product value
- A "sentinel" to learn direct information from patients to enable improved service, CAPA, clinical trial completion
- Better understanding of human factors
- Product loyalty

- Added value to biopharma products
- Reduced overall costs for many stakeholders.

This article contains opinions, not advice. Your regulatory advisers can provide specific guidance. These observations are not endorsed by PDA, FDA or other entities. PDA would almost surely welcome your participation in future CPIG conferences.

The author and his clients have commercial interests in medication telemanagement: www.freepatentsonline.com/8149111.html.

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