INTEGRATING CONNECTED HEALTH IN RESPIRATORY: THE MANUFACTURING CHALLENGE

In this article, David Belton, Director, Quentis, highlights an often undiscussed aspect of the move towards connected drug delivery devices, the impact on manufacturing. Using inhalers as a reference point, he runs through several of the concerns and decisions that will need to be addressed for successful mass production of such devices.

INTRODUCTION

For anyone monitoring current drug delivery trends, it is now clear that connected health devices are the next significant change to drive the industry forward. The impacts to patients, payers and healthcare providers has been thoroughly examined with many of the benefits and disadvantages now well understood by the industry as a whole.

What has received less focus is the potential impact to pharmaceutical manufacturing supply chains. This is a topic worth consideration, as the precedent set over the last decade by the ever-increasing integration of electronics into modern life, alongside the rising expectations of patients as informed consumers, is creating a driving force that will likely lead to increased integration of electronics into pharmaceutical manufacturing as well. This article focuses on disposable, multiple-dose drug delivery systems, comprising of mainly respiratory products, such as metered dose inhalers (MDIs) and nasal sprays, rather than reusable refillable systems where manufacturing of electronics and pharmaceuticals can be kept separate.

> "We expect our phones to move invisibly between network coverage and wi-fi and our peripherals to self-install when we plug them in. Extrapolating this trend to connected health, what will a patient expect from a connected medical device?"

PATIENT EXPECTATIONS

Looking beyond the capabilities and needs of a connected health device, one of the most significant trends we have seen in the computer and smartphone arenas over the last 10–20 years is seamless connectivity. We expect our phones to move invisibly between network coverage and wi-fi and our peripherals to self-install when we plug them in. Extrapolating this trend to connected health, what will a patient expect from a connected medical device?

- Simple, automated connection, for example to a smartphone
- The device to be "self-aware", knowing what product it contains, its strength, number of doses remaining, etc.

Simple connection has been addressed through the use of Bluetooth Low Energy (BTLE) and similar technology. We can see this trend in the development of smart insulin pen-injectors with the development from stand-alone "memory" pens with no connectivity, to docking stations and ultimately to modern self-connecting devices.

The second area, having a "self-aware" product, will become more important as connected health becomes more common, particularly for inhalers. This is because asthma and COPD patients will very often carry multiple inhalers, for the following possible reasons:

- They've been prescribed one or more inhalers for maintenance/reliever purposes
- They keep multiple inhalers of the same product in parallel
- Family members use similar products (and each wishes to track his or her own use on one device).

David Belton
Director
T: +44 1920 413 246
E: david.belton@quentis.co.uk

Quentis Ltd

www.quentis.co.uk

While it is well understood from prescribing guidelines that many patients will receive multiple products, the use of the same product in multiple inhalers is also common. For relievers, patients will often hold one at home, one at work and keep one in a bag or pocket. For maintenance therapies, patients will often ensure they get their replacement early, may use them in an *ad hoc* overlap or can also deliberately manage an offset so, for example, they have enough product for a holiday.

In these cases of multiple products and multiple devices, the expectation of connected health is that all of these products will not only be uniquely identifiable, but also clearly identifiable to the patient within an app. This shows how important it is that each inhaler is "self-aware" and capable of indicating key information, such as what type of product it is and how many doses remain, to a phone or other device.

Another probable expectation for increased integration between a drug delivery device and electronics is the ability to deliver additional functionality to patients and healthcare providers, moving beyond recording dose and time to measuring physical use properties, such as orientation, shaking and flow rates, which will likely require additional sensors and therefore deeper integration.

IMPACT ON MANUFACTURING

With a requirement for "self-aware" and easily connected products, this leads to two main conclusions that can be drawn with respect to the supply chain:

- The pharmaceutical and electronic manufacturing processes will become more interconnected.
- There will be a need to program, or otherwise associate, the device with product information within the supply chain.

Interconnected Manufacturing

There are a number of points where the electronic element of a drug delivery system can be brought together with the primary packaging:

- By the patient
- During packaging
- As an add-on process to standard drug delivery system manufacture
- As part of the drug delivery system assembly process
- As part of a pre-made sub-assembly.

> "Early design decisions on electronics will tend to have far more fundamental implications for manufacturing than for standard drug delivery devices."

Considerations that inform when this integration occurs in the supply chain include ease of compliance with electronic disposal standards, such as the waste electrical and electronic equipment (WEEE) directive, and the design needs or restrictions. A crucial point to note is that early design decisions on electronics will tend to have far more fundamental implications for manufacturing than for standard drug delivery devices. The following section looks at some of the fundamental manufacturing impacts of these decisions.

Product Identification

With many patients carrying multiple inhalers, standard pharmaceutical product identification is achieved by adding manufacturing labels at the end of the manufacturing process. These contain product, strength, batch number, expiry and serialisation information, and are usually specific to a particular geographic region. This typically requires a high number of label variants to be held in stock. This works because labels are low cost and holding many variants is not an issue. It often allows primary and secondary product manufacturing to be standardised with only late-stage customisation of labels and packaging.

When looking at connected devices, one option is to have an equal number of electronic variants as there are label variants, containing the same level of information. These would need to be pre-programmed by the electronics manufacturer, held in stock and added to the product at the appropriate time. This poses some challenges:

- **High Cost:** While labels are costed in cents, electronics are costed in dollars and holding a high number of variants may not be cost effective to the supply chain.
- **Shelf Life:** The electronics will be expected to have a shelf life, most likely based on the battery being used. A five-year shelf life sounds comfortable but if there is a three-year on-market requirement and six months is taken up in the external supply chain then the effective time in a pharmaceutical supply chain may effectively be only 18 months. Low-volume, small-market variants could certainly approach this, especially if the electronics supplier has a large minimum order quantity.
- **Unique Data:** Some data will not be pre-programmable, like a finished batch number. If the app allows for elements of production data to be accessed, giving the patient access to this data would allow them to know the expiry date of their product and potentially allow them to confirm that it is not counterfeit.

The natural alternative to this is to build a level of programmability into the device itself. This has different pros and cons:

- **Stockholding:** If the electronics element can be programmed with data at a late stage there may only need to be one variant held in stock. This reduces the cost impact and the risk of having high-value, low-volume products held in stock and also allows simpler management of logistics with a product of limited shelf life.
- **Programming/Data:** Programming will need to occur in final assembly of the device or during packaging operations. Options include contact or non-contact data transfer. Decisions on this would depend on the technology being used. Non-contact via Bluetooth is unlikely to be viable in a manufacturing environment due to the time to synchronise, the need for internal power and ensuring that the intended product is programmed rather than ones adjacent in the line. An RFID option would be relatively straightforward as the chip is powered via external induction and data transfer can be local to the intended device. A third option is for data load via direct contacts. Similar to the RFID option the data can be loaded quickly and the device externally powered but does require electrical contacts to be in a position the equipment can access.

"Consider a low cost pMDI actuator failing an airflow test. As a single moulded item, it is of low value and is scrapped. If the same failure occurs with high value electronics integrated, this failure may now prompt a different response."

Independent of the option for programmability there are other key factors which apply to any device electronics:

Battery Power

In any design the issue of battery power and battery life will be a significant challenge. The three areas to consider are:

- The energy required by the device over the lifetime of the product
- The total energy in the battery
- Energy losses from the battery.

Energy requirements and battery capacity will be core design considerations in product development. In the supply chain, it is generally energy loss that requires management. A fundamental consideration is that energy losses from a battery will be much lower before it is used if it is isolated from the circuit. In terms of manufacturing, having a disconnected battery brings two challenges: first, as previously discussed, any data loading would need to be externally powered (as would testing); second is how to connect the battery for use by the patient. Options include an isolation pull-tab that is to be removed by the patient and, more elegantly, a battery that activates on first use.

Product Quality & Testing

It is a reasonable assumption that the functionality of any electronics will need to be tested during manufacture at the supplier. With any fully integrated device there is a question of whether testing of the electronics' performance also needs to occur once the device and primary pack is complete. This will be very much dependent on its functions. If, for example, it has a primary function such as dose counting or confirming dose delivery, then it can be expected that the same quality expectations as are required of equivalent mechanical systems will apply. Secondary functions, such as patient reminders and tracking of data will need to be considered on a case by-case basis as to whether late-stage testing is required.

If testing is deemed necessary, options include full physical testing by operating the device and checking if the expected output occurred, simulating use with representative input signals and confirming outputs, or by testing specific sub-systems. Much like the decision on when to program the unit with product date, these requirements need to be considered early in the development process as they will affect both how the electronics are designed and how the device is assembled.

Skills and Capabilities

With the introduction of electronics into a pharmaceutical supply chain, new skills and capabilities will be required. While some may be obvious, with engineering teams requiring electronic and software manufacturing/test knowledge, the majority of supply chain functions will also be impacted. For example, production and logistics areas may need to understand special handling and storage requirements, such as electrostatic prevention. Quality groups will be expected to understand electronic products and to support testing, investigations and audits of suppliers. Similar expectations also apply to procurement and external technical supply-chain groups to ensure electronics suppliers are meeting appropriate standards.

Cost

It is clear that the addition of high-value electronics will increase product unit costs. In manufacturing the impact of where high-value items are introduced into the supply chain also needs to be carefully considered, particularly around the cost of waste. This is best demonstrated using an example.

Consider a low cost pMDI actuator failing an airflow test. As a single moulded item, it is of low value and is scrapped. If the same failure occurs with high value electronics integrated, this failure may now prompt a different response. This could be a retest, recovery and reuse of the electronics or, if still scrapped, segregation for recycling purposes.

This type of reconsideration will not only affect cost impact assessments after integration, but may also drive enhanced testing or testing of components earlier in manufacturing to ensure they pass before integration.

"In manufacturing the impact of where high-value items are introduced into the supply chain also needs to be carefully considered, particularly around the cost of waste."

CONCLUSION

With patient expectations on ease of use for smart devices increasing, the lessons learnt from other business areas, such as refillable insulin pens, will need to be adapted to respiratory products. A drive towards integrating self-connecting, "self-aware" devices will move electronics into the pharmaceutical manufacturing supply chain. With deeper integration, a range of new challenges will be seen, including programmability, testing and both component and cost management.

Nearly all of these factors will be constrained based on the product requirements and the design choices made. To guide these concepts towards a product capable of effective industrialisation, early application of Design for Manufacture (DfM) and understanding of manufacturing impacts right from the point of concept will become ever more important in the development process.

ABOUT THE AUTHOR

David Belton is Founder and Director of Quentis, a medical device engineering consultancy specialising in providing design assurance and industrialisation know-how throughout the product lifecycle. Mr Belton has a degree in mechanical engineering from Loughborough University (Loughborough, UK) and has spent 20 years in both the electronics and drug delivery industries, bringing new products to market ranging right from the world's first 3G phone network to world-class dry powder inhalers.