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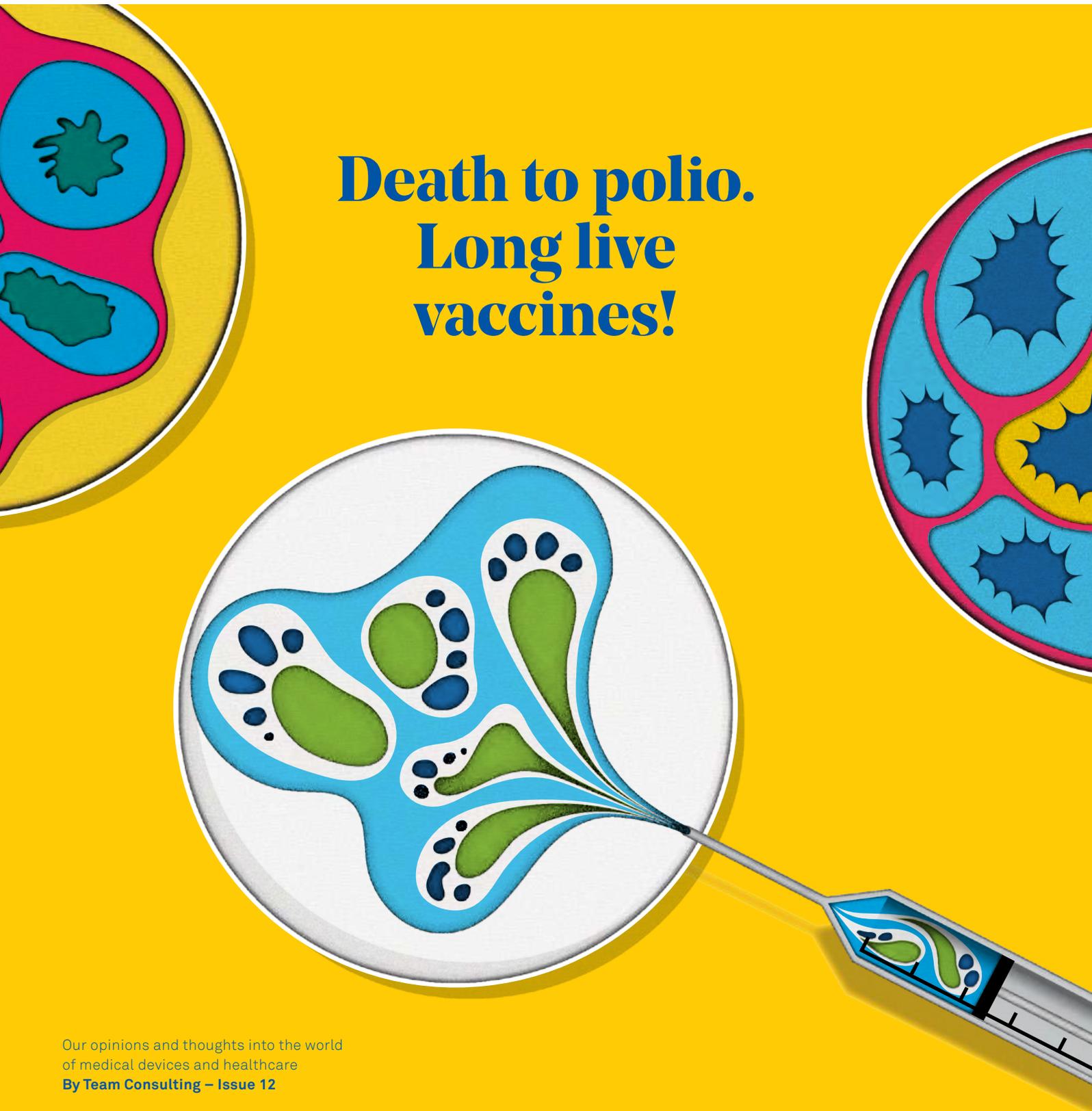
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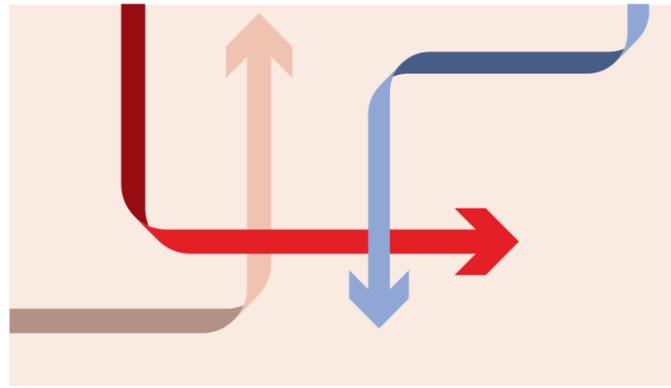


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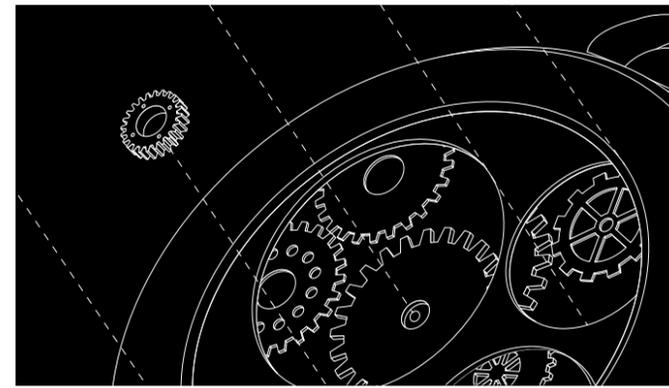


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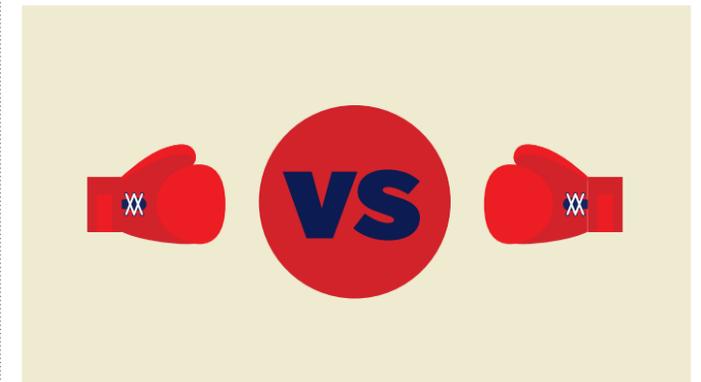


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We're back with another *Insight* and it's a bonus, bumper issue. So if you're ready for it, get yourself comfortable, put the kettle on for a mug of tea, or a cup of coffee, and have a flick through some of our latest thoughts on all things medical.

In this twelfth edition, we've cast our net wide to provide a bounty of information. One of our newer joiners, Hannah, braces us for recent changes to regulation for in vitro diagnostic devices and this is Thomas's first solo article where he talks us through root cause analysis. Another first timer is Carl, who has shared his knowledge on how to apply agile thinking to medical devices.

And it keeps going. In the first of our author pairings in this issue, Jess and Andy take us on a 220 year trip through the development of vaccines, Paul and Cécile Balloffet (another guest!) share stories about the impact and role of colour in medical and last but not least, Brennan and Matt, two mechanical engineers, take us on a James Bond metaphor driven ride through the unexpected similarities between expensive watches and disposable medical devices.

On that note, I think your tea or coffee should be about the right temperature to drink, so sit back, and see what's been going on in our minds recently. Enjoy.



Dan Flicos, CEO

It's time



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Hannah is responsible for the maintenance of Team's quality management system. She has a range of regulatory experience in medical technology products and frequently writes for Quality World Magazine.



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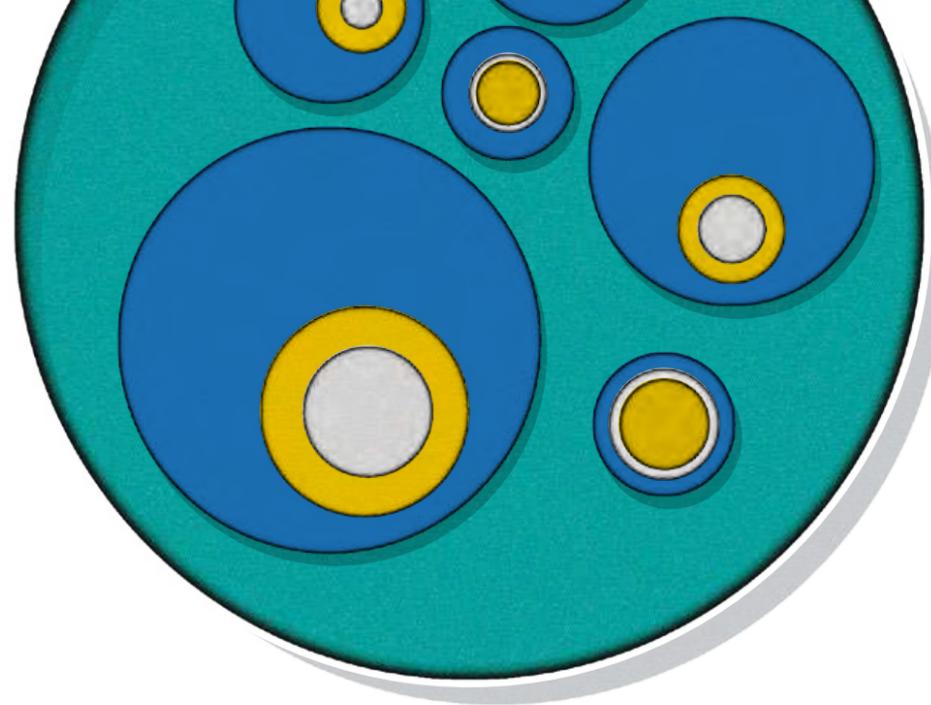


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Death to polio. Long live vaccines!



By Jess Fox

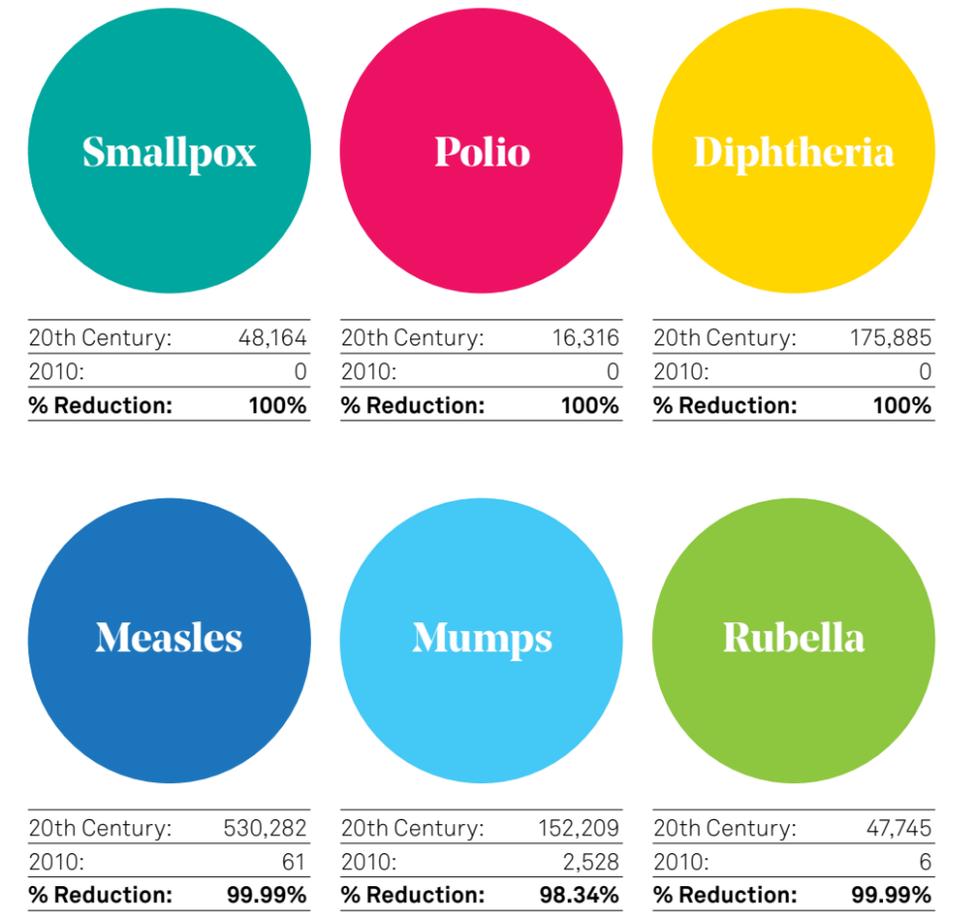


If you've been vaccinated you no longer need to worry about smallpox, polio or many other viruses. There is no doubt about it – vaccines save lives! It is estimated that 9 million lives a year are saved by vaccination.¹ Only clean water has had more of an impact on public health than vaccinations.²

In the 17th century 12% of children in the UK died before their first birthday.³ Babies and children died of tetanus, whooping cough, diphtheria, dysentery, tuberculosis, typhus, typhoid fever, rickets, chicken pox, measles, scarlet

fever, smallpox and plague. Babies in the UK are now routinely vaccinated against 13 potentially life threatening diseases and consequently the infant mortality rate is 0.36%.⁴

Vaccines have played an enormous role in this huge reduction in infant mortality but have also had an impact on the general reduction of morbidity. The table below shows the substantial reduction in the average annual number of cases for various vaccine-preventable diseases in the US during the twentieth century and in 2010.^{5 6} →



The first vaccination

Back in the 17th and 18th centuries, smallpox was a virulent disease and massive killer claiming an estimated 400,000 lives a year within Europe.⁷ Smallpox victims experienced fever and a distinctive skin rash which progressed to sores, pustules and scabs. 30% of people who contracted smallpox died. Those who survived had permanent scars over large areas of their body and some were left blind. Smallpox (which is caused by the contagious variola virus) was spread through coughs and sneezes as well as contact with the fluid that oozed from the patient's sores.

Doctors used variolation to help protect patients from smallpox. This technique involved either blowing dried smallpox scabs into a patient's nose or inserting them under the skin. This resulted in patients contracting of a mild form of smallpox where the associated mortality was 1-2% compared to 30% if the disease was contracted naturally. Edward Jenner, a country doctor in the UK, was aware of folklore that said milkmaids didn't get smallpox and instead only caught a weakened, non-life threatening version called cowpox (also known as vaccinia). He believed that the pus within with cowpox blisters offered protection against smallpox. In May 1796 (long before the days of research ethics committees) he put his theory to the test. Jenner first took pus from cowpox lesions collected from the hand of a

milkmaid, which contained live virus. He then made a few scratches on the arm of an 8 year old boy and inoculated him by applying the pus from the milkmaid into the scratches. The boy developed cowpox and recovered after a few days. A month or so later, Jenner exposed

the boy to smallpox. As predicted (and presumably to Jenner's relief) the boy did not go on to develop smallpox, on this or any subsequent occasion. Jenner had identified treatment to prevent smallpox which did not have the mortality rates associated with variolation.

Inoculation

Introduce (an infective agent) into an organism

Variolation

Inoculation of material from the pocks of smallpox

Herd immunity

Protecting a whole community from a contagious disease by vaccinating a significantly high proportion of its populace

Vaccination

Technique of introducing material under the skin to produce protection against disease

Attenuation

To reduce the effect of a microorganism

Eradication of smallpox

The public were initially uncertain about Jenner's smallpox vaccination, particularly being treated with material originating from cows. In a time before clean working practises were understood, cowpox samples became contaminated and patients were sometimes accidentally inoculated with smallpox, compounding public uncertainty! Variolation was forbidden in 1840 and compulsory inoculation with cowpox followed in 1853.

The smallpox vaccination process continued and remained virtually unchanged for the next 150 years. The game changer for the vaccination process occurred in the 1950s with the development of a vaccinia virus suspension. This permitted freeze-drying into ampules which allowed long term storage without refrigeration.

In 1967 the WHO launched the "Intensified Smallpox Eradication Programme". This was a massive undertaking and involved vaccinating at least 80% of the population in each country which proved particularly challenging in developing countries. This comprehensive vaccination programme worked. The last naturally occurring case of smallpox was in 1977 and in 1980 the WHO declared smallpox had been eradicated.

It is primarily due to Jenner's work that information on this deadly disease is now written in the past tense. It has been claimed that the work carried out by Jenner has saved more lives than any other person.

Development of further vaccines

Attempts to emulate Jenner's vaccination process by inoculating with live organisms from the sores of similar diseases failed. It wasn't until the late 1800s that Louis Pasteur discovered that microorganisms could be attenuated (modified) in the laboratory so that they were weakened but would still produce an immune response in the body. The first example of this type of vaccine for humans was against rabies. The rabies virus was collected from spinal cords of infected rabbits and then weakened by drying the tissue out. By 1900, five vaccines had been developed, against smallpox, rabies, typhoid, cholera and plague.

"The rabies virus was collected from spinal cords of infected rabbits and then weakened by drying the tissue out."

There are 4 main classes of vaccines. They all act by exposing the immune system to part or all of the pathogen but without causing the full blown disease. The immune system is then able to react if the pathogen reappears.

Live Attenuated Vaccines (LAV)

These vaccines contain a live pathogen which has been weakened (attenuated). When administered, the weakened pathogen will only cause a very mild form of the disease, if any. Examples are vaccines for rabies, typhoid, tuberculosis, polio (Sabin vaccine), measles, mumps and rubella.

Inactivated Vaccine

These vaccines contain intact pathogens which have been killed. They tend to elicit a weaker immune response and therefore require several doses, or boosters. Examples are vaccines for influenza, cholera, polio (Salk vaccine) and hepatitis A vaccines.

Subunit (purified antigen)

For some viral diseases, an immune response can be generated following exposure to a fragment rather than the whole virus itself. Vaccines for hepatitis B, human papillomavirus and plague are subunit vaccines.

Toxoid (inactivated toxins)

Some pathogens cause harm by releasing toxins (usually peptides or proteins). In these instances a vaccine can be created using modified toxins which allows the immune system to recognise and eliminate the toxins before they can cause any ill effects. Tetanus and diphtheria are both prevented with toxoid vaccines. →

Vaccine side effects and controversy

The holy grail of vaccine preparation is to develop durable, long-term immunity against the target disease in the minimal number of doses, whilst avoiding adverse events. Moreover the vaccine needs to be suitable for mass production, stable for prolonged periods at extreme storage conditions and affordable.

“In the 1970s, 36 children in the UK suffered severe neurological damage following immunisation”

The WHO says that vaccines used in national immunisation programmes are considered safe and effective when used correctly.⁸ It is accepted that vaccines are not risk free, therefore in order to have a successful vaccination programme, the public's trust is a necessity to ensure adequate and sustained vaccine uptake which is critical to obtain herd immunity.

Ironically, the more successful a vaccination campaign and the less visible the disease becomes, the more the public focuses on the vaccine's adverse events which can lead to decreased acceptance of the vaccine.

In the 1970s, 36 children in the UK suffered severe neurological damage following immunisation with a combined vaccine for diphtheria, tetanus and whooping cough. The whooping cough portion of the triple vaccine used inactivated whole cells and it was found this could result in an excessive immunological response, which was associated with the reported adverse events. However, the risks were very low - serious neurological illness was rare (0 to 10.5 per million vaccinations) and the risk of permanent brain damage even lower. But as a result, whooping cough vaccination rates reduced from 77% to 33%, and as low as 9% in some areas. Consequently, there were 3 major epidemics of whooping cough, 200,000 additional cases where at least 100 children died. In response, an acellular version of the vaccine (using cellular

material rather than whole cells) was developed in the 1980s and is now used in combined childhood vaccinations.

A more recent controversy surrounded the combined measles, mumps and rubella (MMR) vaccine. In 1998, the Lancet published (although later retracted) a now widely discredited and “fatally flawed” paper by Andrew Wakefield. The paper studied 12 children and claimed to have found a causal link between the MMR vaccine and autism. However, Wakefield had employed dubious research methods and had undeclared conflicts of interest. He received over £400,000 to try and disprove vaccine safety and had also filed a patent relating to treatments for bowel conditions (which that vaccine apparently caused). Following skewed media coverage, public mistrust increased which led to a 10% fall in vaccine uptake rates and a sharp rise in cases of measles. While numerous studies have shown the MMR vaccine does not increase the risk of autism (the largest of which was over 95,000 children), vaccination rates have yet to recover to pre-scare levels.



“Chickenpox is more severe in adults with risks of severe infection and secondary complication with increasing age.”

Childhood vaccination programmes differ from country to country depending on government policy. For example, the chickenpox vaccine is part of the immunisation schedule in the USA, Japan and Germany but not in the UK. The NHS is concerned that vaccinating children against chickenpox could increase the risk of chickenpox and shingles in adults. Chickenpox is more severe in adults with risks of severe

infection and secondary complication with increasing age. Additionally, if you have chickenpox as a child, further exposure to the disease as an adult boosts your immunity to shingles. However, there is unease that the chickenpox vaccine is not included in the programme due to public mistrust linked to the MMR scandal. Perhaps the MMR battle needs to be fought and won before the chickenpox vaccine is included in the vaccination programme?

The vaccination scares which have occurred tend to reflect political and social concerns rather than critical appraisal of the real risks. Celebrities and newspapers have used vaccines to peddle their own attacks on governments and pharmaceutical companies. The public often follows medical advice given by celebrities, who can use their influence for good. However, in recent years the media has given inappropriate level of coverage to celebrity opinion of public health matters; and social media allows celebrities to directly communicate to their thousands or millions of followers. Worryingly, the public appears to mistake celebrity status for medical authority, and this extends to the anti-vaccination movement. In February 2017, the New York Times published an article¹⁰ suggesting that the “anti-vaccination movement was gaining ascendancy in the US”. There is genuine concern that the high number of non-medical exceptions for school vaccinations will result in the loss of herd immunity, consequently outbreaks of diseases like measles are inevitable.

Conclusion

Medicine has advanced beyond all recognition in the 220 years since Jenner inoculated a little boy with pus from a cowpox lesion. The impact of vaccines on human health rivals any of the advances of modern medicine, from antibiotics through to genetics, biologic therapies and tissue engineering.

Vaccines allow science to turn the malevolent face of nature against itself. Pathogens that previously caused untold death and disease have now virtually disappeared from living memory in developed countries. Vaccination programmes are a true public health triumph, saving many millions of lives.

Significant progress in vaccine development is now being made for many diseases previously thought to be incurable, such as HIV, ebola and malaria. However the challenges are not simply scientific. We also face ongoing challenges in education, communication and compliance. As we have seen, when immunisation rates drop, we can quickly find ourselves battling against diseases we thought had been consigned to history. ^{ENDS}

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Preventable disease cases

Number of worldwide vaccine preventable disease cases 2008–2017⁹

Measles	1,461,247
Mumps	35,740
Other	46,117
Polio	2,611
Rubella	82,986
Whooping Cough	124,727





There's something in the water

Polio: Growing up before there were vaccines

By Andy Fry



I grew up in the 1950s in the leafy North London suburb of Finchley. As a little boy with two brothers, living close by a brook flanked by a ribbon of woodland, we went out to play 'down the woods' with our mates most weekends. Before we left the house, my mum would warn us to keep our wellington boots on (building dams across the brook was a major sport) and NEVER to drink water from the brook – because that was how we could catch polio. At primary school,

I accepted the fact that every year group seemed to include at least one child with a withered arm, leg callipers or at least a noticeable limp, because of polio. At senior school, JP, one of my best mates, wore a leg brace and a special shoe as polio had left him with one crippled leg. Not that it bothered JP or me, we copied each other's homework, smoked behind the bike sheds and spent the late sixties travelling to blues gigs all around North London anyway. →

“To date, there is no cure for polio, and 1 in 200 infections result in irreversible paralysis”

Photo: Ian Dury (1942–2000), iconic bard of punk, contracted polio at a public swimming pool in 1947. ‘I woke up in hospital and the kid next to me was in an iron lung. I realized I was lucky,’ he said in 1978. After several years in hospital and a home for disabled children he was left crippled for life. This didn’t stop him topping the charts and gaining a cult following. ‘I’m charismatic and I’m not ashamed of my stage appearance,’ he told the Guardian.



Ian Dury contracted polio as a child (Photo). Poliomyelitis is a highly infectious viral disease which attacks the nervous system and, once contracted, can lead to total paralysis within a few hours. To date, there is no cure for polio, and 1 in 200 infections result in irreversible paralysis,¹ and of those paralysed, 2%–5% of children and 15%–30% of adults die from respiratory failure.² The disease is predominantly transmitted by the faecal-oral route, person to person (my mum was forever telling us to wash our hands after using the toilet), though contaminated water or food can also provide a vector for transmission (so she was more or less correct here I guess – especially as sewage contamination to the brook was not unknown). Once the disease strikes, the virus multiplies in the intestines, with initial symptoms of fever, headache, vomiting, extreme tiredness, and stiffness in the neck and pain in the arms and legs.

It seems especially cruel that polio most commonly afflicts children less than 5 years old. Although polio has been around for centuries (there is evidence that it was known in ancient Egypt), the

epidemics of the post-war period in the USA, the UK and continental Europe were defining events. Previous attempts at cures or vaccines had all been failures (some tragically so – a vaccine tested on 10,000 children at Temple University in Philadelphia in 1935 conferred no immunity but killed nine subjects and left several others paralysed).

In 1952, a team at the University of Pittsburgh, led by Dr Jonas Salk, developed an inactivated poliomyelitis vaccine (IPV), administered by injection, and incorporating a ‘killed’ polio virus. Salk launched a human trial of unequalled scale at that time, involving nearly two million children in the US. The successful trial results were announced in April 1955, and shortly afterwards the same year, IPV was licensed and a mass vaccination campaign launched in the US. In parallel, a team at the University of Cincinnati led by Dr Albert Sabin was developing an oral polio vaccine (OPV); this used a weakened but live virus, administered as drops applied to a sugar cube. In a fascinating twist, Sabin was unable to conduct trials for OPV in the USA (as by then the Salk vaccine was already in extensive use) so he was forced to conduct trials abroad. Initially this was in the Belgian Congo, and then in the Soviet Union on an unprecedented scale, involving ten million children (this at the very height of the cold war). In recognition of his work, Sabin was awarded The Order of Friendship Among Peoples, the Soviet Union’s highest civilian honour.

Both IPV and OPV were used in mass vaccination campaigns here in the UK, with a young and vigorous National Health Service rising to the task. My brothers and I remember having ‘polio jabs’ (obviously IPV), whereas some of my younger cousins escaped the needle and received the sugar cube-delivered OPV, which replaced IPV in UK campaigns in 1962. Today, polio vaccination in the UK is only given as part of a combined product which also protects against diphtheria, tetanus and whooping cough (pertussis); this uses acellular pertussis vaccine and incorporates IPV (OPV is no longer routinely used, though it is retained for outbreak control).

Figure 1: Polio endemic countries



“Since 2015, the disease remains endemic in only two countries, Pakistan and Afghanistan.”

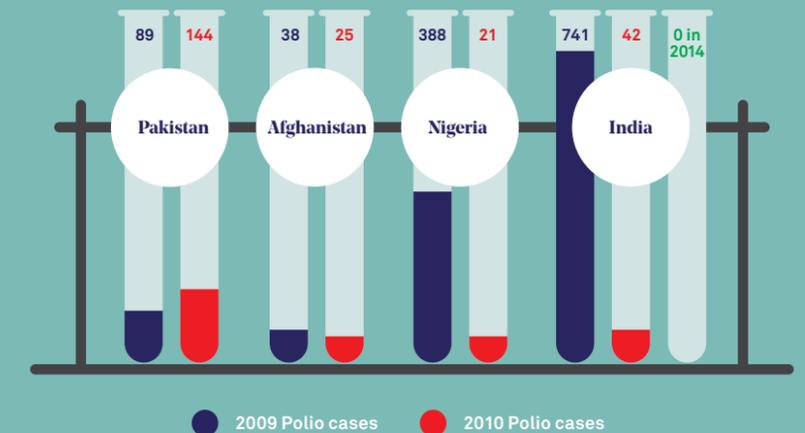
Figure 2: Polio cases in 2009–2010

The poliomyelitis vaccination campaign in the UK has been an unquestionable success; since 1984, no cases of polio have been contracted naturally within the UK.¹ Equivalent campaigns around the world have had similar, remarkable results; polio has been eradicated across Europe, the Americas and virtually everywhere else (Figures 2 and 3).³ Since 2015, the disease remains endemic in only two countries, Pakistan and Afghanistan.

“Since 1984, no cases of polio have been contracted naturally within the UK”

Most survivors of the UK and US post-war epidemics are, like me, now senior citizens or at least heading that way. Neither my children nor my grandchildren would ever give a thought to the risk of polio – why should they after all? So they will, I suppose, never realize the gratitude they owe to Jonas Salk and Albert Sabin, neither of whom patented their vaccines. Ed Murrow, the famous CBS journalist and correspondent, once asked Salk in an interview, who held the vaccine patent. Salk simply replied, ‘There is no patent. Could you patent the sun?’ ENDS

Polio has never been stopped in four countries



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An agile approach

What can we learn from applying “Agile Thinking” to medical device design?

By Carl Warren



“Agile is generally taken to refer to methods and practices associated with the Manifesto for Agile Software Development”

In issue 10 of Insight, Ben Wicks referred to the potential commercial advantage that companies developing medical devices might gain by being ‘agile’. There are many ways in which this might be interpreted, and in this article I would like to consider what agile can mean in the world of medical product development. Anyone familiar with modern software engineering practices will I’m sure already recognise the relevance of Agile in the development of software applications, but let us take a deep breath and look beyond software to consider the benefits that might be gained by applying Agile to the development of physical medical devices.

For the developers of software applications, Agile is generally taken to refer to methods and practices associated with the Manifesto for Agile Software Development published by the Agile Alliance in 2001. This Manifesto, and the associated 12 principles of Agile software

development, were born out of the real life limitations and challenges experienced with using traditional waterfall development methods when developing complex software systems. Instead of the extensive planning, requirements definition and analysis upfront normally associated with a waterfall development, Agile methodologies allow for evolving requirements over time by allowing cross-functional teams (covering the main software development functions of planners, designers, developers and testers) to work on successive iterations of the product, typically over fixed time periods.

Agile therefore relies on a more incremental and evolutionary approach than the sequential flow associated with a traditional waterfall development. A classic waterfall development process is illustrated below. This is a series of sequential steps that cover the entire development. →

Figure 1: A Simplified view of a traditional waterfall development

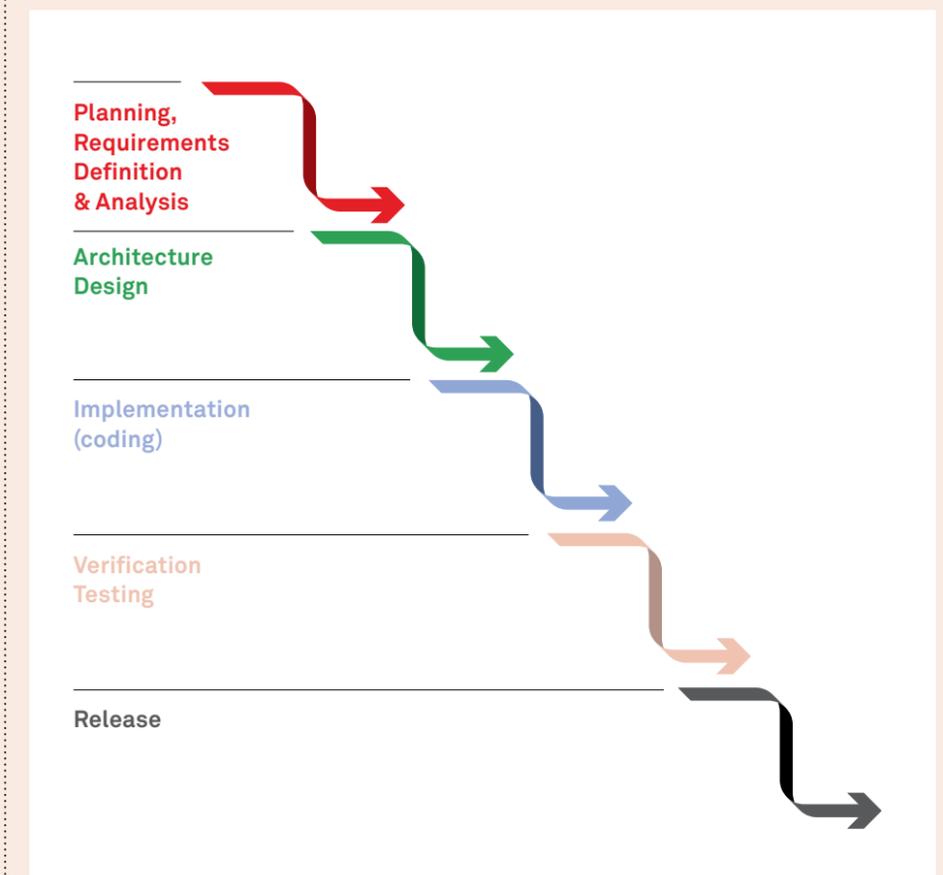
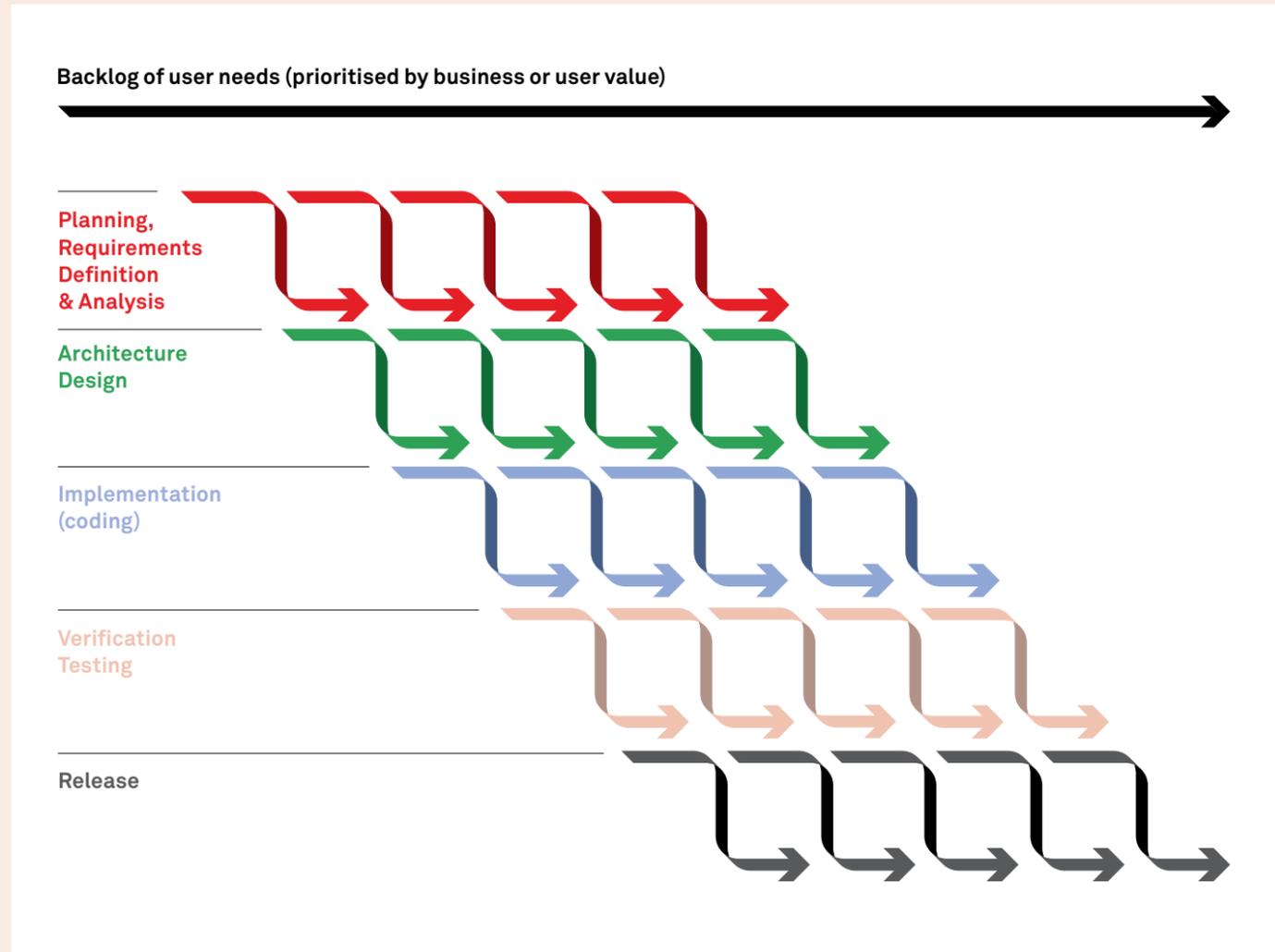


Figure 2: An Agile incremental development road map



In contrast, an Agile approach would seek to slice the development into a series of incremental design iterations, each building on the previous release and the feedback gained from actual use of a released, tested software product, as illustrated above.

One of the key principles behind the use of Agile for software development is to satisfy customer needs through the early and continuous delivery of working software. Agile provides regular and frequent releases of software that are viable products that satisfy a sub-set of the user needs. Done well, Agile can provide a number of benefits over a more traditional, sequential product development approach, including:

- **Speed to market** – a working product is delivered more quickly and successive iterations can be delivered frequently at a regular pace.
- **Closer communication** – Agile can promote closer collaboration between developers and the business. Agile also provides a highly transparent approach to working, in terms of activity, progress and issues.
- **Flexibility** – changes to requirements can be incorporated at any point of the process – even late in development.
- **Robustness** – the feedback mechanism inherent in most agile practices provides a good opportunity for continuous improvement.

At first sight, the use of an incremental approach with evolving requirements may seem to be a poor fit with the regulated world of medical device development, whether it is for the development of software as a medical device or for a physical medical product. However, in 2012, The Association for the Advancement of Medical Instrumentation (AAMI) published TIR45:2012 “Guidance on the use of Agile practices in the development of medical device software”. This guidance has shown that it can be possible for businesses to gain the benefits of using Agile practices in the development of medical device software while still maintaining compliance with international standards, including IEC 62304:2006 Medical device software –

Software life cycle processes, and U.S. Food and Drug Administration (FDA) guidance documents.

There would undoubtedly be many more challenges associated with applying Agile beyond a software-only product development. While it is relatively straightforward to release working code at regular and frequent intervals, this is not necessarily the case when, for example, a development requires the release of several hundred mechanical

drawings to multiple vendors. They will almost certainly not be able to provide specialist or custom product within the 2-3 week sprints that software developers can work to. Hardware is also not as easy to change as software late in the development. In general changing requirements late in a development doesn't work well! Traditional medical device development has a need for lock down, which conflicts with the Agile mind-set of welcoming change.

However, look closely at the 12 principles of Agile and substitute product for software, and most business owners, regulators and developers would agree that – whilst hard to do – these are all good things to apply! →

Figure 3: 12 Guiding Principles of Agile



In September 2016, AAMI ran a training course entitled “Agile for Medical System Development”. This course provided guidance on how Agile practices could be applied beyond software development. It was interesting to note that more than half of the attendees at this course were from large, well-known organisations in the medtech world. The course looked at how the Scaled Agile Framework could be applied to a medical system development and emphasised the close alignment with modern system engineering practices, referencing work done on Agile systems by the International Council on Systems Engineering (INCOSE).

What was evident to me from this course is that Agile can provide similar benefits and improvements in medical product development, as well as development of their software applications. The key message is to apply the principles of Agile at the most appropriate stages in the development process and to do this systematically as a business improvement initiative.

For example, an organisation could use Agile practices to develop a set of user needs into a product that proves particular elements of technology, or to meet an investor milestone. Another approach may be to use Agile practices for a particular phase of development, such as translating user needs into product requirements (where the “product” developed may be a set of documents) or by generating user stories during the feasibility phases that will augment requirements documents and help developers during the detailed design phases.

One of the biggest challenges in applying Agile successfully is the shift in mind-set away from what work needs doing, to what needs to be achieved. This can work against long standing organisational processes and so create inefficiencies. Agile methodologies (e.g. Scrum, XP, Kanban, Crystal, etc) are often more difficult to understand than linear, sequential methodologies (at least initially). The terminology used (e.g. sprints, stories, epics, increments, release) is probably familiar to most

software engineers but may have little meaning to a mechanical engineer or human factors specialist. A linear Gantt has its downsides, but most developers and business stakeholders can easily align expectations in terms what needs to be done, when by and with what dependencies. There is no such equivalent in Agile, but a Feature Gantt chart that focuses on the work (and not on the workers) can be very helpful in wider communication about progress and priorities.

One common misconception associated with Agile is the lack of emphasis placed on documentation (this perhaps stems from a misinterpretation of the reference to documentation in the Agile Manifesto, see below). There is no reason why the user stories used in Agile cannot be used to describe documentation as value adding features in exactly the same way that they describe product features (which also negates the need for a complex integrated Agile and requirements documentation management tool!).

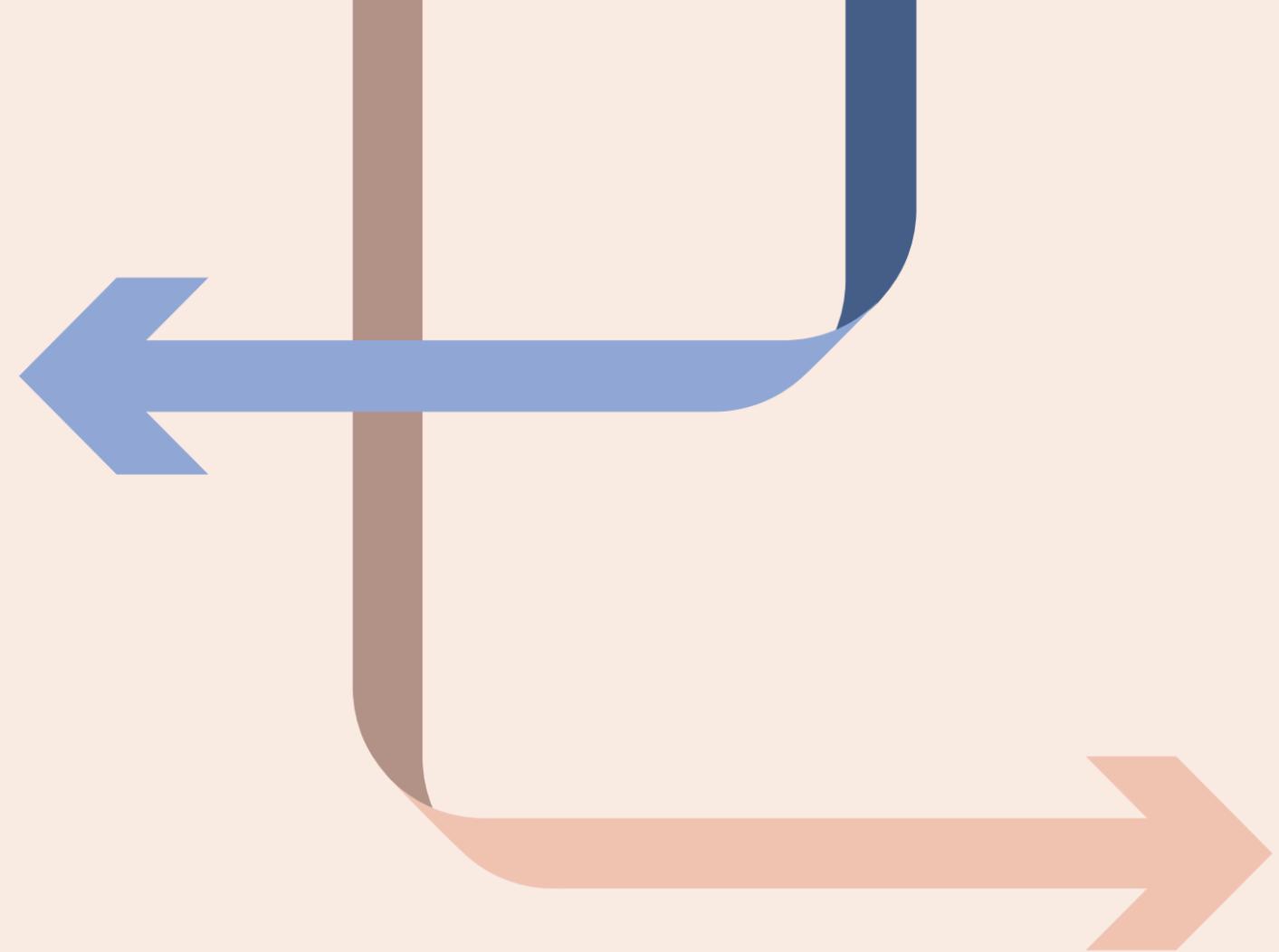
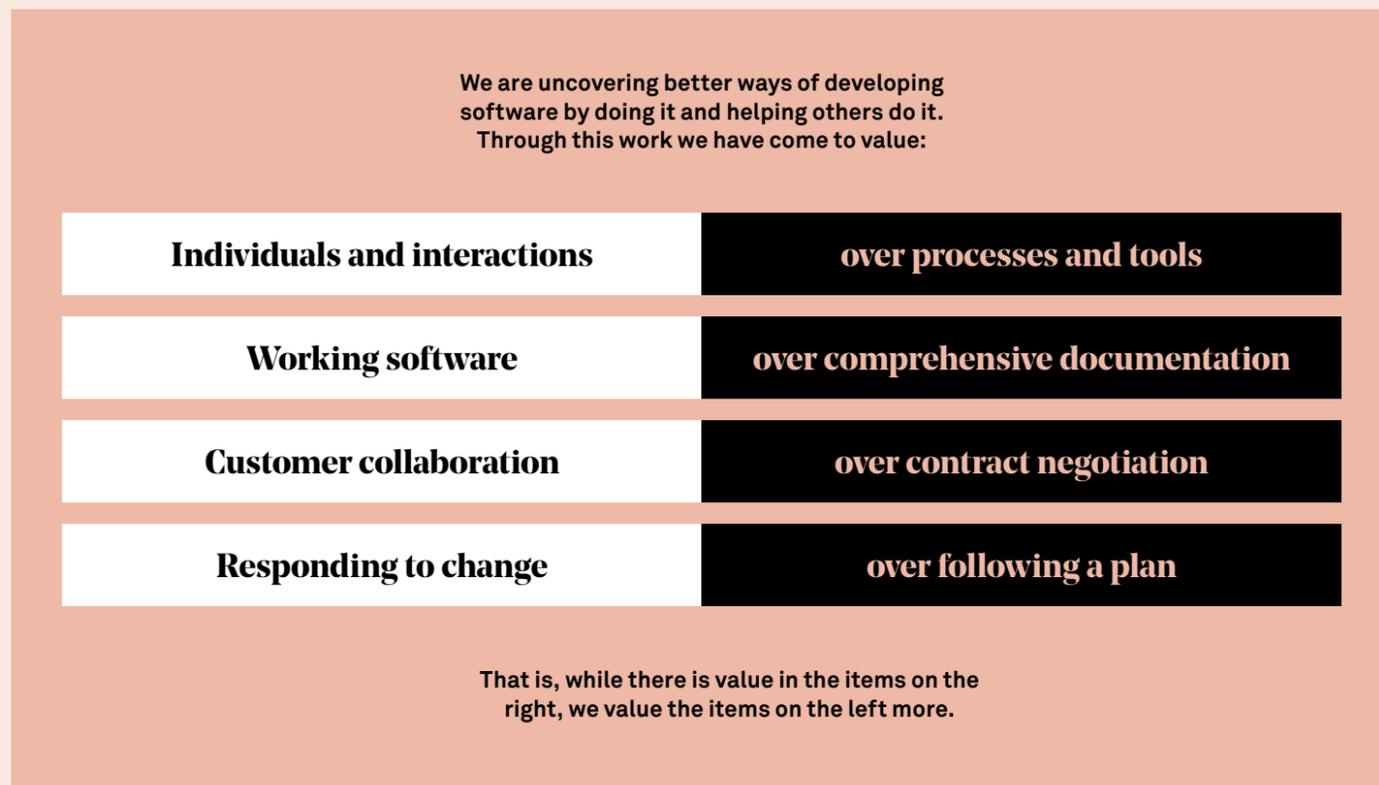


Figure 4: The following are based on the Agile Manifesto



“The key differences between an Agile approach and a more traditional waterfall approach is the extent to which design inputs are defined and analysed in the initial stages of a product development”



For me, one of the key differences between an Agile approach and a more traditional waterfall approach is the extent to which requirements are defined and analysed in the initial stages of a product development. I believe this is why Agile has proven to be so popular for software development. Trying to analyse the multiple pathways and interactions of a complex software system can actually be better performed by developing working code, to “make it real”. Where requirements can be well defined early in a development, Agile may offer little benefit over a traditional waterfall development approach. However, for organisations developing innovative medical products where this may not be the case, or where it is possible to flex scope and adopt an incremental release train, then Agile development practices may well offer advantages to organisations prepared to look beyond the traditional ways of developing a medical product.

Unfortunately Agile can also be seen as an excuse for having poorly controlled product development processes, which clearly should have no place in the medical product development world. But as software developers following AAMI’s TIR45 guidelines are discovering, Agile practices can be used to provide effective controls in their development processes.

When designing medical products Agile might provide clear advantages when the requirements aren’t clearly defined. ENDS

COLOUR

The role of colour in medical devices: a designer's perspective

By Paul Greenhalgh
and Cécile Balloffet



Colour is a powerful tool we can use when designing medical devices. Unlike in many consumer products, the primary purpose for using colour is not in making devices look attractive to command a higher price, nor is it about launching ranges of products targeted at individual market sectors; it can however be used to improve the user experience. The importance of user experience has become much more recognised in our industry in recent years. We are no longer focused just on safety in use but on effectiveness too, looking for ways as device designers to better tailor products to the needs of users, and helping to improve both usability and engagement.

How does look and feel play a part?

We cannot assume that look, feel and interface design of a product alone will help tackle compliance and adherence issues. Adherence is an extremely complex subject where many factors need to be considered. Those include: education, the quality of training and support material, how the benefits of a therapy are communicated, and of course cost.

However, by carefully considering the practical, emotional and lifestyle challenges faced by the users of our products, we can design an experience which at least helps to reduce the barriers to compliant use – and choosing the right colours can play a key role in helping to achieve this. →

Practical issues

The considered use of colour can help us to overcome numerous practical design challenges. Colour can emphasise key interaction points on a user interface (such as an actuation button, or a dose selector), and by using a hierarchy of colours we can influence the user's interaction, helping them to follow the correct usage steps in the correct order. Colour can also be used to aid with instructions – by colour coding different components it can make it easier to provide written or graphical instructional information. For example, the EpiPen uses colour-coded features referred to in the on-board instructions such as 'pull off blue safety release' and 'push orange tip against outer thigh'.

Regulators are encouraging the use of colour in packaging and labelling to help users identify between different types, strengths and dosages of drug. The FDA produced simple guidelines (*Recommendations for Developing User Instruction Manuals for Medical Devices Used in Home Health Care, FDA*) which encourages using colour to help identify key information. The colour used can be more sophisticated and we can use it to tie different elements of a system together. For example, if someone had two capsule inhalers from two different brands, it might be easy for them to get confused over which capsule goes in which device. If however there was an overriding colour scheme in the device, drug packaging and instructions, this could provide a clear and easy to understand visual aid which would improve usability and compliance.

Emotional issues

Colour can also be used to trigger emotional responses. Think about how the packaging of your favourite brand of chocolate can trigger the sensation of taste and smell long before you've opened the wrapper. Our perception of the size and weight of a product can be altered depending on its colour. Darker colours can make something feel heavier and more robust whilst a semi-translucent colour feels lighter. Colour can also affect the value we place on a product. Some colours encourage a disposable attitude after a device

is used one time because "it feels low cost and throw-away". Other colours instil a feeling of cleanliness, such as pure whites, aqua blues or fresh greens. Think about the colours typically used on your toothbrushes – it might feel odd to put them in your mouth if they were khaki. Certain colours can also indicate whether a tool is made for professionals, novices or even children.

Carefully chosen shades and hues or metallics can create particular ideas or perceptions; it is important for medical devices to appear of an appropriate value and quality to gain confidence and trust from users. It is therefore extremely important to get the colour just right –



Courtesy of Clariant

but in the design of medical products life isn't quite so simple, as we don't have the freedom of choice from standard colour palettes that we would if designing consumer products. For example, we may have a single shade of yellow to choose from in a standard medical range whilst we'd have 15 shades of yellow in a range of colours suitable for consumer product use – marigold, jasmine, canary, sunflower, sherbet lemon, and so on.

Getting the right shade is important

Having a standard colour palette is helpful as a starting point: if we select a colour from a pre-approved medical range then we greatly reduce the amount of test work required to prove the colour is safe and achievable. However due to the limited choice on standard colour palettes more often than not it is likely that a custom colour will need

to be processed – and this isn't always entirely straightforward. However this is not an issue if planned ahead. An example is the surgical haemostat spray developed for ProFibrax. Aesthetically, the device needed to feel disposable as it is a single-use device; clinical with a hygienic feel; professional as it is used by surgeons, but practical so it was not too complicated to use. We chose to use colour to clearly identify key interaction points; and settled on a clean, minimal colour palette of just three colours – white, blue and grey. However, the device also had several specific material requirements. It needed to be gamma-stable for post-sterilisation, a flexible material was needed for a compliant

“Not all colours are physically achievable”

vial seal and low friction for its nozzle attachment and a strong durable material for the handle.

The white of the body was straightforward – we used a pre-compounded white ABS which we'd used successfully many times before on other devices. The grey available from the standard Mevopur range met our needs, but our key accent colour needed something custom.

Initially, a teal colour was chosen to highlight the key interaction points of the device and to complement our client's core brand colours. However, not all colours are physically achievable in the world of medical device design. The colour we specified required three different pigments; a blue, a white and a green. Whilst all pigments were

pre-approved for medical use the green pigment had a low processing temperature compared to the blue and white, and the material to be coloured had a high processing temperature.

“While we need to find a colour that helps to communicate the right message”

Because there was such a small amount of the green pigment, it was burning out during the compounding process, making it difficult to achieve a robust manufacturing process. Following discussions with our supplier (in this instance Clariant), we were presented with further options – a darker teal or a more similar shade of blue. As medical device designers a practical approach is necessary when presented with decisions like this. While we need to find a colour that helps to communicate the

right message, we also need to de-risk the manufacturing process. Working together with Clariant we were able to develop a blue colour that has the same vibrancy and clinical connotations, but by reducing the number of pigments used we also reduced the risk of any unforeseen interaction with other materials. Again, getting the right shade is not an issue if the process is planned well in advance.

Colour and regulations

Choosing a colour is also dependent on regulations. Many colour manufacturers are leading the way with regulatory compliance. When choosing a colour, you have to bear in mind the regulations and impact on mechanical properties. By choosing the wrong pigment, you could influence the device reliability and thus administrate the wrong dose. Another issue to consider while choosing colours is that the raw materials could change leachable profiles and invalidate testing done in development. This is true even

when choosing a preapproved colour. Final leachable and extractable testing must always be undertaken with the final combination of masterbatch and polymer.

Consideration must be given to the raw materials supply chain as changes may occur over the device life cycle (see FDA potential for leachables and extractables scheme) and thus could change leachable profiles and invalidate testing done in development (see pyramid).

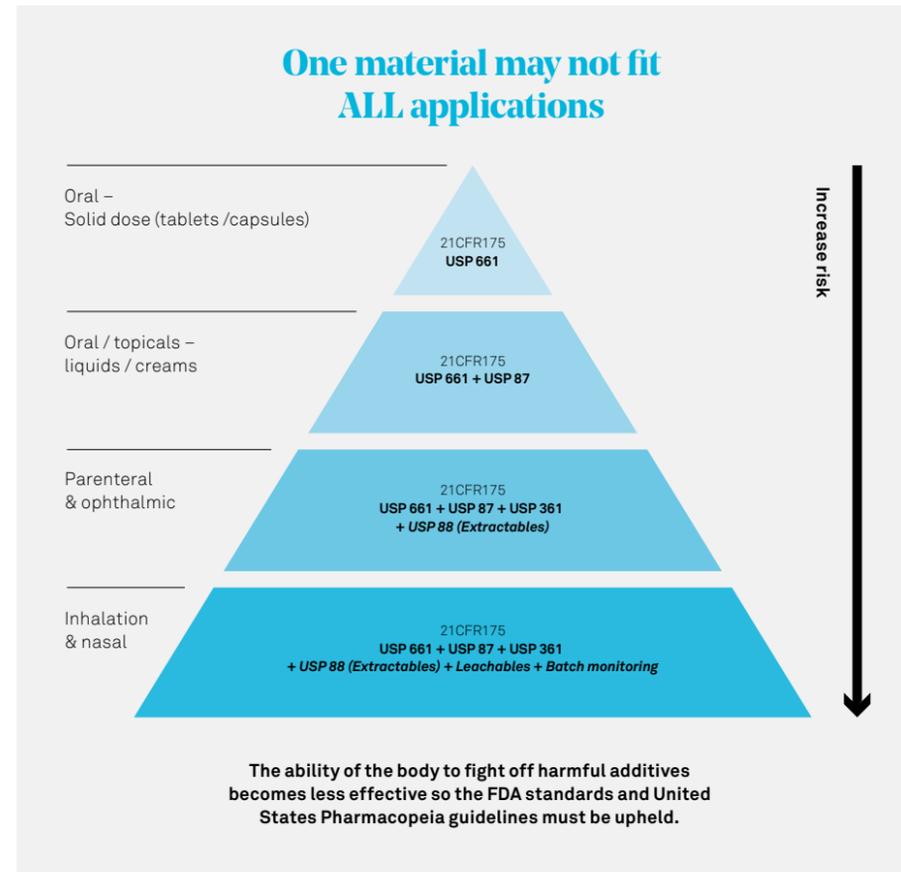
The FDA has started to understand the risks of change in materials in product lifecycle. This is why it is important to design 'risk management' into the manufacturing process, looking beyond the 1st upstream supplier and discussing what is possible: having a Change Control agreement with the colour supplier and using pre-tested raw materials so it can be understood where risks may stem from. This will not only help to reduce potential risk, but will create opportunities to improve the process as well as the product.

“Where possible the use of preapproved colour and material combinations will help to reduce risk during the manufacturing process”

Conclusion

Colour plays an important part in the design of medical devices – through carefully considered colour schemes it can help us tackle both practical and emotional design challenges. Helping to build trust and confidence with both patients and health care professionals in the devices we develop.

Where possible the use of preapproved colour and material combinations will help to reduce risk during the manufacturing process. But as long as you build time into your plan and engage early input from a duly experienced colourant manufacturer, you will increase your options and should have a full spectrum of choice. ENDS



THE NAME'S BOND JAMES BOND



We took James Bond's Rolex apart and found a medical device

By Brennan Miles and
Matt Chandler

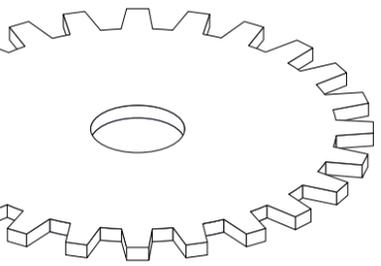


Borrowing an everyday item from James Bond could have unforeseen consequences – from an umbrella with killer spikes, to bagpipes which double as a flame thrower and a machine gun. One gadget in particular had no limits in its powers – 007's watch. Supplied by the fictional Q-Branch – it has hidden gizmos such as lasers, explosives, garrotte wires, and even a tele-printer (state of the art in the mid-1970s!) In the films, Bond has been seen wearing several watch brands but in the books, he would not be 007 without his Rolex (Ian Fleming was known to wear a Rolex himself).

It may come as a surprise that hidden within a Rolex watch we have also found a medical device – well, perhaps more figuratively than literally. But unscrew a hermetically sealed Rolex case and you will discover a complex and intricate mechanism that is comparable in some ways to the inside of a disposable inhaler device.

Outwardly the engineering of disposable medical devices, such as inhalers, does not appear to share much with the intricate mechanics, ultraprecision and lavish materials found in watch mechanisms. Even so, medical device engineers tackle similar technical challenges as the watch designers, employing engineering excellence, skill and craftsmanship to deliver a product which maintains a balance of the user needs, unfailing performance and overall safety. →

RIGHT. NOW PAY
ATTENTION,
007.
I WANT YOU TO
TAKE GREAT
CARE OF THIS
EQUIPMENT.
THERE ARE ONE
OR TWO RATHER
SPECIAL
ACCESSORIES...



Even without Q's aftermarket modifications Rolex watches radiate an aura of high-quality engineering and luxury. As Rolex states on their website:

“Rolex watches are crafted from the finest raw materials and assembled with scrupulous attention to detail. Every component is designed, developed and produced in-house to the most exacting standards.”

These components are made of many interesting and exclusive materials such as ceramic, titanium, gold and even jewels – some are embellishments, but some have special qualities like hardness for low friction bearings. The most basic Rolex requires 115 different pieces to be assembled with precision. Over the years, the development of wrist watch movements has been more about evolution than revolution: characteristically they use energy derived from a wound flat steel band (the mainspring). This energy is

transmitted to the oscillating section of the watch (called the balance) by a gear train and escapement, and consequently to the rotation of the watch hands.

SHAKEN NOT
STIRRED...

It would be an understatement to suggest that the manufacturers of inhaler devices and Rolex watches are anything but obsessed by product quality; for both, it is essential that all products leaving the factory are defect free. But there are some big differences in how the quality of the final products are ensured.

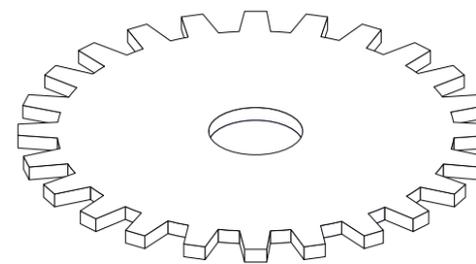
Rolex prefer to take a hands-on approach to both product assembly and testing. They ‘quality-control’ their watches for accuracy by simulating wear before they are released to the retailers. Of course, some of the testing is automated, but the fact that it is done on every one of the watches and that it takes several days to complete, means that it is not an approach that many other industries can adopt; especially those mass-producing products such as medical devices. An advertisement for Rolex once claimed that it takes about a year to make a single Rolex watch. This is almost certainly untrue, but it does highlight that Rolex customers believe that a slower production rate implies a higher quality product.

On the other hand, medical device engineers will design safety-critical products for high-speed manufacturing – as high as one per second, not one per year – from the early concept stages. The care and craftsmanship of the component parts is achieved in a very detailed production method which could be compared to that of high-end watches. But device developers follow a rigorous and detailed process of analysis, trial and verification to ensure that the final design intent is suitable for industrialisation (production

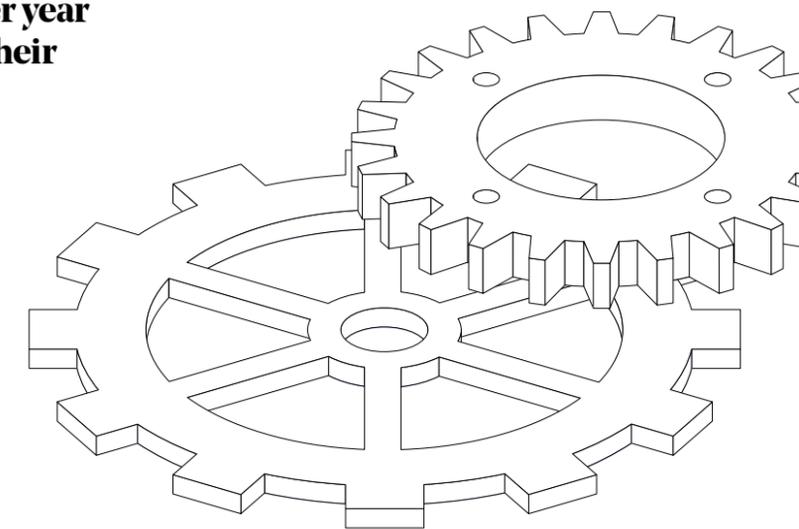
scale-up). Later, the manufacturing processes are validated to demonstrate, and prove statistically, that the final product will consistently meet specification, irrespective of all the possible manufacturing tolerances and variables. In this way quality is assured rather than controlled.

I BELIEVE I
SAID, ‘BRING
IT BACK IN ONE
PIECE’, NOT,
‘BRING BACK
ONE PIECE.’

As an example, a discus type inhaler has 12 plastic components – plus a blister strip – and over 7,500 inhalers can be made per hour by just one production line at a GlaxoSmithKline site (over 68 million per annum)! In contrast Rolex produce about 1 million watches per year across all their brands. This means that GSK are making and shipping over 60 times more devices per year at a product cost that is approximately 2,000 times cheaper than a Rolex. →



“Rolex produce about 1 million watches per year across all their brands.”



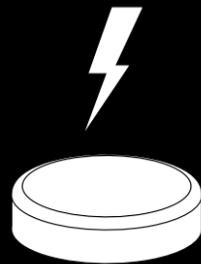
DPIs

DPIs are an alternative to the aerosol-based inhalers known as a metered-dose inhaler (MDI). The medication is commonly stored internally in sealed packages or blisters which are opened and exposed to the internal airflow pathway on device actuation by the user. Using the patients’ inhalation (inspiratory flow), the powder is entrained and the active pharmaceutical ingredient (API) is separated from the carrier particles for delivery to the lungs.

**There are two types of watches:
quartz and mechanical.**



Quartz watches are powered by a battery while mechanical watches are powered by the regulated release of energy from a wound spring, and use purely mechanical components to keep time.



MISS ANDERS! I DIDN'T RECOGNIZE YOU WITH YOUR CLOTHES ON.

On the surface DPIs appear to be 'low-tech', however, just because they are perceived as basic and cheap compared to wrist watch mechanisms it does not mean that the engineering and development that goes into them is any simpler.

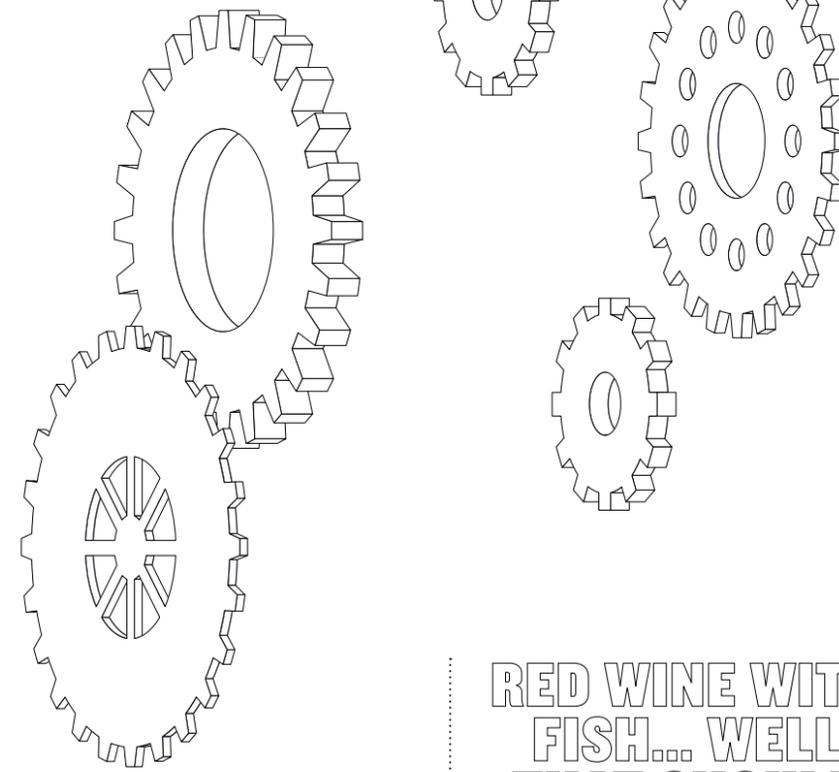
GSK's Ellipta®, another DPI device, is designed to be used once-daily for the delivery of both mono- and combination respiratory therapies and can hold

up to 1 month's supply (30 doses) of medication.

From the outside, the device is quite plain, the external case is white with a coloured mouthpiece cover to indicate the drug type. There is little in the way of embellishment except for some small ridges, which exist to indicate to the user the simple mode of operation (open, inhale, close), and a small counter to display the number of doses remaining. However, the basic shell conceals a complex internal gear mechanism that is comparable in intricacy to many watch movements.

To prime the Ellipta device the user opens the mouthpiece cover, by this single movement and hidden to the user, the device mechanism simultaneously performs five actions:

- 01 Advances the blister strip and aligns a blister with the mouthpiece manifold airflow path;
- 02 Peels the blister foil laminate to expose the contents of the blister(s) for inhalation;
- 03 Gathers the used portion of the blister foil laminate;
- 04 Drives the dose counter gears to move the dose counter display by a one unit decrease;
- 05 Provides an audible 'click' at the end of the mouthpiece cover movement.



RED WINE WITH
FISH... WELL
THAT SHOULD
HAVE TOLD ME
SOMETHING.

“they are not made of precision-machined and hand-finished materials as you would find in a Rolex mechanism”

What is remarkable is that the gears inside the mechanism are all plastic and are mass-produced on multi-cavity injection mould tools; they are not made of precision-machined and hand-finished materials as you would find in a Rolex mechanism. This means that each part has a natural variation, caused by small fluctuations in the moulding process. That variation is multiplied by the number of tool cavities, with each mould cavity very slightly different from the next.

For a device like this, which is manufactured in high numbers, there will be at least three sets of tools to allow for repairs and refurbishment. When you consider the potential combinations between interacting parts, the permutations become significant. This places a high demand on rigorous engineering in design and manufacture to accommodate the part-to-part variation and most importantly, their interaction, to ensure the device functions correctly every time.

The functional challenge with watch engineering is mainly to do with maintaining a consistent movement with very low friction and wear. The gear trains in DPIs also feature solutions that are similar to those found in wrist watch movements; features like idler gears, ratchets and escapements can be found, but unlike a watch mechanism, it is not always appropriate to have liquid lubricants in systems because they may be inhaled by the user.

The plastic materials used in the DPIs have been chosen to optimise their frictional performance whilst they are still able to be moulded with high precision. However, the pool of materials is limited further, as the plastic components are made from a relatively small range of medical grade polymers that have the appropriate USP class IV and ISO 10993 certification for use in medical applications.

The mechanism design for both Rolex watches and mechanical inhaler devices is based on broadly the same engineering fundamentals. The engineers for both products carry out analytical analyses using the same basic equations and principles, some common examples are:

- The involute gear equations – used to describe the interactions and forces between involute gear teeth profiles.
- Hooke's law – to describe spring constants.
- Coefficient of friction – which describes the ratio of the force of friction between two bodies and the force pressing them together.

THE THINGS I DO FOR ENGLAND!

Occasionally it is interesting to draw similarities across industries, because after all 'engineering is engineering', whether it be for James Bond gadgets, Rolex watches or medical devices.

Comparing DPI design to Rolex watches – two seemingly very different products – helps to paint a better picture of the complexity and challenges that medical product engineers tackle and overcome. It is worth remembering that the best examples of engineering design are sometimes the ones that remain hidden from view and are concealed inside the plain and functional devices that we use daily; or to put it into 007's words:

James Bond:
YOU KNOW,
YOU'RE
CLEVERER THAN
YOU LOOK.

Head of Q-Branch:
STILL, BETTER
THAN LOOKING
CLEVERER THAN
YOU ARE. ENDS

Watch mechanism vs inhaler mechanism

Skilled engineers create precision devices but which is the watch and which is the inhaler?



We're only human after all



Root cause analysis in medical device development: acknowledge System 1, engage System 2

By Thomas Grant



“the resulting data might not be valid or reliable, leading to poor design decisions and ultimately, an unsafe medical device”

Root Cause Analysis (RCA) is the basic system of trying to find out the cause of a problem. It is used to identify methodically why there are problems - not just focusing on the symptoms. It was famously used in the 1950s by NASA to solve rocket launch problems. RCA is now renowned as an integral part of Human Factors (HF) research. In the context of medical device development it refers to the qualitative analysis of issues observed during human interaction with a medical device or system be it use difficulties, deviations, close calls or use errors.

The Food and Drug Administration (FDA) considers RCA during usability testing a best practice approach for identifying and eliminating use error (ANSI/AAMI HE75:2009). This analysis must be 'considered in relation to the associated risks to ascertain the potential for resulting harm' in order to determine whether additional risk mitigations are required (FDA, 2016).

Those with experience of conducting user studies will have an appreciation for the intricacies and minutiae of details that must be captured and understood in order to establish probable root cause(s). Moderators of HF studies will have no doubt found themselves questioning how the device and/or instructions might have led to the user's confusion. While participants of studies will have inevitably found themselves assigning

blame on themselves for simply not paying attention or rushing a task.

Observing, recording and subsequently asking participants about their interactions with a device requires the moderator to quickly process information and then exercise judgement on how best to facilitate discussions with participants in a non-leading manner. The qualitative data collected from such studies should then inform suitable corrective and preventative actions to be implemented in order to enhance device design.

One can see therefore that it is critical that moderators and observers of user studies establish the correct root cause(s) to an observed use error, difficulty or close call in order to mitigate or reduce the identified risks as far as is practicable.

By the very act of conducting RCA, the medical device industry recognises that moderators and observers alike are required to exercise judgements based on the information they observe and collect from test participants. While we recommend that these judgements are supported by experienced professionals with prior knowledge of HF principles, with studies conducted in accordance with best practice, it is imperative to recognise the potential for bias and error in decision making. After all we are only human. →



'Characters of the story'

As human beings much of our behaviour, decisions and thoughts, whether we like it or not, indeed whether we acknowledge it or not, are automatic. In the international bestseller, 'Thinking Fast and Slow', Daniel Kahneman narrates two systems of thinking, which he refers to as the characters of the story, namely System 1 (Lewis Hamilton) and System 2 (Thomas the Tank Engine's Fat Controller):

System 1 thinking

Operates automatically and quickly, with little or no effort and no sense of voluntary control.

System 2 thinking

Allocates attention to the effortful mental activities that demand it, including complex computations. The operations of System 2 are often associated with the subjective experience of agency, choice and concentration.

To experience System 1 thinking try the following example. Do not try to over think, just write down the first answer that comes to mind.

A drug and its delivery device costs \$1100. The drug costs \$1000 more than the delivery device. How much does the delivery device cost?

At the moment of completing the final sentence above a number instantly came to mind without effort or conscious control. That answer, was inevitably \$100. The answer came intuitively to you, possibly the speed with which you came to a conclusion surprised you, yet on consideration we know that this is the incorrect answer to the problem. If the delivery device was \$100 then the total cost of the drug and delivery device would have been \$1200 (i.e. The drug costs \$1100 and the delivery device costs \$100 equating to \$1200). Therefore the correct answer to the example above is \$50.

Those familiar with the problem, or indeed 'Thinking Fast and Slow' to which the basis of this article is credited, may well have come to the correct conclusion. However, it is reasonable to assume that the intuitive answer did still come to mind, yet System 2 enabled you to resist the incorrect and 'intuitive' answer. This raises a very significant concept for the context of this article - cognitive ease.

Cognitive ease refers to the extent to which information can be processed automatically and unconsciously without the need for 'cognitive strain'. As Kahneman describes, the human brain is constantly processing information to assess system status and determine whether increased effort or cognition is required. Questions such as "Is anything new going on?", "Is there a threat?", "Should attention be redirected?" These are just a few of the 'automatic' assessments controlled unconsciously by System 1. In cases when the answers to those questions is 'Yes', System 2 is engaged to audit and control the suggested actions and thoughts of System 1.

Why does it matter?

If there is one take-away point from this article it is to acknowledge that System 1, also coined the associative machine, has the potential to jeopardise RCA in medical device development. The implications of association based on previous experiences and intuitions, a hunch if you will, not only poses a risk to conducting effective user studies but also have a direct impact upon device safety and efficacy.

"the resulting data might not be valid or reliable, leading to poor design decisions and ultimately, an unsafe medical device"

'If usability testing is not conducted carefully and systematically, the resulting data might not be valid or reliable, leading to poor design decisions and ultimately, an unsafe medical device.' (ANSI/AAMI HE75:2009).

As with the drug delivery device question, moderators and observers of user studies are susceptible to intuitive answers based on previous experiences and the extent to which an answer feels familiar and true. Interestingly, one could argue that those with greater experience of conducting user studies and a failure to acknowledge such bias, perhaps studying a similar device to one previously tested but for a different indication, are more likely to be influenced by their preconceptions of what they may or may not observe.

In 'Thinking Fast and Slow' Kahneman describes two facets of System 1 that are particularly relevant for the context of this article and ultimately have the potential to be harmful during RCA.

1. "System 1 excels at constructing the best possible story that incorporates ideas currently activated, but it does not (cannot) allow for information it does not have".¹

2. "System 1 is radically insensitive to both the quality and the quantity of the information that gives rise to impressions and intuitions".¹

Both of these characteristics of System 1 refer to what Kahneman defines with the following acronym 'WYSIATI' – 'What You See Is All There Is'. In light of this moderators must challenge their intuitions and remain objective when a use error, difficulty or close call is observed. In short they must engage System 2 and resist the temptation to assign a root cause based on the 'best possible story' or 'intuitive answer' (remember the \$100).

Acknowledge it exists

The question is therefore: How do we mitigate against the potential for bias during root cause analysis in medical device development?

The answer is in part attributable to the acknowledgement that the bias exists. Failing to recognise the bias in the first instance leaves those conducting user studies vulnerable to acting upon previous experiences and establishing an incorrect root cause to an observed use error, difficulty or close call. As an advocate of HF principles, my first recommendation would be to refer to FDA guidance to understand the very basis of what conducting a user study is trying to achieve.

Current guidance from the FDA, Applying Human Factors and Usability Engineering to Medical Devices, states that:

The observational data and knowledge task data should be aggregated with the interview data and analysed carefully to determine the root cause of any use errors or problems (e.g., "close calls" and use difficulties) that occurred during the test. The root causes of all use errors and problems should then be considered in relation to the associated risks to ascertain the potential for resulting harm and determine the priority for implementing additional risk management measures'.²

Following this approach will challenge any preconceptions that moderators and observers of a user study may have and emphasise the need to focus upon both characters of the story; System 1 and 2.

Understand the criticality of tasks

Critical tasks are tasks that if performed incorrectly or not performed at all would or could cause serious harm to the user. Prior to conducting a validation study it is imperative to have a firm grasp of the critical tasks that users should perform correctly for device use to be considered safe and effective.

System 1 thinking may lead you to falsely assume that observing zero critical use errors during early formative testing means you have a safe and effective device that will pass validation testing. Remember the acronym 'WYSIATI'. One must remember that just because a potential use error has not been observed during early formative testing does not preclude them from being observed during validation testing.

The FDA highlights that the list of critical tasks is dynamic and will change as the device design evolves through iterations and preliminary analyses thus validation study protocols should 'include mechanisms to detect previously unanticipated use errors' (FDA, 2016).

Seek expert advice

Finally, and it may sound like a cliché, but seeking advice from professionals with experience in human factors engineering is advisable. It should be stated that involving HF specialists can only be truly effective if they are incorporated into the design, preparation, implementation and analysis of a user study. Only then can you be assured and take confidence in the approach and results attained through conducting a user study during medical device development. If your intuitive reaction to that last sentence led you to the conclusion 'here comes the sales pitch' then you may be surprised to hear that this advice is taken directly from FDA guidance.

In ANSI/AAMI HE75: 2009, the FDA state the following:

'Usability testing plans should be developed in collaboration with professionals with human factors expertise. Human factors expertise is also needed in the interpretation and analysis of results.'³

Summary

Conducting RCA in user studies during medical device development is inherently a cognitive activity that requires moderators and observers alike to exercise judgements. As a result, RCA in medical device development is exposed to potential biases through association and repeated experience.

Unconsciously our minds constantly seek connections or relationships to scenarios where we feel familiar and comfortable making us vulnerable to biased judgements that are based on our previous experiences and observations.

This might come as an alarming conclusion to some, however it is critical to acknowledge the limitations of conducting user studies in order to address, minimise and control the bias introduced into a study. This article reinforces the criticality of agreeing a methodical protocol amongst the project team that is supported by a documented human factors evaluation process and risks analysis. **ENDS**

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3. ANSI/AAMI HE75:2009. Human Factors Engineering – Design of Medical Devices



ALL OF THESE

ALL THESE

ALL OF THESE

How the EU IVD Regulation brings us forward from the 1990s

Hannah Murfet



In vitro diagnostic (IVD) devices are a complex group of products that have been regulated in Europe in the same way since the 1998 IVD Directive. Importantly, since the 1990s, the level of complexity of IVD devices has dramatically changed and continued to evolve, with the emergence of companion diagnostics and higher complexity tests. The new EU IVD Regulation has long been on the cusp of publication, and as this gets closer it is clear that all will change.

Looking back

Looking back at 98/79/EC or the IVD Device Directive, the European framework for these products is essentially a positive inclusion list.¹ There are two lists within the IVD

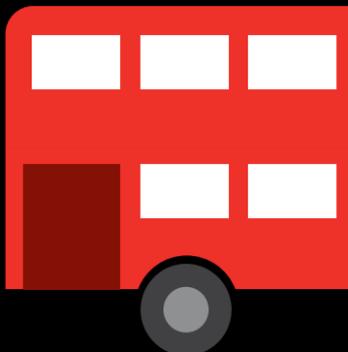
Directive, namely List A and List B. If a product is not included in either list, is not a self-test or is non-sterile, the product is 'classified' as a general IVD.

Note the significant contrast with 93/42/EEC, the Medical Device Directive, containing classifications of I, IIa, IIb and III which allow conformity assessment based on risk.²

List A of the IVD Directive contains a set of product types that were perceived to have the highest level of risk (e.g. reagents for detection of HIV infection). List B contains a set of product types that were perceived to have a lower level of risk, for example reagents for determining infection to specific human infections (e.g. cytomegalovirus).

With the IVD Directive lists being so prescriptive, it naturally lost pace with new developments. In fact, it has lost pace to such an extent that most new, genetically-based cancer tests are likely to have been regulated as general IVDs, including companion diagnostics.

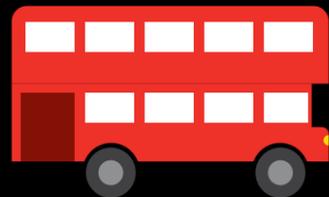
Most IVDs are categorized as general IVDs. Consequently, the majority of IVDs on the market have been self-certified by the manufacturer. This means that to date, IVDs have required limited notified body involvement, and responsibility has been placed on the manufacturer to ensure compliance to essential requirements and performance characteristics for around 80% of IVDs.³ →



Looking forward

With the new IVD Device Regulation in Europe, IVD products remain distinct from the now consolidated regulation for medical devices and active implantable medical devices. It makes sense for IVDs to continue to be regulated separately, as there are many differences between the two groups, including the indirect application and risk.

The IVD Device Regulation has several changes and requirements in common with the new medical device regulation, such as the requirement for a person responsible for regulatory compliance, increased focus on unannounced audits and Unique Device Identifiers



(UDIs). However, for IVDs, unlike medical devices, there have not been high-profile post-market events, such as the metal-on-metal implant issues or the PIP (Poly Implant Prosthèse) scandal. Given the relatively safe profile of IVDs, a lot of additional regulatory oversight will come with the new IVD Device Regulation.

“The regulation introduces four classes, class D being the highest risk and class A the lowest”

The new regulation brings into place a risk-based classification system, moving away from positive inclusion. The regulation introduces four classes, class D being the highest risk and class A the lowest, thereby providing greater regulatory agility. Only class A devices that are not for self-testing, sterile or for near patient testing, escape direct notified body product review, only around 20% of IVDs.³ A significant contrast for both the regulators and industry.

What is an IVD?

An IVD can be anything from a specimen receptacle, to a urine test, to a molecular diagnostic screening instrument. The key differentiator is that IVDs never interact directly with the human body, as their diagnostic purpose is based on specimens derived from the human body, for example a blood glucose meter.⁴ A test that analyses body fluids directly, for example a continuous glucose meter, would be regulated as a medical device instead.

What is conformity assessment?

Conformity assessment is the process by which products are assessed against the requirements of the Directive in order for the products to be CE marked and placed on the market. For lower risk devices conformity assessment is often performed by the manufacturer, whereas for higher risk devices an independent and authorized party, the notified body, may be involved in the assessment process.

What are companion diagnostics?

A device that is essential for the safe and effective use of corresponding medicinal products. They can be used to identify patients that are likely to benefit, or patients who are at risk of adverse reactions or to monitor responses to treatment.⁵

What are self testing IVDs?

Devices for testing carried out by lay persons.⁵

What is ‘near patient testing’?

The use of devices for testing carried out outside of controlled laboratory conditions, generally by a health professional near to the patient.⁵

Brace for impact

Moving to a classification system for IVDs allows for the regulatory framework to remain more agile as technology develops. For newly classified B to D IVDs, the classification changes are significant for the industry, as there may be further administrative burdens on many small and medium-sized companies in this sector.³ The change will require involvement of notified bodies during the conformity assessment before a product can be placed on the market, and for many IVD manufacturers this will be a new experience.

For companion diagnostics, the changes under the new regulation are even more significant as many of these IVDs are currently self-certified. The new regulation introduces a definition and special provisions for companion diagnostics, to be regulated as class C. In addition, for companion diagnostics, the proposed regulatory changes include European Medical Agency (EMA) involvement. This unique requirement has caused industry concern since the EMA are likely to be already involved with the regulation of the companion drug and the review process is currently unclear.⁴

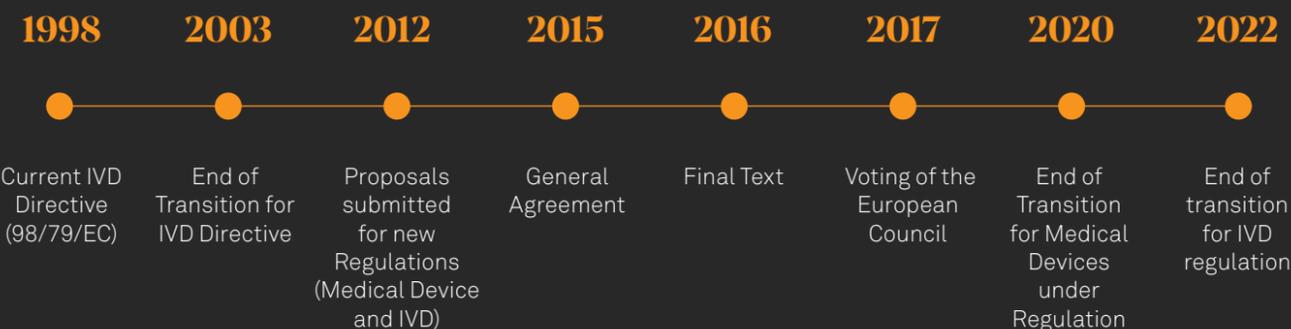
Clinical evidence will be required throughout the product lifecycle of IVDs, including scientific validity, analytical performance and clinical validity.³ This means that the amount of performance evaluation and the number of clinical studies are likely to increase, adding further cost to development. Manufacturers will also face a stronger post-market element with continual assessment of new scientific evidence to determine any impact on clinical validity. In-house developed tests (e.g. those developed and performed by hospital laboratories) will be exempt from the regulation for all bar some specific provisions for class D devices. This exemption is if they are used in facilities running under the same quality management system, typically to ISO 15189.

Currently this exemption extends to in-house companion diagnostics, potentially raising further concern by industry due to the difference in costs of development and regulatory scrutiny. The new IVD Regulation certainly brings about significant change for both the industry and the regulators. However, it is likely that for several

manufacturers similar processes have been undertaken to place the product in the US or Canadian markets. There is only a little time, with the new IVD Regulation expected to have a 5-year implementation period. During this time, it will be important for the industry and regulators to remain proactive and responsive, implementing the necessary changes.

All change please, all change. ENDS

Everything changes in the new IVD Regulation



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★ **THOUGHTS FROM A FORMER FUND MANAGER PRESENTS:** ★

PHARMACEUTICAL



MEDICAL DEVICE INVESTMENT

Most investors understand the mechanics of investing in a new pharma or biotech company. It usually starts with a group of scientists identifying a drug molecule with potential therapeutic effect. Investors are then found and pump in cash so that the drug can go through pre-clinical and subsequently clinical testing. It takes a lot of money and the rate of attrition is quite high, but it is well known that big pharma will pay handsomely for promising new drugs.

Medtech on the other hand is less easy to understand and hence the investment community tends to view it differently and more cautiously. This may sound like a gross oversimplification but familiarity with a market sector plays a huge role in investment decision making.

SPREADING THE RISK

A "typical" medical device company is difficult to describe. The sector covers a broad spectrum, from orthopaedic joint replacements, cardiovascular stents and insulin pumps, to the monitoring devices used in hospitals and point of care diagnostics.

When I used to run biotechnology funds, their remit was wide enough for me to spread the risk by investing in both specialist and large pharmaceutical companies. However, to construct what the finance professors describe as "a well-diversified portfolio", I broadened my investments beyond the life sciences, by swapping some big pharma for some medical device companies.

This added some necessary diversification, largely because there is a significant difference in the commercial, regulatory and even clinical dynamics of medical devices and small or large molecule drugs. Should the biopharma sector have a bad day, medical device stocks may hold up the combined

portfolio. In addition the dynamics of medical device companies provide a contrast with those of drug development companies and can, with sufficient research, be nearly as profitable.

TIME TO MARKET

For medical devices such as cardiovascular stents and pacemakers, pre-clinical testing generally leads to proof of principle and the improvement of an existing design far more quickly than is the case for drugs. Clinical studies can therefore start much sooner, reducing the time and cost involved in bringing a product to market.

This is partly because stents, pacemakers, neurostimulators and orthopaedic implants, for example, have very a localised function, and don't present the same risk of off-target effects as pharmaceutical products. For local ethics committees, principal investigators and regulators to approve the first human administration of a new chemical entity drug, any effects must be monitored in large pharmaco vigilance studies.

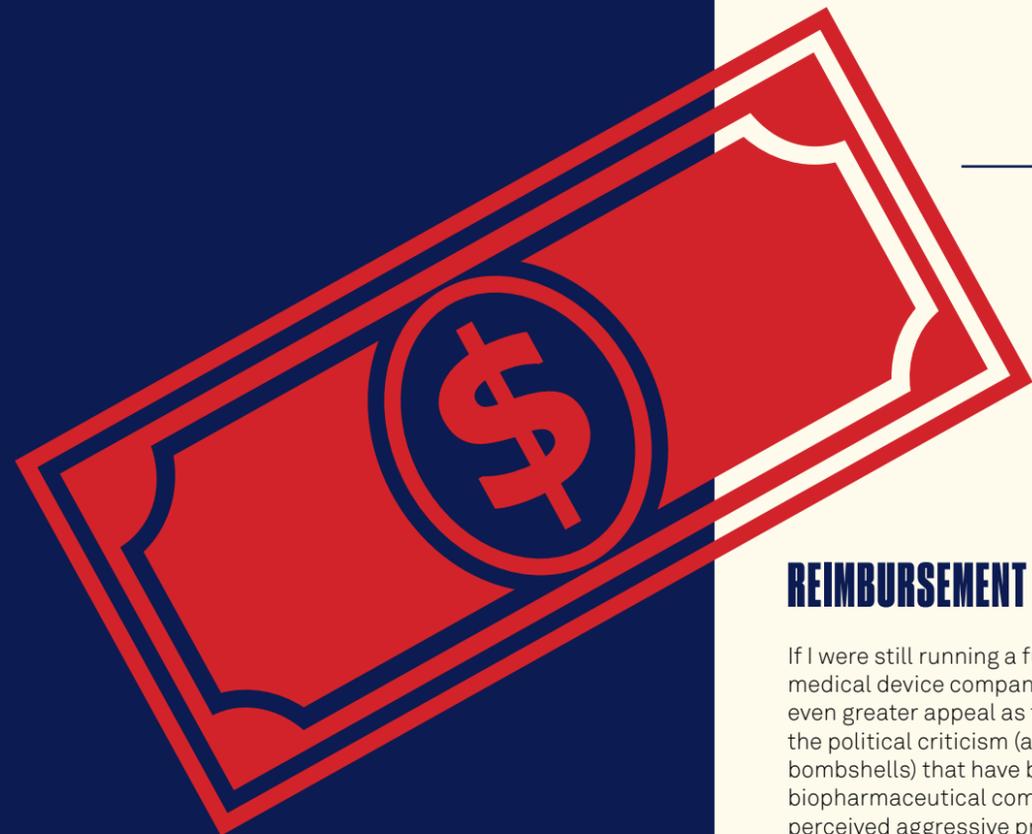
Medical device trials are smaller. My guess is once 10 pre-clinical trials have been done successfully clinical trials can begin. An orthopaedic implant, or even a continuous glucose monitor – by virtue of its essentially mechanical nature – will work in a similar way during trials. While drug companies will try to lure investors by describing how close their clinical model of disease is to the human patient, experience has shown, in Alzheimer's disease or schizophrenia for example, that this isn't always the case. Our brains are a little more complicated than those of mice, whereas our joints and blood vessels are more comparable. This all serves to help bring medical devices to market far more quickly than drugs. →

Andy Smith



"IT USUALLY STARTS WITH A GROUP OF SCIENTISTS IDENTIFYING A DRUG MOLECULE WITH POTENTIAL THERAPEUTIC EFFECT"

“MEDICAL DEVICE COMPANIES RECEIVE LESS BACKLASH FROM PAYERS THAN DRUG COMPANIES”



REIMBURSEMENT

If I were still running a fund today, medical device companies might have an even greater appeal as they have avoided the political criticism (and social media bombshells) that have been levelled at biopharmaceutical companies for their perceived aggressive price increases. The medical device sector has not been without its pricing issues however. The Affordable Care Act (ACA) included a medical device tax that had companies celebrating at its temporary suspension and salivating at the prospect of ACA's repeal under the Trump administration.

But even with high sticker prices, medical device companies receive less backlash from payers than drug companies. The \$1,000 gross price per pill of the anti-HCV medicine Sovaldi (sofosbuvir) was met with howls of objection from pharmacy benefit managers and US senators. Conversely, a similarly priced orthopaedic implant or pacemaker generates little reaction.

Another small but potentially helpful advantage for medical devices over pharmaceuticals is that (outside the case of special licenses in the UK) a charge cannot be made for an unapproved drug in a clinical trial, whereas devices can be charged for. The rationale for this may be that, once implanted, devices are expected to be long-lasting and spare the patient the cost and side-effects of drugs.

“MEDICAL DEVICE COMPANIES NEED ACCESS TO A SKILLED WORKFORCE WITH FIRST-HAND EXPERIENCE”



ACCESS TO TALENT

Medical device development is a highly specialised industry and, in order to succeed, medical device companies need access to a skilled workforce with first-hand experience. This means that medical device companies tend to form around geographic clusters. The same is also partially true for biopharmaceutical companies but I would suggest that the range of skills needed to get a biopharmaceutical into Phase 1 are slightly more widely accessible than those needed to get a medical device into the clinic. This is something which investors and entrepreneurs should bear in mind when investing or building new device companies.

A ROSY PICTURE?

Medical device companies do not always represent a lower risk investment option compared with pharmaceuticals. However when the underlying technology is proven (even in principle), the market need is understood and quantified, and a team with sufficient experience has been assembled, then I would argue that a medical device business can provide an investment opportunity which is more transparent than a new drug candidate. ENDS

“MEDICAL DEVICE COMPANIES DO NOT ALWAYS REPRESENT A LOWER RISK INVESTMENT”

Andy Smith is an experienced life science industry professional who has spent many years in global healthcare, spanning academic research, product development, global marketing, consultancy and fund management. He holds an MBA in International Marketing, a BSc (Hons) in Microbiology and a PhD in Molecular Biology.

As the manager of the best performing technology fund listed on the London Stock Exchange, Andy was awarded Techmark Technology Fund Manager of the year in 2006. He joined AXA to manage the AXA Framlington Biotech Fund from venture capitalist SV Life Sciences in April 2008 and has written the Stockwatch column in Scrip since 2011.



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