

# Insight

Team Consulting's opinions and thoughts on the world of medical devices and healthcare

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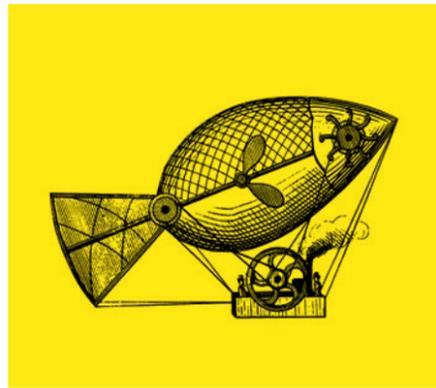
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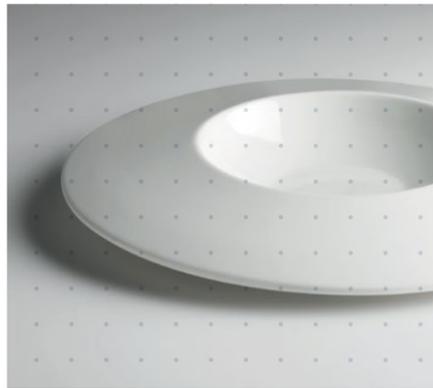


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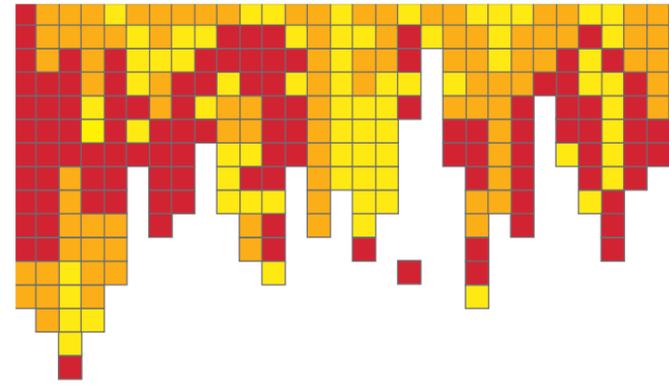


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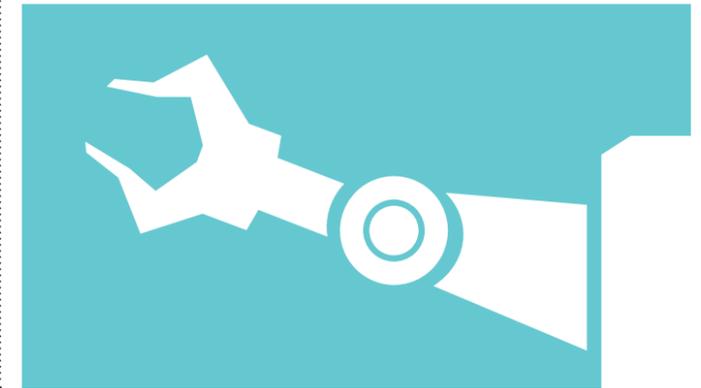


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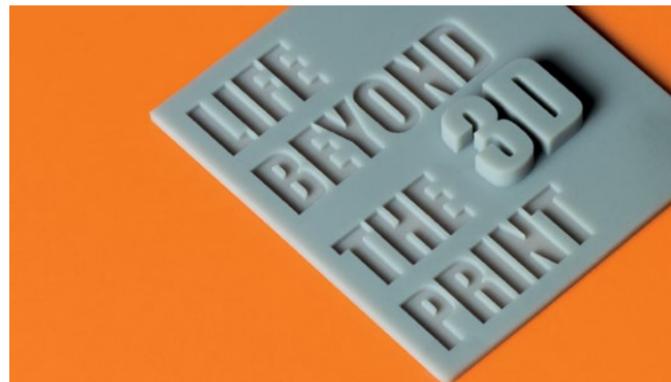


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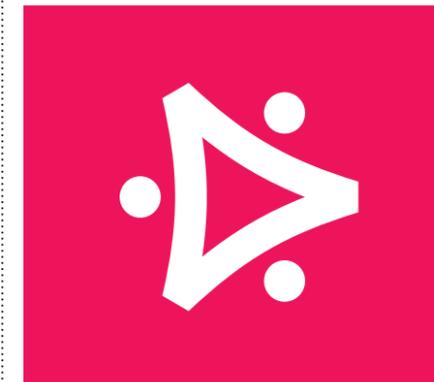


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# Unlucky 13

Welcome to the thirteenth issue of *Insight*. While the number 13 may be unlucky for some, we're rejecting triskaidekaphobia and instead embracing Robert A. Heinlein's assertion that there's no such thing as luck. In fact, we've got so many great articles for you to peruse that we're feeling pretty lucky.

In this issue, Ben breaks down the blood-brain barrier for beginners, dynamic duo Stella and Laureline shine a spotlight on excipients, and Amy analyses how to make failure a friend. Our guest author Sebastian Stanley looks at life beyond the 3D print, while Alex discusses his design drivers.

Fingers crossed you enjoy it!



Dan Flicos, CEO



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## An engineer's perspective of medical device failure

By Amy Evans



# Failure is a friend

Failure is something that people don't like to talk about. "Tell me about a time you failed" is a question dreaded by most and, at best, often gets a very guarded response; however, engineers and designers can share their many lessons and learn from failure. As Henry Ford said, "The only real mistake is the one from which we learn nothing".

History shows many great examples of learning from -often catastrophic- failure. In 1912, the sinking of the Titanic after hitting an iceberg led to major improvements in maritime safety, including the establishment of the International Convention for the Safety of Life at Sea (SOLAS) and several new wireless communication regulations. In 1940, the collapse of the Tacoma Narrows Bridge due to aeroelastic flutter boosted research in the field of bridge aerodynamics and aeroelastics, which significantly improved the subsequent design of all long-span bridges. In the 1970s, the Dalkon Shield contraceptive intrauterine device (IUD) caused sepsis

and other complications that led to the Medical Device Amendments, which mandated the US Food and Drug Administration (FDA) to require the testing and approval of medical devices.

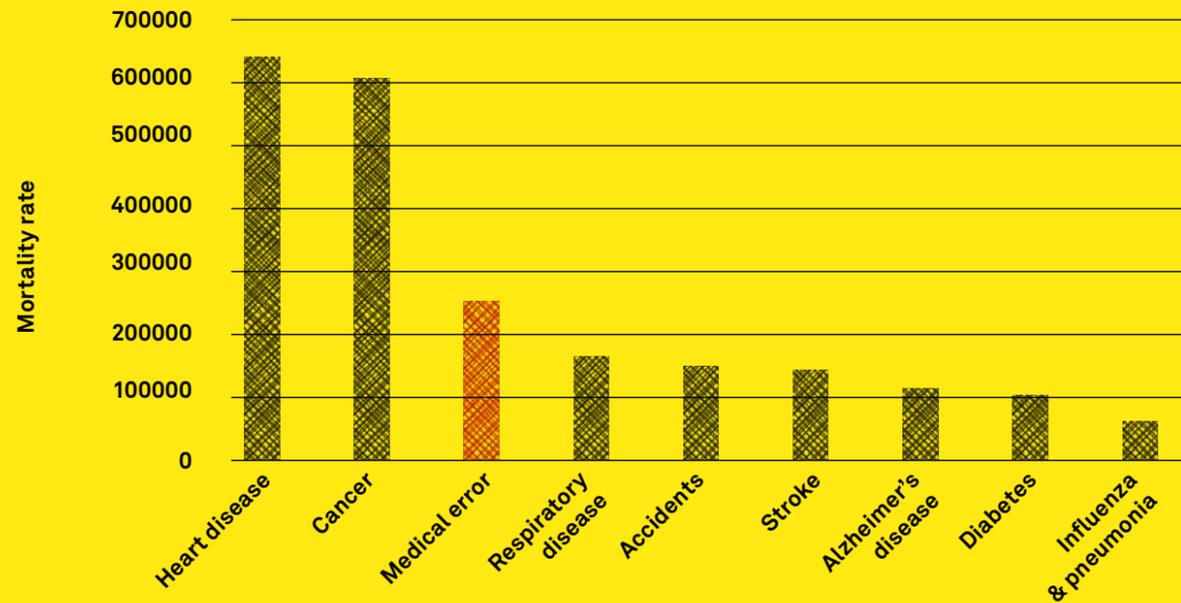
Medical error has been estimated to be one of the leading causes of death in the US, accounting for over 250,000 deaths annually<sup>1</sup>. This is only exceeded by the two big killers, heart disease and cancer<sup>2</sup>. Medical devices are intended to sustain and improve quality of life. Unfortunately, there is inevitably a risk that failure of these products or the associated procedure can result in injury, disability, threats to life or even death.

The medical device industry is highly regulated to help ensure that devices are safe and effective. Each year, the FDA receives several hundred thousand reports of suspected medical device-associated deaths, serious injuries and malfunctions. It is important to note that failure is rarely the result of a single cause and lessons from history show

that, especially in complex systems, major failures often result from a sequence of seemingly unrelated small deviations or events. Nevertheless, analysis of root cause data reveals that failures of product design and manufacturing process control caused more than half of all medical device recalls<sup>3</sup>.

Having worked in post-market surveillance for a multinational, orthopaedic company, I have seen numerous product failures. I have developed a keen interest in understanding why things fail and how we, as engineers and designers, can learn from this to minimise future risk. The following sections describe seven key learnings based on case studies of medical device failure. →

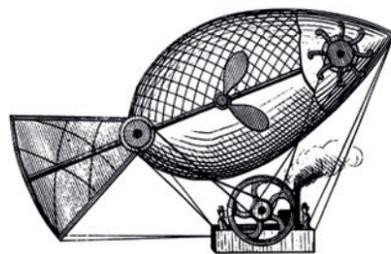
Table 1: Leading causes of death in the US, 2015



## 1 Conduct extensive background research

Without striving to benefit from learning, history will repeat itself. Accordingly, when undertaking a new device development project it is important to understand relevant previous events.

In the early 1980s, Vitek, Inc. released their Proplast-Teflon Interpositional Implant (IPI) for the jaw, designed for the surgical replacement of dysfunctional discs in the temporomandibular joint (TMJ). Within a few years patients began to experience serious health-related problems. Teflon had been abandoned as a bearing surface for total hip replacements as a result of research conducted in the 1960s. This indicated that failure would be unlikely in the jaw, an allegedly non-load-bearing joint. It was subsequently shown that the jaw is load bearing (up to 89 N) and if it had been tested to this load, Vitek would have noticed the rapid failure of the implant<sup>4</sup>.



Background research should include a review of the following sources of information:

- Applicable standards, guidelines and regulations,
- Competitor comparisons,
- Manufacturer and User Facility Device Experience (MAUDE) database of Medical Device Reports (MDRs),
- Product recalls of equivalent products/materials, and
- Internal complaints.

From this research, quantitative techniques such as hazard analysis can be used to identify, rank and eliminate or control foreseeable hazards according to the risk profile. Not only is it advisable to carry out research to inform development, it is also a requirement of the standards that we work to.



**“Failure and negative feedback in the early stages of product development are much easier and cheaper to accommodate and control than complaints and lawsuits after product launch.”**

## 2

### Establish and understand user requirements

The inclusion of input from potential users is invaluable for defining and understanding the technical/functional requirements that the device must fulfil in conjunction with issues from previous attempts or techniques.

From 2005 to 2009, the FDA received approximately 56,000 reports of adverse events associated with the use of infusion pumps, including numerous injuries and deaths. During this period, 87 infusion pump recalls were conducted by firms to address safety concerns. These adverse event reports and device recalls were not isolated to a specific manufacturer, type of infusion pump, or use environment, but rather occurred generally across the board. The reported problems included confusing or unclear on-screen user instructions, which may have led to improper programming of medication doses or infusion rates. For example, the design of the infusion pump screen may not make clear which units of measurement should be used to enter patient data, leading to inappropriate dosing, and having the power button adjacent to the start infusion button could lead to accidental shut down of the infusion pump.

Input from potential users can be obtained through market surveys, focus groups and design research activities as well as previous case studies. This can give engineers and designers insight into who uses the device, how the device is handled and stored, when and where the device is used, other products the device might need to interact with, and the benefits and shortfalls of existing products. Many user-related risks can be avoided at the design stage by minimising complexity for users.

## 3

### Don't rush the device development process

By definition, development of a new device involves a number of uncertainties, including political, social, technological, legal and market changes. Accordingly, a degree of flexibility is essential in the development timeline. Manufacturers can take a faster route to market through the FDA 510(k) process, which doesn't require clinical data for medical devices where substantial equivalence can be claimed. In 2015, the FDA approved 3,006 510(k) devices compared with 47 Premarket Approval (PMA) devices<sup>5</sup>.

The DePuy ASR hip system became commercially available in 2003 to resurface the hips of younger patients diagnosed with non-inflammatory degenerative joint disease. In 2010, DePuy issued a voluntary recall after receiving data from the National Joint Registry regarding higher than normal revision surgery rates. The metal-on-metal bearing was vulnerable to shedding metal particulates, resulting in component loosening, malalignment, infection, bone fracture, dislocation, metal sensitivity and/or pain<sup>6</sup>. The FDA approved the ASR hip system through the 510(k) process, thus not requiring clinical trials.

Engineers and designers should be encouraged to not only identify failures but celebrate learnings from failure during product development as an important product investment. Failure and negative feedback in the early stages of product development are much easier and cheaper to accommodate and control than complaints and lawsuits after product launch. We need to ensure that our development plan and timelines include, where possible, scope for design review and iteration. →

# 4

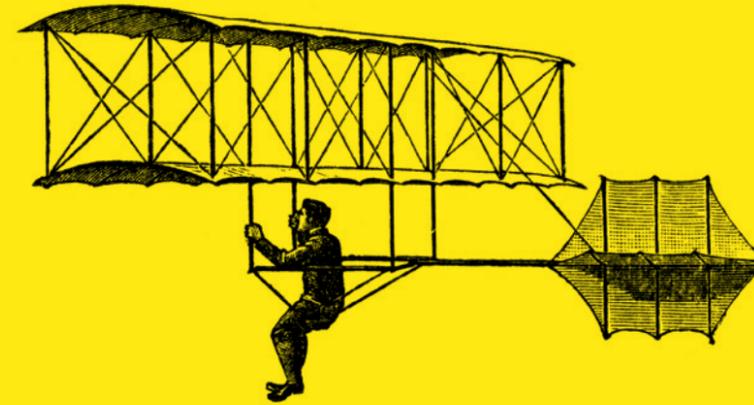
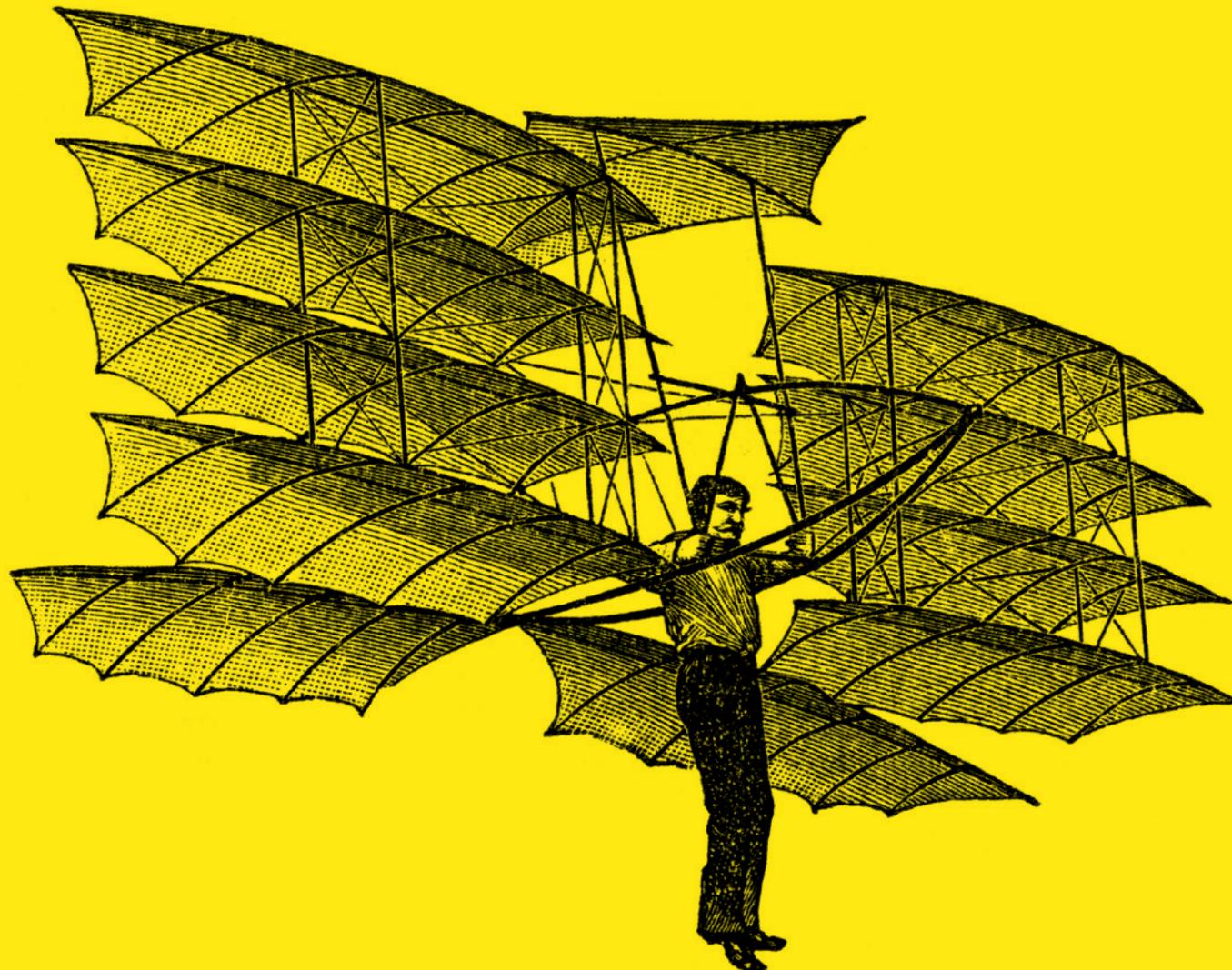
## Design for ease of manufacturing and assembly

By knowing your target market and sales volumes, scalable production methods should be considered from the outset. Inhalers and auto-injectors are often manufactured in high volumes, using multi-cavity moulds and high-speed automated assembly where 100% inspection is not always practical or cost-effective.

Pressurised metered dose inhalers (pMDIs) are small, unobtrusive devices that remain the most commonly used inhalation device worldwide, with annual production of over 800 million units<sup>7</sup>. The GlaxoSmithKline (GSK) Ventolin HFA is a pMDI with a built-in dose counter that is used to treat or prevent bronchospasm. GSK voluntarily recalled more than 590,000 inhalers in 2017 due to the canister leaking, resulting in fewer doses than shown on the dose counter<sup>8</sup>. The defect was isolated to three lots, manufactured at their site in Zebulon, North Carolina<sup>9</sup>. pMDI valves are technically complex and critical to delivering a consistent and precise dose of medication.

To facilitate efficient transfer of the design concept to the manufacturing environment, processing methods must be considered throughout the development process. Design for Manufacture and Assembly (DFMA) and process risk assessments (pFMEA) can not only improve cost effectiveness and timeliness but also improve quality and reduce defects. Consideration of materials selection, manufacturing and assembly processes, finishing processes, inspection and testing methods during development helps ensure that devices can be produced using capable, stable processes.

**“Murphy’s law says that anything that can go wrong, will go wrong”**



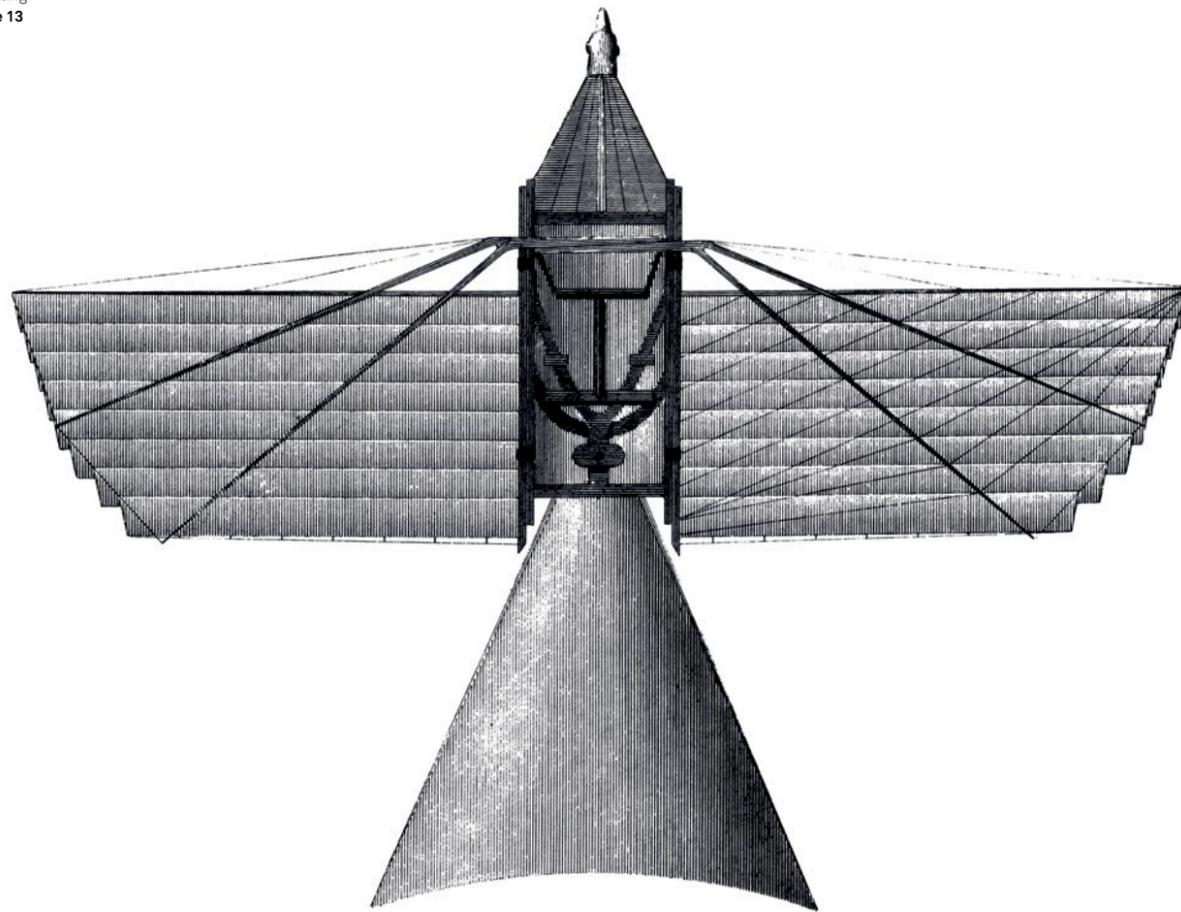
## Take a risk based approach

Murphy’s law says that anything that can go wrong, will go wrong. As engineers, we know that medical devices have a design life. Accordingly, a risk-based approach is needed to ensure that if failure occurs, it happens safely and predictably, in a way that is obvious to the user and beyond the intended life and operating conditions of the device.

Evita and Babylog ventilators, manufactured by Dräger, are used to provide constant breathing support for adults and children. Both ventilators can be used in conjunction with the PS500 power supply. In 2015, Dräger recalled 2,422 PS500 power supplies due to a software issue causing shorter than expected battery run times. The issue prevents the appropriate alarm from sounding five minutes before the battery runs out of power and the device shuts down<sup>10</sup>. Fortunately this issue has not resulted in patient injury or death; however, a thorough risk analysis might have discovered the fault earlier.

**“A risk-based approach is needed to ensure that if failure occurs it happens safely and predictably”**

Risk management for medical devices is described in ISO 14971:2012 and there are many ways in which we can comply with this standard. It is not only used throughout the device development process, but is also a valuable tool during post-market surveillance. The risk management system adopted needs to be fit for purpose for the intended product and the associated risks. Periodic, independent review of the risk management process is also encouraged. →



## 6

### Test beyond design requirements

Design verification testing is a formal process based on pre-defined and agreed testing specifications to ensure that design input requirements have been fulfilled by the design outputs. If possible, however, additional engineering testing should be performed that goes beyond basic design requirements. We can learn a lot more about the robustness, limitations and failure modes of our design if we test under extreme or unusual conditions, to failure.

The Acroflex artificial disc was developed by Acromed in the 1980s for the treatment of degenerative disc disease of the lumbar spine. The device had a polymeric core made from polyolefin rubber, which was fused between two metal end plates. Acroflex was subjected

to biocompatibility and biomechanical tests, including cytotoxicity, compressive creep, peel strength and compression, torsion and shear endurance testing. Despite some incidences of local material failure, the tests were deemed successful. Acromed did not obtain permission to conduct animal testing so proceeded to human trials. Thirty-six percent of patients experienced tears in the polyolefin material, which led to revision surgery after 2–4 years<sup>12,13</sup>. Given that animal testing was not possible, overstress testing may have identified the shortcomings of the polyolefin material prior to human trials.

To identify any vulnerabilities associated with a device during development, an exhaustive stress testing regime should consider:

- Being representative of real life use: fatigue testing and aging are often accelerated to reduce time; however,

they may not be representative of – or worse than – real-life use.

- Testing to failure: is the failure mode safe? Is the safety factor adequate? For example, we could drop test from 2x and 3x the maximum specified height to see what breaks when, and/or establish a safety factor for the specification.
- Worst case conditions: have we considered reasonable worst-case conditions (e.g. heavy patient, small implant, poor bone quality) or Multiple Environment Over Stress Testing (MEOST), which uses a combined environment of extreme stresses?
- Principles testing: use an experienced but objective engineer (or group) who tries to 'break' or fail the device.

## 7

### Be vigilant with post-market changes

Inevitably, companies will want to make efficiency and continuous improvement changes to suppliers, materials, processes and/or the design after market approval. These changes will not necessarily be reviewed by the original design team so vigilance is required when assessing their impact.

Silicone gel breast implants, manufactured by the French company Poly Implant Prothèse (PIP), were introduced worldwide from 1991 for breast augmentation or reconstruction. In 2000, the FDA banned silicone breast implants in the US, which led to a decline in PIP sales. In order to reduce costs, the company decided to use unapproved, industrial-grade silicone in their implants<sup>14</sup>. Surgeons in France began reporting abnormally high rupture rates; the PIP implants were 2–6 times more likely to rupture or leak than other implants. The PIP implants were recalled by the French regulator in 2010. There are two key issues here: firstly, the use of an unapproved material, and secondly, the lack of testing to demonstrate that the new material meets performance requirements. Testing prior to implementing the material change would have potentially uncovered failures and prevented the issue.

As engineers and designers, we need to be aware of our responsibilities in the face of commercial pressures and drivers that will arise during product (re-) development. Therefore, we need to be extremely vigilant when assessing the impact of material, design or processing changes, especially post-market approval. It is imperative that preclinical and clinical testing is conducted on production devices, and that extensive testing and analysis are carried out when making post-market modifications. Even seemingly insignificant changes can lead to unintended consequences.

**“However great or small the failure, there is always something we can learn. Failures can be a friend if we take the time to understand and respond to them.”**

### Conclusion

We have seen many great examples of lessons learned from engineering failure throughout history. ‘Failures’ happen around us all of the time – in our industry, in our company and in our projects – and are often, though not always, intentional. However great or small the failure, there is always something we can learn. Failures can be a friend if we take the time to understand and respond to them. **ENDS**



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# Design Drivers

## What drives great design?

By Alex Driver



It should be a familiar scenario for most designers you've waved goodbye to the client after a successful briefing and returned home with reams of loose sketches and a head buzzing with ideas. The next morning you find yourself staring at a blank piece of paper wondering how on earth you're going to give structure to the swirling mass of possibilities that lie in front of you. Moreover, you have to consider how you're going to demonstrate to the client that the concepts appearing at the other end answer the brief.

## Where to start?

Many desk-based tools are available to help focus our activity and encourage divergent thinking at the start of a project:

- We can use tools such as 'User journey mapping' or 'PCA analysis' to identify 'pain points' in the use sequence.
- We can break a system into sub-systems to help focus our attention on specific user or mechanical interactions, i.e. how might we deploy a needle shield or how might we aid removal from packaging?
- We can focus our brainstorms on themes, e.g. size reduction, ease of manufacture, robustness, reducing cost of goods, etc.

These tools are a great way to help identify, prioritise and solve practical design challenges; however, they are less well suited to more emotive issues.

How a product feels or, more accurately, how a person feels about a product needs a slightly different approach.

To tackle these challenges I like to use a tool called 'Design Drivers'. It's useful not only as a method to highlight areas on which we want to focus, but also for defining a vision of 'where you want the product to be' rather than improving incrementally on what you already have.

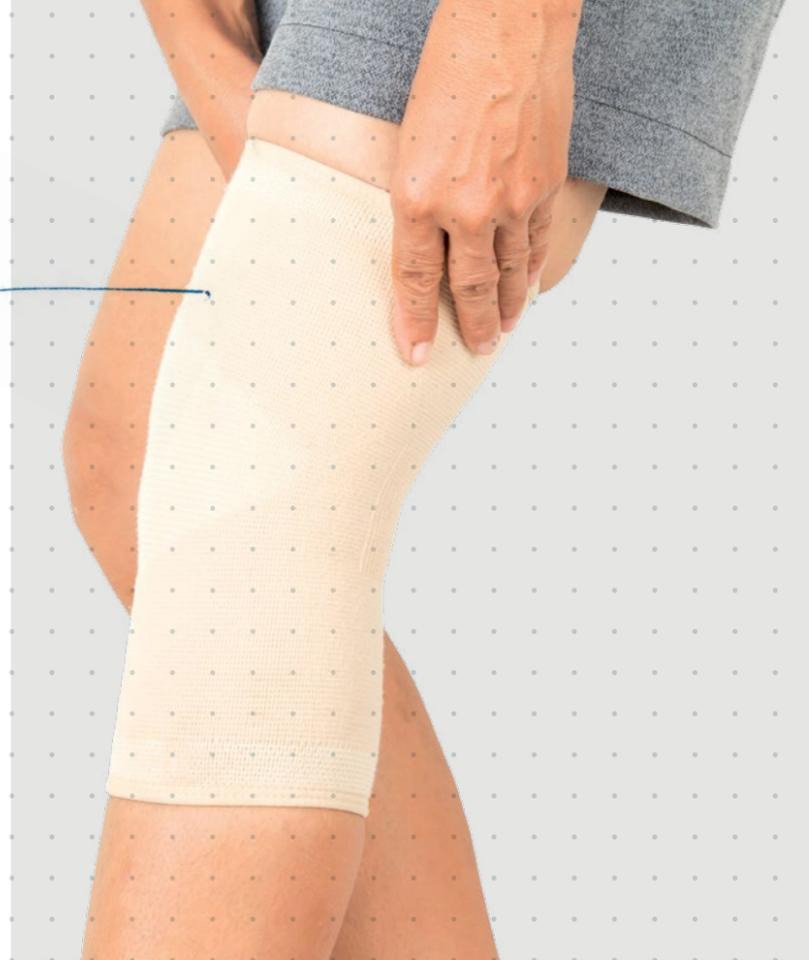
## What are Design Drivers?

"Design Drivers" are really just a list of headings that describe what you want the product to do or be; however, their power comes in the (often provocative) wording and careful selection of imagery chosen to accompany them. They help us to capture in a tangible way an example of what a well-executed solution might feel like, helping to define our aspirations and providing a vision against which we can quickly judge our design as it inevitably evolves. So why is it important to take this approach? Can't we rely on a well-written specification? Well yes, your spec will clearly define your requirements, and yes, you can solve each requirement individually to prove you've met the spec, but you might still fall short of what was actually needed from the overall product experience. →

## Invisible beneath clothing

Take the following example, which could be a driver for the design of a wearable injector: a more functionalist approach might have been to say “small” or “compact”, but the use of the word “invisible” in combination with a stimulating image might encourage participants in a brainstorming session to push their thinking into areas previously considered out-of-bounds. How could the internal components be reconfigured to create a slimmer profile? What forms, materials and colours are least conspicuous beneath clothing? Could the device move or flex with the body? The goal is to inspire more divergent thinking in the hope of landing on something truly innovative.

More than that, the image elicits an emotional response, reminding you that these are frequently worn on intimate areas of the body and must be used throughout the day, whether at work or in bed. A picture tells a thousand words as they say.

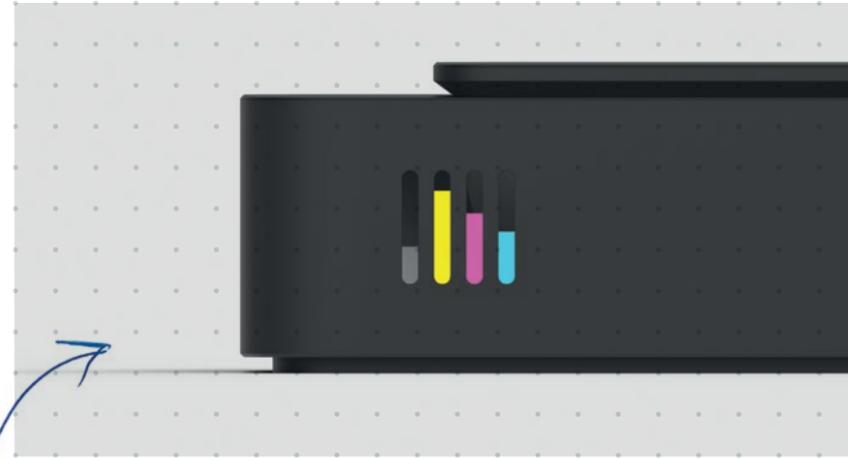


**“You find yourself staring at a blank piece of paper wondering how on earth you’re going to give structure to the swirling mass of possibilities that lie in front of you.”**



### Never feels dirty

This image makes me think of materials with inherently dirt-resistant qualities and smooth forms that are easy to clean. This might lead us to consider construction methods that avoid dirt-traps or the selection of materials and surface finishes that won't mark easily, rather than just making it 'easy to clean'.



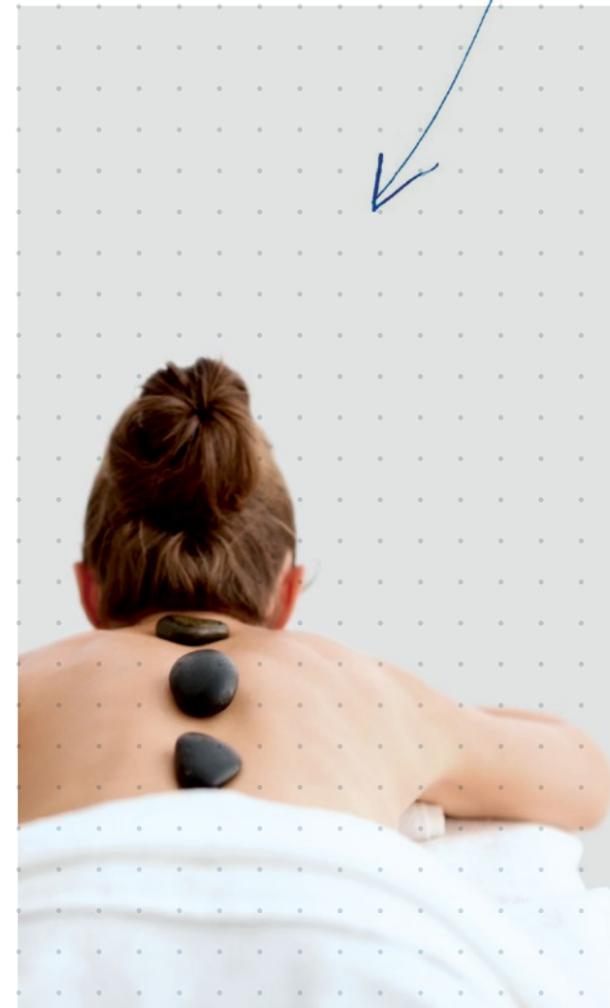
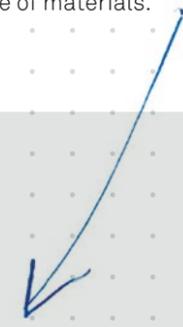
### At-a-glance feedback

It's all-too common for the user interface of a modern medical product to be cluttered with labels, icons, screens, LEDs and buttons, with the result that the user becomes lost in the noise of information. By contrast, the user interface in this image provides relatively complicated feedback on the device status in a very pared-back way. Could a similarly elegant solution communicate the number of remaining doses in an inhaler 'at-a-glance'?



### Comfortable against the skin

When designing a device that is worn against the skin, the emphasis is often on reducing discomfort, but this image poses the question, “Could a wearable device actually be comfortable?” Form is an important consideration, but the image also leads us to consider the inherent tactile qualities and temperature of materials.



## How are Design Drivers useful?

Design Drivers are primarily a powerful tool for encouraging divergent thinking during brainstorming sessions, but they have several additional advantages:

- They provide a tangible example of the ultimate aim at the start of a project; their highly visual nature makes it easier for the team (client – engineer – designer) to discuss and agree the nuances of what is required.
- The selection of imagery can often help to establish the desired visual look and feel of the product early in the process.
- Walking through Design Drivers at the start of a client presentation can help to establish a context for the concepts that are to follow.
- They provide a set of aspirational goals for a project against which designs can be 'measured' both at the outset and throughout the development process.

For example, during a recent project to develop a piece of lab equipment, Design Drivers helped the team to stay on-track as manufacturing and time constraints threatened to water down the original design intent. The Drivers were frequently referred to during the project as they succinctly described the key aspirations for the product at a high level.

As the 'design literacy' of the average consumer grows, we'll look increasingly at how a product makes us feel to differentiate the myriad options available, so tools such as Design Drivers may see more use in our field of work.<sup>ENDS</sup>

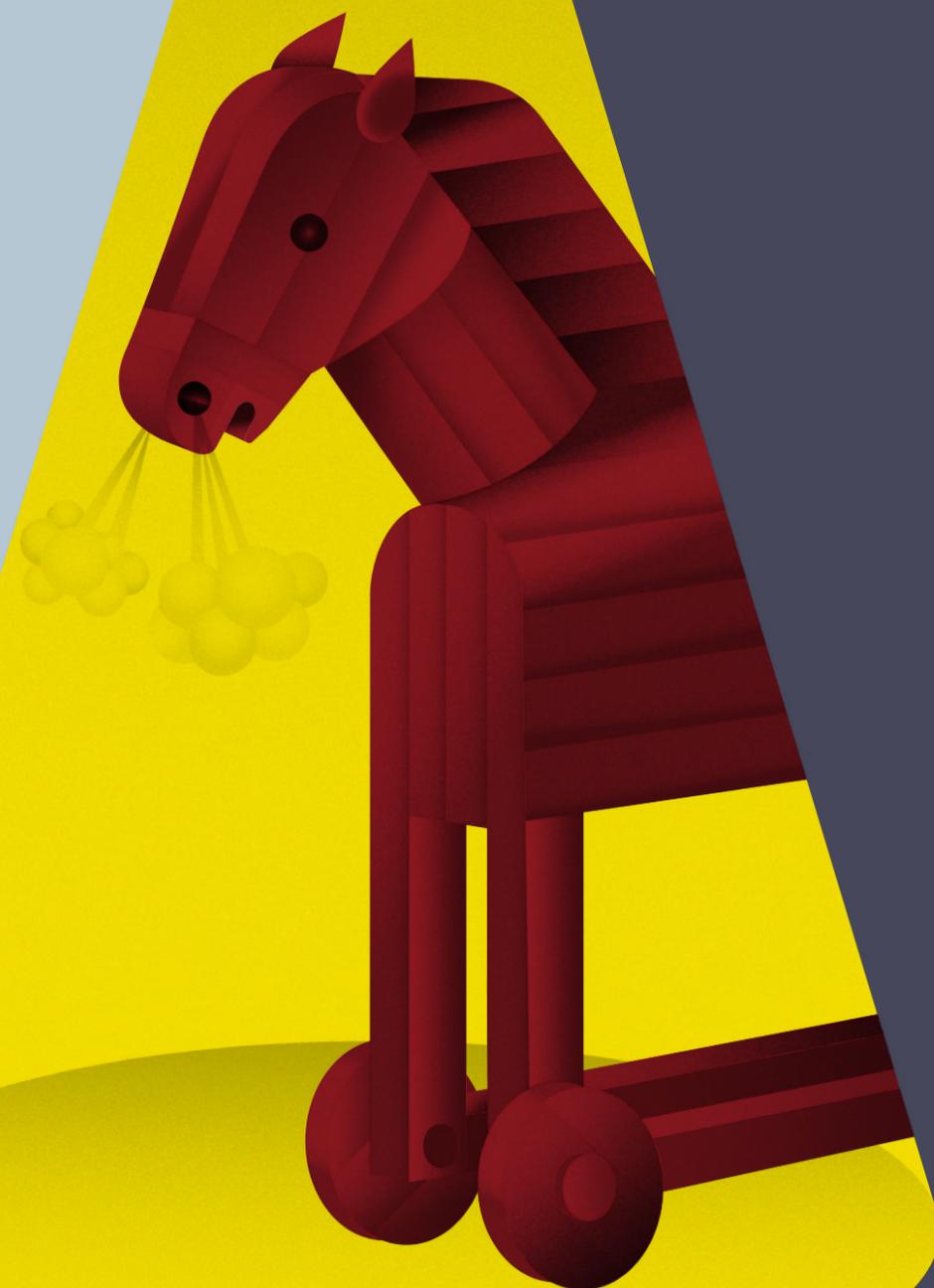
#### Footnotes

<sup>1</sup> Perception, cognition and action (PCA) analysis refers to a form of task analysis which explores the different elements of device interaction.

# More than a walk-on part

How excipients play a role in making a drug successful

By Laureline Mahe and Stella Wooder



## “Acting rather like a Trojan Horse, it is able to navigate inside the body without challenge or rejection”

We take medication because of the benefits it offers, benefits which are delivered by the active pharmaceutical ingredient (API). However, the tablets, capsules, injections, liquids or suppositories we use typically contain less than 10% of the API. What makes up the bulk of the medicines we take is the inactive ingredients, also known as excipients. Whilst the API may be the “star of the show”, the excipients play a strong supporting role: to make sure that the medicine is able to do its job. It is an important role; so much so, in fact, that an excipient can often make or break the API’s performance.

### An ideal role

Research conducted by Rutesh Dave, at Long Island University, looked at the excipients used in the top 200 most commonly prescribed tablets<sup>1</sup>. Over 94 excipients were used in this list of most frequently prescribed medicines. The most prolific excipient, magnesium stearate (used as a lubricant to stop the API sticking to the industrial machines during manufacture), appears in 108 of the top 200 prescribed medicines.

Excipient roles are wide-ranging; a cast list including not only lubricants, but coatings, preservatives and antioxidants. Improving the API by providing a better taste or texture, stabilising the formulation, or extending the drug’s shelf-life, are further roles. The nature of excipients means that they must also be non-toxic, stable, able to avoid being rapidly cleared by the kidneys and non-reactive in the body. Although they are often referred to as inactive components, it is these properties and behaviours of excipients that have a significant impact on the success of a medicinal product. In short,

the ideal excipient must provide a cost-effective and unobtrusive supporting role, ensuring the API is able to perform effectively and efficiently. A number of interesting applications are explored in this article.

### Coming out of the cold

Maintaining the cold-chain, from a vaccine’s point of origin to where it is needed, is a significant barrier to global vaccination campaigns. The cold-chain process accounts for up to 80% of vaccine campaign costs and is tricky to sustain in remote and low-resource settings<sup>2</sup>. Keeping a vaccine at its optimum storage temperature – usually lower than the ambient temperature – is an ongoing challenge when targeting human papillomavirus (HPV), the antigen responsible for most of the cases of cervical cancer. For example, around 80% of all cervical cancer patients reside in developing countries and, despite the availability of several liquid vaccine formulations (Gardasil, Cervarix), it is difficult to get the vaccines to where they are needed and at the right temperature. The vaccines are thermal-sensitive and need to be kept under tightly controlled temperature conditions (between 2°C and 8°C) – from production to administration – in order to keep their long-term potency.

Developing formulations with enhanced resistance to freezing and heating could significantly increase the reach of these vaccines. This is where excipients can help. Current strategies to prolong vaccine shelf-life and their thermostability involve adding excipients to both liquid and dry formulations, either to protect against freezing damage, or to remove the need for a cold-chain by enhancing the

heat resistance of the product (using stabilising and buffering excipients)<sup>3</sup>. Adjuvanted vaccines<sup>4</sup>, for example, containing aluminium salts, are particularly sensitive to freezing, as the vaccine adjuvant-antigen protein bond is susceptible to damage by the formation of ice crystals during the freezing process. Excipients, such as polyethylene glycol (PEG) or sucrose, are therefore added to preparations for their cryo-protective properties<sup>2</sup>. Non-liquid formats, such as freeze-foam and spray-dried, are generally preferred as they can greatly improve the vaccine’s long-term stability compared to a liquid format<sup>3</sup> (although it is still difficult to produce non-liquid, thermostable adjuvanted vaccines).

### “Excipient roles are wide-ranging”

Non-liquid forms do not always need to be reconstituted before use and offer alternative routes to parenteral, such as oral, dermal and pulmonary. Excipients used to stabilise the dry formulations include sugars, polyols (e.g. PEG) and even silk fibres<sup>4</sup>. For the HPV vaccine, a spray-dried, virus-like particle formulation containing an excipient combination of three sugars (mannitol, trehalose and dextran) and the amino acid leucine was shown to retain high levels of potency (i.e. immunogenicity) after being stored for more than a year at 37°C<sup>5</sup>. The increased robustness offered by this excipient-supported formulation has the potential to reduce the number of cases of cervical cancer in areas such as sub-Saharan Africa. →

### A Trojan Horse approach

The role of drug carrier is a powerful example of where excipients come into their own. Take the case of paclitaxel, which belongs to a group of compounds known as taxanes, produced by plants belonging to the yew family. Taxanes are widely used as chemotherapy agents, as they inhibit the process of cell division in tumours. In an alternative to the “taxane in solution” formulation, paclitaxel is bound to albumin nanoparticles<sup>6</sup>. As the most abundant plasma protein in human blood, albumin is a good choice for the role of ‘carrier excipient’. Acting rather like a Trojan Horse, it is able to navigate inside the body without challenge or rejection, to deliver its therapeutic (though toxic) payload where it is needed. Early indications from clinical trials<sup>7</sup> for treatment of bladder cancer suggest that using a nanoparticle carrier method of administration, delivered directly to the tumour site, improves the therapeutic benefits of paclitaxel (compared with the usual systemic treatment) due to better specificity and reduction in toxicity, as there is less uptake by other organs via systemic distribution. Another possible benefit in receiving taxane via albumin nano-carrier and administered in solution, is that it may mean faster uptake. Treatment duration reduces to 30 minutes per session, compared to up to 3 hours via the usual method (the volume of medication varying from patient to patient).

### Going viral

US biotech company Ceregene uses an unusual method to improve delivery of growth factor treatment (via gene therapy) for a range of neurodegenerative diseases, such as Parkinson’s, Alzheimer’s and Huntington’s diseases, age-related macular degeneration, and glaucoma: not just an excipient, but something far smarter – a disabled virus.

Neural growth factor treatments are potentially able to halt the degeneration and restore the function and vitality of damaged or failing neural cells in the brain or eyes. However, the growth factors are large proteins, which are difficult to deliver to the target tissues using conventional methods. To circumvent this problem, Ceregene has developed adeno-associated virus (AAV) vectors – a harmless version of a virus that infects

## “Treatment duration reduces to 30 minutes, compared to up to 3 hours via the usual method”

humans – for delivering the genes for the growth factor to the site where they are needed, i.e. the degenerative or failing neurons<sup>8,9</sup>.

The modified AAV, containing genes for specific disease targeting, reaches its specific target cell destination and releases its genetic payload into the cell nucleus (Figure 1). Now permanently incorporated into the targeted cells, the genes signal the production of the required growth factors on a sustained basis. Using the fiendish ability of a virus to survive and get to its target, and modifying the AAV to ensure it cannot replicate or reproduce itself, a usually unwelcome visitor in the human body makes successful delivery of a therapy possible.

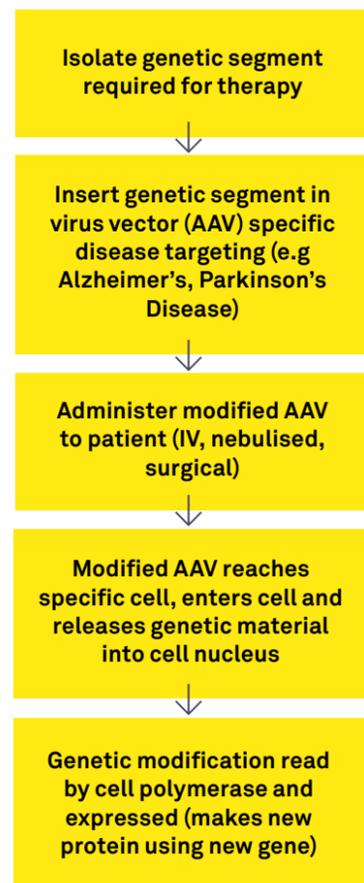
### “The role of drug carrier is a powerful example of where excipients come into their own”

#### Nose-to-brain

Recent research suggests that the effects of statins in lowering cholesterol levels may also have a beneficial role in Alzheimer’s disease, rheumatoid arthritis, and other neurodegenerative disorders<sup>10</sup>. Using an intranasal route for delivery of drugs to the brain has been investigated for specific neurodegenerative diseases. There are benefits in the nose-to-brain route, such as avoiding the GI tract and the risk of irritation of the stomach, intestine and liver, where the drug may be broken down too rapidly. However, the amount of drug transported directly from the nose to the brain is generally very low, with normally less than 0.1% getting to its target. This is where nanoparticles consisting of chitosan, lecithin, and different oil excipients encapsulating the statin

may be the answer to improved delivery. These nanoparticle excipients are picked for their desirable characteristics, i.e. their small particle size, positive surface charge, long-term stability, and their ability to improve nose-to-brain transport, whilst lowering the toxicity of the statin. Early results from simulated studies show that a statin dose can be delivered nasally, using this safe, biocompatible, biodegradable delivery system.

**Figure 1: Gene therapy via viral delivery**



**Table 1: The role of excipients in medicine treatment outcomes**

Excipient	API	Indication	Excipient's role
Mannitol, trehalose, dextran and leucine	Virus-like particles for HPV (human papillomavirus)	HPV	Eliminates need for cold-storage for vaccines
Albumin nanoparticles	Paclitaxel	Bladder, breast, pancreatic and other cancers	Drug carrier
Adeno-associated virus (AAV) vectors	A variety of growth factor treatments	Parkinson's, Alzheimer's, Huntington's disease, age-related macular degeneration and other neurodegenerative diseases	Drug carrier
Chitosan, lecithin, and different oil excipients	Statins	Alzheimer's disease, rheumatoid arthritis, and other neurodegenerative disorders	Drug carrier allowing a higher payload

### Getting under your skin

One of the challenges of biopharmaceutical drugs (also known as biologics) is their instability due to their large molecular size and high viscosity, making drug delivery tricky – particularly when the API is delivered subcutaneously. As a result, biologics (such as the best-selling drug, Humira, used in the treatment of auto-immune conditions) are typically delivered intravenously, or as a cycle of multiple injections. Research with Halozyme’s ENHANZE technology is focused on overcoming these challenges to create a better patient experience. ENHANZE is based on Halozyme’s proprietary recombinant<sup>†</sup> human enzyme, rHuPH20. This enzyme excipient temporarily degrades hyaluronan, a chain of natural sugars in the body, and increases interstitial space for the injected API. Rather like opening up a “temporary door” in the body, the result may allow biologics and other compounds that are administered intravenously to be delivered subcutaneously. Once the medication is delivered, the body acts to reinstate the hyaluronan “door” again. Whilst regulating a therapeutic action like this will no doubt prove challenging, it opens up a potentially useful mechanism for delivering biologic therapies. Should it prove successful, the

result for the patient and the healthcare-giver could be a reduction in the need for multiple injections (due to the improved dispersion and absorption) and a shorter time for drug administration.

### Excipients moving upstage

What will the excipients of the future look like? How far can the boundaries of the so-called ‘inactive’ ingredient be extended? Looking to the future, we may see personalised medicine in which the API is invariant and it is the excipient which is customised – tailored to the patient’s physiology and specific genetic mutations, to provide optimum delivery of the drug. Electrochemical ‘sensor’ excipients may emerge which bolster supply-chain compliance, by detecting when the API has exceeded its shelf-life, has not been stored appropriately or has been tampered with in some way – maybe even deactivating the API or at least providing a visual indication that it is no longer safe or active. What is clear is that whilst the API will continue to take centre stage, the role of the excipient is still important in therapeutics, sometimes determining the success of a new medicinal product. Excipients may not be right in the spotlight, but their place in patient treatments continues to be vital. <sup>ENDS</sup>

### Footnotes

\* Adjuvanted vaccines contain added substances to increase the body’s immune response to the vaccine.

† Produced when segments of DNA derived from different sources are joined together.

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# HUMAN FACTORS

WORLD TOUR

5,592 PARTICIPANTS  
58 CITIES

*A core team of 11 human factors specialists with 162 years' experience*

**Includes studies of:**

Acromegaly  
AMD/Macular edema  
Anaphylaxis  
Ankylosing spondylitis

Asthma  
Cancer  
Cervical dystonia  
Chlamydia  
Colitis

Contraception  
COPD  
Crohn's  
Cushing's syndrome  
Cystic fibrosis

Diabetes  
Flu vaccine  
Gonorrhoea  
Haemostat  
Hepatitis C

Hormone  
Hypogonadism  
Infertility treatment  
Lupus  
Limb spasticity

Multiple Sclerosis (MS)  
Neuroendocrine tumours  
Osteoporosis  
Parkinson's  
PMI

Psoriasis  
Psoriatic arthritis  
Pulmonary hypertension  
Renal anaemia  
Retinopathy of prematurity

Rheumatoid arthritis  
Sarcopenia  
Statin drug treatment  
Venous leg ulcers



**What prototype  
do you need?  
It's best to ask  
an expert**

By Sebastian Stanley  
Guest author,  
Director of Complete  
Fabrications Modelmakers



The prototyping industry is constantly evolving. Having experienced 25 years of prototyping, starting on a bench with traditional tools and hand skills, to running a company with some of the latest rapid-prototyping technologies, I have witnessed the changes firsthand. When I entered this industry, I would never have predicted the model capabilities of today, and 3D printing has undoubtedly aided that achievement.

However, there is a tendency to believe that 3D printing should be used for all prototyping requirements. This overlooks the value that an experienced prototyping company can contribute to product development. When it comes to printing, I believe that a little knowledge is worse than no knowledge at all. It is important to engage with a prototyping company and seek their expert advice based on the desired

outcomes of your project; the hand skills of a modelmaker are as relevant today as ever. Rapid-prototype technology has strengthened this skill, and seeking advice will only extend the possibilities. Such advice should be based on all services and techniques, and not just the technology a company possesses in its armoury – it is about using what is available in today's market to achieve the best outcome. I will expand on some of these additional services and how they stand alongside 3D printing.

The invention of 3D printing is not as recent as many may think. A patent was first registered in 1986 by Charles Hull for the first stereolithography machine (or SLA machine as it is now often called). The original output print, although extraordinary for its time, was somewhat difficult to use in many applications. It was brittle and of much lower resolution

compared to what clients would expect now. Although the SLA machine remains very similar commercially, today the surface finish of the parts is flawless and the resins are more advanced.

**A little knowledge**

Ten years ago when I told someone I ran a range of printing machines they would look puzzled. Now it seems everyone knows someone with a 3D printer. With so many printers in the market place where does this leave the prototyping industry and the clients it relies upon? Some would say this proliferation of 3D machines has thrown the industry into confusion; others would confidently claim that for every prototype requirement there is a specific printer that can supply an exact solution. I feel there is a little truth in each.

**It's not just a need for speed – clients want more!**

The 3D printer is fast – there is no other method of manufacture that will provide parts for fit and function testing or a space model quicker. There is no substitute for this at the start of any prototyping process. But what if a client wants more? What if a client is confident that the form now fits its application, but wants to know how colour will affect the look of the product? What if they want a gloss finish, a texture finish or rubberised touch points? All of this can be achieved with the skills of a modelmaker. →

**“THE INVENTION OF  
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Splitting the model up from a client's computer-aided design (CAD) into colours and finishes means the modelmaking process can begin. Each coloured part will be printed independently, then hand fitted to one another to create high-quality surface finishes with flawless colour breaks, without the need for masking. Once these parts are painted, the model can be reassembled, leaving a fully finished 'block' model. All of this requires the skills of a modelmaker.

With advances in the painting field it is now possible to create simulated chromes and high-lustre metallic finishes. It is even possible to affix metal plating directly to a printed part, in copper, nickel or precious metals, giving a cold touch and a heavier part that denotes further quality. Graphics can then be applied to the model to add finishing details. This can be done via a screen print, tampo print or the latest direct digital printing straight onto the product, saying goodbye to the fragile rubdown transfer. With this level of finish, it can be difficult to distinguish the model from the intended final product, and is something that simply cannot be obtained from even the best colour output 3D printers.

#### Achieving the correct fidelity to test interaction

Next it is necessary to consider user interaction with the model – how can clicks, button pushes and door closures be replicated in a realistic way, to gain feedback from users in human factors studies? The technology is certainly available with 3D printing to achieve the dimensional accuracy required (if high-quality Viper SLAs are employed, and a build layer of 0.05mm in an epoxy-based resin). But this level of interaction often requires prototyping before the design team have entered the detailed design phase – a realistic mock-up is needed, to simulate just the interaction and not necessarily the final method of achieving it. This is where once again the skills and experience of a hand modelmaker

come into play – typically, an experienced modelmaker will have tackled these challenges many times before and will have a number of tricks up their sleeve to achieve a robust solution more quickly and at lower cost than it takes to build a CAD model and print the components.

#### What if you need more than one?

In order to run multiple tests at once, present in multiple locations or send copies to many interested parties, vacuum casting is the next logical step in prototyping. This process is a step closer to an injection-moulded part.

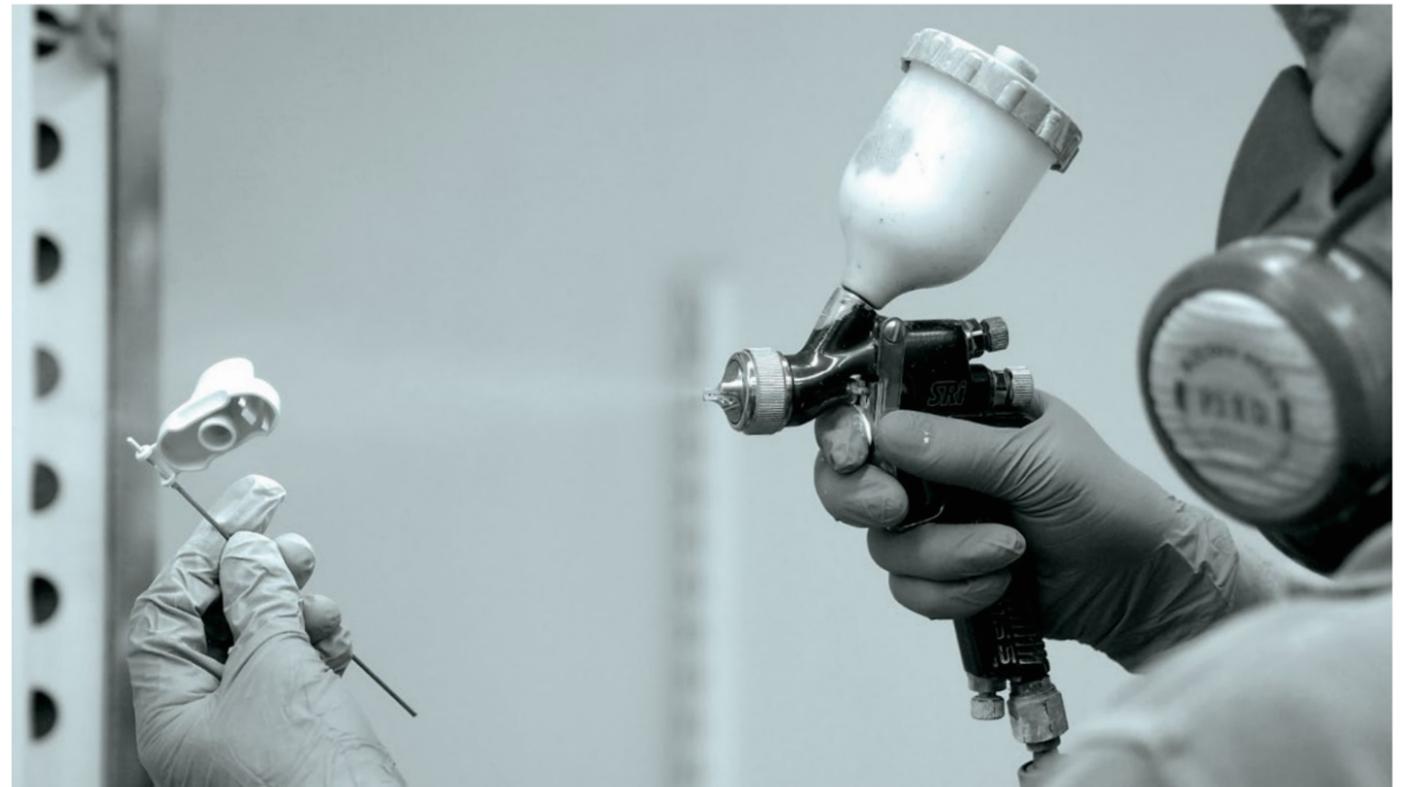
In this type of casting, silicone rubber tools are filled under vacuum with a polyurethane resin. The silicone tool is created from a 3D printed SLA master which is then hand-finished in all ways to replicate the surface finish of the intended final production part (just like in the space model). The castings will be processed through the silicone tool to create a self-coloured part in a mimic polyurethane resin, replicating what would be the intended injection-moulded material.

#### More accurately mimicking mechanical function

Vacuum casting not only makes a more robust model by removing the risk of paint wear on parts during handling; with both rigid and flexible materials available in the polyurethane range, all aspects of the product can be replicated including live hinges, compliant features, even twin-shot parts. Now the prototypes will display repeatability from one assembly to the next, delivering on both finish and fit.

The introduction of CNC (computer numerical control) machined metal inserts to the silicone tooling process means that very tight-tolerance parts can be manufactured akin to injection-moulded parts. These prototypes will be hard to distinguish from a final production assembly, and will demonstrate any function (even housing electronics, if required) to give all aspects of interface. With a production time from single-part CAD delivery to cast parts in less than five days, this process can be incredibly time-efficient.

**“THE HAND SKILLS OF A PROTOTYPE ENGINEER ARE AS RELEVANT TODAY AS EVER”**



The vacuum-casting process can be used not only for prototyping, but also for low-volume manufacturing. When volumes are expected to be in the region of less than 100 units per year, this method of manufacture can be practically perfect. The investment in tooling is low and part design forgiving. The parts do not need draught – it is possible to manufacture with negative draught and undercuts. Differential wall section will also not cause an issue. With these forgiving parts it can be a great way to get products out to customers with a smaller initial investment than injection moulding.

#### Sometimes simulation is not enough

Simulating injection-moulded products is not always good enough, and the actual material is needed to assess the longevity of the true function of a part under load without compromise. To achieve this, there are two options: actual injection moulding or CNC machining.

Rapid injection moulding has developed over the years and it is now common to make a soft aluminium tool or even steel tooling for a low-volume production. The challenges of injection moulding remain the same in “soft tooling” as in production tooling; draft is needed and side cores may also be necessary. Unlike the vacuum-casting process, there is no way

around this. Simple parts can be made very rapidly but complex parts can be slow and expensive. This may be where CNC has the advantage.

CNC machining is a process that removes material from a block (as opposed to 3D printing, where material is added in layers to create the part). A block of the required material is presented to a cutting tool that is spinning at high speed, which then moves over the surface of the block, removing material in stages until the final part is produced. This process is normally a slower process than 3D printing, as parts tend to be machined one by one rather than in a cluster, as in the printing process. Parts machined from solid material have a consistent structure throughout, whereas printing processes such as selective laser sintering or fused deposition modelling produce a structure in the final intended material, but one made from fused granules and the other a printed strand of material; each inevitably changes the mechanical function.

CNC machining leaves a clean surface finish that can be polished to enable free movement of assembly. However, there are some limitations to CNC machining – some corners will require corner radii,

where the cutter is not able to achieve sharp corners, and not all parts can be machined due to limited cutter reach or obstructed access. Again, advice from a prototyping company will inform the decision as to whether or not a CNC process is beneficial for a particular product.

**“THIS ARTICLE SHOULD DEMONSTRATE THAT IT IS IMPORTANT TO THINK OUTSIDE OF THE ‘CUBE’ OF 3D PRINTING.”**

#### Not just picture-perfect models

This article should demonstrate that it is important to think outside of the 'cube' of 3D printing. Whilst the impact it has had on speeding up the product development process is huge, it is only part of the picture when it comes to developing effective prototypes. It is worth engaging with a prototyping company early on, to seek their expert advice based on the desired outcomes of your prototype. Naturally, given my position, I would say this, but it is amazing how much the hand skills of a modelmaker are as relevant today as they were 25 years ago. <sup>ENDS</sup>

# Informing product design with analytical data

By Charles Dean



## Balancing theoretical and empirical approaches in device development

When developing new products, engineers and designers are challenged to make well-informed decisions to create solutions that meet the requirements. Good design practice encourages an evidence-based approach (while regulations often require it) and, throughout all stages of product development, analytical data is relied upon to support and verify device-design decisions. Herein lies the necessity for engineering analysis, in which the primary objective is to assess and determine quantitatively whether a device, mechanism, sub-system or component is fit for purpose. Depending on the maturity of the design and the scope of the project, different approaches can be used to obtain the

relevant analytical information, but how do you go about choosing the right tool for the job?

### Engineering with applied science

The analytical engineering activities referred to here are scientific, logical and methodical investigative measures that are conducted to aid in design development. A vast spectrum of methods is used with, at one extreme, the purely theoretical and, at the other, the purely empirical. Examples of theoretical approaches are mathematical-modelling methods, such as Finite Element Analysis (FEA), Computational Fluid Dynamics (CFD), Tolerance Analysis or bespoke mathematical system simulations. Empirical methods usually involve physical testing, measurement, and observation of device components for direct assessment of their performance. Broad applications include tensile/

compression load tests and metrology, as well as many function-specific attribute or quantitative tests, such as the indicator function or moisture-vapour transmission rate.

In reality, analytical work conducted during device development is a combination of these approaches, employing tools from both ends of the spectrum to provide the data required via the most efficient route. Planning this route depends on the information sought, the resources available and the development stage of the product. Using the example of a preloaded active medical device, different analytical processes will be explored to assess the deflection of the components within the assembly.

### An example of analytical engineering

Figure 1 shows a simple sub-assembly, in which the dimension between the two internal faces is of critical importance. This could be a controlled dimension for many reasons: perhaps a compartment for a third component or separate sub-assembly, such as a pre-filled syringe (PFS) or battery cell. The level of control required is dependent on how critical the dimension is to the function, and hence the level of risk.

### Tolerance analysis

Early in the design process, theoretical tolerance analysis will be conducted to ensure that the output dimension will meet requirements, despite the geometrical variation from manufacturing. In the tolerance 'stack' shown in Figure 1, the nominal value for the output dimension is determined by equation (1). In order to consider the worst-case cumulative geometrical variation, the tolerance of each dimension is summed, as shown in equation (2). It can then be determined whether a third element, let's say a PFS, will 'fit', under the assumption that all three elements are manufactured within specification.

This analysis, from which initial design decisions will be taken, is purely theoretical. Closer to production, when large numbers of manufactured parts are

available, empirical verification that each PFS assembly will fit within each device becomes feasible, but this will be far too late to discover that the objective has not been achieved.

### Metrology and process capability

In the detailed design or pilot manufacturing stages, access to many parts for a full attribute test such as this may not be feasible, but a small number of parts may give sufficient insight if used appropriately. This is where a combination of empirical and theoretical techniques can be employed. Capturing metrology data of the key dimensions from sampled components and using statistical methods, such as process capability, to determine the predicted variability of the measured features, can help highlight potential errors in production. Engineers and designers are thus provided with valuable data, part empirical, part theoretical, to inform design decisions, reducing to acceptable levels (ideally zero) the probability of defective devices going into production.

### Complexity with increasing variables

To further illustrate how a balanced approach can be deployed, consider a more challenging example, in which a load is applied to the components of

such an assembly. This occurs for many medical devices on the market, such as auto-injectors or breath-actuated inhalers. The majority of components of such drug-delivery devices are manufactured from injection-moulded plastic, which when subject to high loads will deflect significantly, that is, their geometry will change. In order to ensure a robust design, engineers must obtain a good understanding of this deflection.

When considering this pre-load early in the design phase, analysis of the tolerances specified on the engineering drawings is no longer enough to ensure that every device will function appropriately. As in the dimensions on the drawing, the magnitude of deflection is also variable. This means that deflection tolerance will need to be specified to determine the permissible limits of variation.

Early in the design process, with no parts to measure in a compression test or within the assembly itself, purely theoretical methods have to be adopted. →

Figure 1: Tolerance stack schematic example

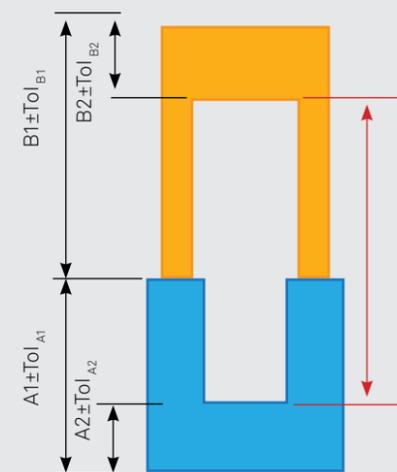


Figure 2: Deflection due to preload

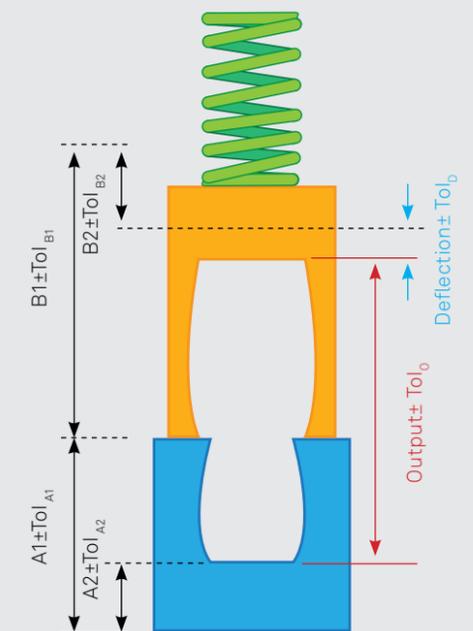
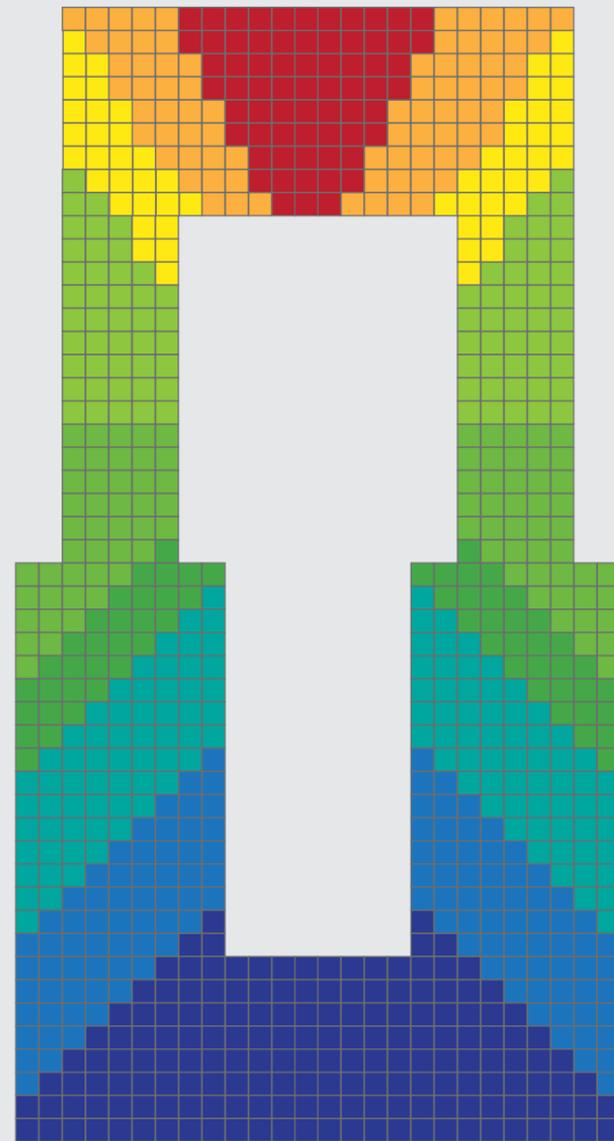


Figure 3: Illustration showing FEA



**B: Static Structural**  
Type: Total Deformation  
Unit: mm  
Time: 1  
05/04/2017 09:55

### Structural simulation through finite element analysis

Using finite element analysis (FEA), engineers can model the component geometries and apply a load with the appropriate material knowledge to determine the predicted deflection (Figure 3). The system geometries can then be adjusted to the extremes of tolerance to gain some indication of predicted deflection tolerances. This can be quite straightforward when considering a static linear scenario and can often provide sufficient data to steer the design in the right direction. However, these loading scenarios within devices usually occur for extended periods of time; 2 to 4 years of storage and 12 months of use, for example. Deflection that occurs instantaneously may change significantly as the parts deform over time (creep). Modelling this time dependency with FEA requires extensive material data, which can be hard to come by, and also computational complexity, which involves non-linear conditions.

### Measurement without compromise

As theoretical uncertainty grows, empirical approaches can be more effective, for example, by measuring the output dimension directly from manufactured device assemblies. Nearer production, obtaining manufactured parts may no longer be an issue, but this method has a whole other set of challenges.

With medical devices becoming smaller and more complex, and the nature of their design making it difficult to access critical internal components, it's not always easy to take measurements without tampering with the device and hence affecting the measured features. However, modern metrology methods, such as CT scanning, make it possible to measure components within a sealed device. This method comes at a cost, a very high cost if large quantities are involved, but in many cases the information obtained well justifies the expenditure.

As mentioned above, the loading scenarios described occur for extended periods of time. Project timescales and deadlines cannot afford 12–36 months of real-time testing to measure this deflection before key decisions are taken, which is why storage and use conditions are frequently replicated through accelerated ageing. To achieve this, device assemblies are stored at higher than normal temperatures (typically 30–50°C) to advance part deformation or degradation over time. While there is still debate on the validity of this artificial procedure for replicating shelf-life, particularly for materials such as elastomers, it has become industry standard practice in product development and is understood well enough for valuable data to be obtained. In some cases, empirical data can be generated to characterise general material properties, and then this information can be fed into theoretical models for specific designs or load cases.

### Combining the right tools for the job

Due to the respective challenges of each different method, it is quite common in product development for the most efficient and relevant route for determining an analytical variable, such as deflection, to involve a hybrid theoretical and empirical approach. In this example, one approach would be to:

- Employ a basic mathematical model or analysis to identify key design parameters
- Empirically measure these parameters and the deflection in a small number of devices
- Develop an FEA model and validate it against the measured deflection data
- Use the validated FEA model to predict overall variability

This combined approach alleviates the need for complex theoretical material data and other simulation parameters, and also addresses the lack of large numbers of components to gain an early understanding of variability.

### “Relevant and high-quality data is required to best inform every step”

The value of analytical engineering is undeniable. It is a vital discipline which, when mastered, ensures the low-risk and methodical development of new technologies and products. The key to its best use is understanding the available tools and how to effectively use them to obtain the required information. These tools are employed throughout all stages of product development. Whether proving a concept, detailing a design, or verifying and validating a manufactured product prior to launch, relevant and high-quality data is required to best inform every step towards getting a product to market. <sup>ENDS</sup>

“It’s not always easy to take measurements without tampering with the device”

**It's easy to turn  
money into  
technology;  
it's not so easy  
to turn technology  
into money.**

## Industrialisation of a product development can be the trickiest step

By Brennan Miles  
and Nick Salt



Developing medical products to prepare them for commercial production is commonly known as industrialisation. Officially, regulators call this either 'Design Transfer' (US Food and Drug Administration [FDA]) or 'Design and Development Transfer' (ISO 13485). These meanings are essentially the same, which is to ensure that 'the design and development outputs are verified as suitable for manufacturing<sup>1</sup>' and that the 'device design is correctly translated into production specifications<sup>2</sup>'.

Industrialisation of medical products is a complex part of the overall development process. It usually involves a lot of preparation and coordination among multiple groups and, as such, the resources and time needed to complete this phase are often underestimated. Even the most capable of medical companies can, and do, experience difficulties in turning prototype technology into a commercial product.

In the early stages of product development, the responsibility lies with the design team. Progress at this stage can be very tangible and exciting: product concepts are created rapidly, evaluated and then reiterated;

prototyping methods are often used to quickly produce early models for mechanical and user evaluations. As the design develops, functional models are necessary to demonstrate and prove the robustness of the technology. These are called 'proof-of-principle' prototypes and closely resemble the final product solution. A typical prototype may include realistic electronics modules and even genuine components produced in the correct materials. These prototypes are very convincing and can easily lead to a false sense of the development process being almost complete. However, it's worth remembering that these samples are still "prototypes" and, in reality, a lot of work is still required to produce actual medical products.

**"It's worth remembering that these samples are still prototypes and, in reality, a lot of work is still required to produce actual medical products."**

### FDA

Design Control Guidance for Medical Device Manufacturers states that 'historically, shortcomings in the production specifications tend to be manifested late in the product life cycle'.

As the process moves towards the industrialisation stage, the rate of perceived progress seems to slow down significantly, which can be less exciting for those who have been involved from the beginning. This occurs because the manufacturing methods and processes need to be developed, which involves everything from the design and build of the production and assembly equipment to validation of the manufacturing processes. The objective is to have systems and processes that are predictable, consistent, and controllable to ensure that the end product reaches the required level of quality to safeguard patient/user safety. →

## To gain some insight into the industrialisation process, we have put together a few rules of thumb to consider when developing a new medical product:

# 1

### Be sure to follow your quality management system (QMS) and the regulation guidance.

This is perhaps the most obvious rule because adhering to your QMS is critical to obtaining regulatory approval from both the FDA and/or the ISO; without a QMS it is not possible to design or manufacture medical products. However, sometimes short-cuts are taken, especially during development when milestones can make or break whether a product continues. If this happens, these short-cuts will need to be remedied before Design Transfer can be completed. In the worst-case scenario, this can mean significant re-working. It's worth remembering that any issues that are deferred will need to be resolved during this phase and that the cost of correcting errors increases exponentially during development, so gaps should be filled as soon as possible.

# 2

### Document and maintain an approach for manufacturing a new product. At Team we call this a Manufacturing Strategy Plan (MSP).

The purpose of an MSP is to build on the commercial production requirements that are usually decided at the very beginning of the new product programme. It should contain information that may influence the design detail, such as the expected production volume, target product and investment costs, information on where the production sites will be located, and how/where the final product inspection and distribution will take place.

This plan should be created as early as possible and updated throughout the development phases. It should be made available to the development teams so there are no surprises regarding the production scale-up requirements. Having the basics well defined can help drive good decision making later in the plan.

# 3

### Make sure that input from manufacturing is included in the design review process from the beginning.

As we have already mentioned, industrialisation really starts in earnest after the development and design verification work has been completed. But it's worth remembering that the preparation for manufacturing needs to overlap the design activities from an early stage to make sure that the transfer process runs smoothly. A good technical development team will find a balance between design creativity whilst also de-risking potential future production difficulties. For example, a detailed review of production transfer trays will probably not be helpful at the design concept stage, but flagging components that have vulnerable design features should trigger further activities to identify product-handling solutions earlier in the program.

# 4

### Understand the skills and experiences of manufacturing partners, both internal and contracted external partners.

The design team should understand the technical strengths and weaknesses of the selected production partners. This will help to guide the product design towards areas of manufacturing strength, making for a smoother transition during industrialisation, and to identify whether new skills/processes will be needed. Questions should be asked, such as: is the manufacturing equipment already available? Have similar assembly processes been proven in the past? What is the expected process capability?

# 5

### Identify any particularly high-risk or complex components or sub-assemblies as early as possible.

It is human nature to be drawn to the simpler aspects of the design detail to 'get them out of the way'. However, during industrialisation it is much more efficient to focus efforts/resources on the most complex product components, sub-assemblies or production processes to ensure that the design solutions can be manufactured (and controlled) as planned. Ultimately, the difficult parts will determine whether the product can be manufactured successfully.

# 6

### Ensure that the product function requirements are correctly translated into production specifications.

This can be one of the more complex aspects of the industrialisation process. For some product functions, it is possible to perform a direct check during manufacture; for example, the position of a component during assembly can be inspected using a camera to compare images of good and bad parts for Quality Control.

For other product functions, a secondary or inferred check may be required; for example, if the counter on an inhaler rotates by one digit in a test actuation this means that the internal mechanism is functioning correctly. These types of tests can be very difficult to establish and validate, so detailed analysis and preparation are to be expected. Where no functional tests can be carried out in production to ensure – directly or indirectly – that input requirements will be met, a detailed understanding of the design space becomes essential e.g. through tolerance analysis. This will allow detailed discussions with commercial manufacturing partners to take place to ensure that production design specifications describe a device that will meet its functional requirements.

No design team can anticipate all factors bearing on the success of the design, but procedures for design transfer should address at least the following basic elements:

*'First, the design and development procedures should include a qualitative assessment of the completeness and adequacy of the production specifications.*

*Second, the procedures should ensure that all documents and articles which constitute the production specifications are reviewed and approved.*

*Third, the procedures should ensure that only approved specifications are used to manufacture production devices' – FDA Design Control Guidance for Medical Device Manufacturers*

# 7

### Don't forget about other ancillary production processes and items.

Processes such as component inspection, sub-assembly handling, labelling and packaging may seem less important during the concept development stages of a new product, but they soon become essential for validation of the manufacturing systems.

Metrology can often be the bottleneck in a validation process, so having fixtures and methods qualified as early as possible can avoid delays and the need to repeat work later on. Prototype moulded parts manufactured during detailed design can often prove very useful in support of such activities.

At Team we know that pioneering medical devices change people's lives for the better so we understand the importance of efficiently transferring a design into commercial product. The principles that we have listed here are by no means exhaustive, but we hope that they give some useful insight into the planning and expertise needed to successfully make it 'off the drawing board' and into production in the most successful way. **ENDS**

#### References

1. FDA - Design Control Guidance for Medical Device Manufacturers
2. ISO 13485:2016 Medical devices – Quality management systems – Requirements for regulatory purposes

# The 'Blood-Brain Barrier' for beginners



## More difficult than you think – why is it hard to get medicines to the brain?

By Ben Wicks



For the last few years I've almost entirely cut out caffeine and alcohol from my diet. Don't make the mistake of thinking I'm some kind of health freak, really I'm not, but I am susceptible to migraines, and avoiding caffeine and alcohol has helped me. One of the side effects is that I feel woozy after even a few sips of red wine; it only takes a few minutes for the alcohol to be absorbed into my bloodstream and make its way into my brain.

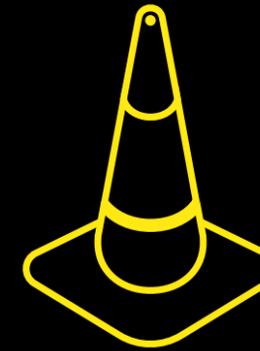
We take it for granted that things like alcohol and caffeine can alter our mental state but it's actually quite surprising that these compounds have any effect on us. Our brains have very sophisticated defence mechanisms to prevent anything nasty in our blood from reaching the brain. The reasons are quite self-explanatory: the brain controls everything you think and do, so protecting it from anything deleterious is a top priority.

In this article we'll explore the 'blood-brain barrier' (BBB), a physical line of defence between the brain and anything

nasty in our bloodstream. We will see how it does its job of protecting us but also explore how such an effective barrier makes it very difficult to deliver new drugs to the brain which could help treat neurological diseases, such as Alzheimer's and Parkinson's.

## The threats

The brain needs to be protected from two main classes of blood-borne threat – microorganisms and toxic chemicals. If bacteria or viruses get into the brain or spinal cord they can multiply, causing meningitis, and kill in a matter of hours, so it's critical to keep microorganisms out. Toxic chemicals could find their way into our bloodstream if we ate poisonous plants, dodgy mushrooms or even mouldy food. These chemicals could kill us directly or cause us to do something life threatening so it's important to exclude these chemicals from the brain as much as possible. →



## The downsides

The construction of the BBB is very good at keeping unwanted things out – similar to a very effective firewall protecting your computer from the outside world – but like a computer firewall, there are times when it is necessary to have more open access.

For example, antibodies and cells of the immune system can't easily get through, so if an infection does take hold inside the central nervous system (CNS) then it isn't easy for the body to fight it off. This is why meningitis can be very serious and cause patients to deteriorate so rapidly.

Another consequence of the highly effective BBB is the difficulty in getting therapeutic drugs into the brain, particularly biological drugs, most of which are very large molecules.

Diseases of the CNS are a growing problem as the world population ages. Multiple sclerosis, Parkinson's disease and Alzheimer's currently affect around 40 million people worldwide. These are all devastating diseases for patients and caregivers, and place a huge strain on healthcare resources.

The pharmaceutical industry is, unsurprisingly, investing a lot of R&D resources to create new therapies for these CNS diseases, but the BBB makes it very difficult to get these therapies into the brain. If you inject the drug into the bloodstream or even the spinal fluid, which has a very similar barrier between itself and the brain, the drug won't get to the neurons in the brain. This is one of the main reasons why so few new therapies have come to market to treat diseases such as Alzheimer's. The failure rate for Alzheimer's<sup>2</sup> disease drug candidates is 99.6%, one of the highest in any disease area, compared with 81% for cancer. →

## The wall

The brain and spinal cord are surrounded by cerebral spinal fluid (a clear, sterile, plasma-like fluid) within a protective membrane, the dura mater; however, this membrane isn't the BBB. Although the brain sits inside this nice sterile cocoon of cerebrospinal fluid, it still needs to be provided with blood, and it's blood which, ironically, poses a major security risk because it can inadvertently carry microorganisms or toxic chemicals into the brain.

So don't be fooled into thinking the BBB is a physical wall around the brain. Instead, the BBB is a 'high-security lining' of blood vessels which supply the brain. Before we look at this in more detail, let's briefly recap how blood is supplied to other tissues in the body, such as your muscles.

Every bit of your body needs to be provided with blood; hence, tiny blood vessels called 'capillaries' run through all your tissues. Capillaries are very narrow (around the width of a single red blood cell) and have very thin walls. The capillary walls are formed by special thin cells called endothelial cells. Oxygen, CO<sub>2</sub>, nutrients and waste compounds pass in and out of the blood through the capillary wall in three main ways:

1. Passive diffusion through the endothelial cells
2. By being actively being transported through the endothelial cells (via several different mechanisms)
3. Moving through the gaps or junctions between adjoining endothelial cells (the endothelial cells touch one another but there are still small gaps between cells).

The capillaries which make up the BBB and supply blood to the brain are structured differently in order to allow oxygen and nutrients to pass through whilst creating a high-integrity barrier to anything nasty. The three main differences are:

1. The cells themselves are much less permeable so only very small molecules can pass through by diffusion (such as oxygen or CO<sub>2</sub>).
2. The cells won't pick up and transport non-specific molecules; in fact, the cells actively pump out any unexpected molecules which find their way inside. So even if something undesirable does get inside an endothelial cell it will be pumped out quickly before it can escape out the far side and get into the brain.
3. The endothelial cells are tightly joined together so there's no gap between the cells for molecules to pass through. These joints are called 'tight junctions': it is as if superglue has been used to join the cells together.

**“This structure creates a very selective barrier between blood and the brain cells. It allows gases and nutrients to be specifically passed through, but very few other molecules can cross.”**

This structure creates a very selective barrier between blood and the brain cells. It allows gases and nutrients to be specifically passed through, but very few other molecules can cross. Only a handful of small molecules which are lipid soluble<sup>1</sup>, such as ethanol, caffeine and nicotine, can pass through unaided. Everything else will only get through if the endothelial cells choose to actively pick them up and transport them inside.

**“Antibodies and cells of the immune system can't easily get through”**



## The new ideas

A number of creative strategies are being explored by researchers to help get drugs from the bloodstream, across the BBB, and into the brain:

- 1 Tricking the endothelial cells so they actively transport a drug into the brain by attaching it to a chemical compound which the cells will take up.
- 2 Temporarily opening up the junctions between endothelial cells so that drugs can diffuse through, using high concentrations of sugar, heat or ultrasound.
- 3 Administering drugs along with chemicals which stop the 'pumping out' activity of endothelial cells, thereby increasing the chance of drug uptake.

All of these approaches have shown some promise but none are highly efficient or reliable, and all have side effects. It is unlikely that any will solve the problem of delivering large molecules across the BBB for the foreseeable future, so drug delivery to the brain remains one of the key challenges in the development of CNS drugs.

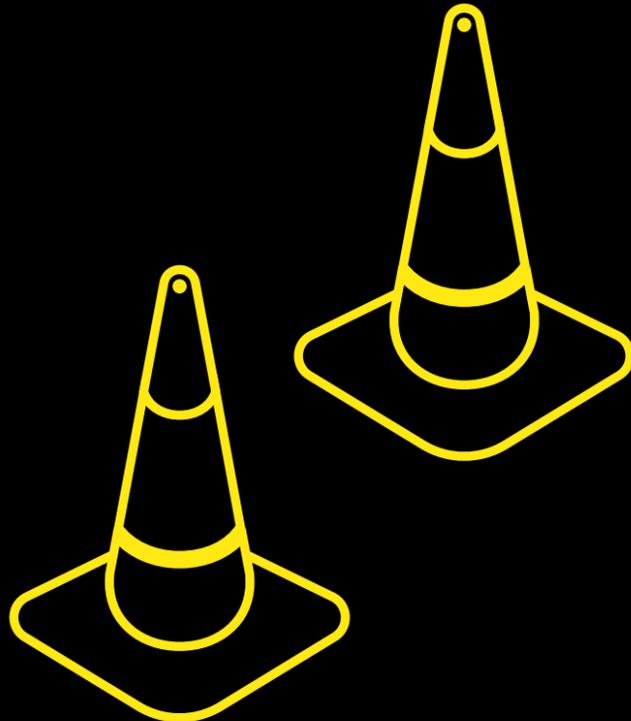
## The conclusion

It seems that we humans are very fortunate to be endowed with such a clever structure in our brains that allows us to enjoy the effects of coffee and red wine, yet which keeps pathogens and nasty chemicals from harming us. However, we still have a huge amount to discover about this amazing piece of biological engineering, particularly if we are to tackle some of the cruellest and most devastating diseases of the brain. **ENDS**

### References

1. Molecules that form the outer membrane of mammalian cells. Water-soluble compounds can't easily get through lipid membranes (because oil and water don't mix); however, compounds that can dissolve in lipids may be able to diffuse through cell walls.
2. Alzheimer's disease drug-development pipeline: few candidates, frequent failures Cummings JL, Morstorf T and Zhong K. Alzheimer's Research & Therapy. 2014; 6; 37

**“Temporarily opening up the junctions between endothelial cells so that drugs can diffuse through”**



# Team Past & Present

In September 2017 we launched our new Team identity. From our beginnings in 1986 we have changed from a team of five to a world-leading medical device consultancy with over 110 employee-owners. Our branding has changed too. Our new style builds on the foundations of our existing identity, with a clear, concise and confident look and feel. Using a monochrome colour palette for our branding allows our work, our people and our expertise to be centre stage – as we are only as good as the team that we have.

Almost a year ago Team transferred into an employee-owned trust. With a trust there are no external shareholders who demand growth at all costs, without really understanding the business. Instead, every employee is effectively an owner and partner. Rather than creating a metric-driven environment, we've evolved into a group that truly cares about the work we do, cares about being transparent with clients and enjoys a supportive working culture. This culture was very firmly established and carefully curated.

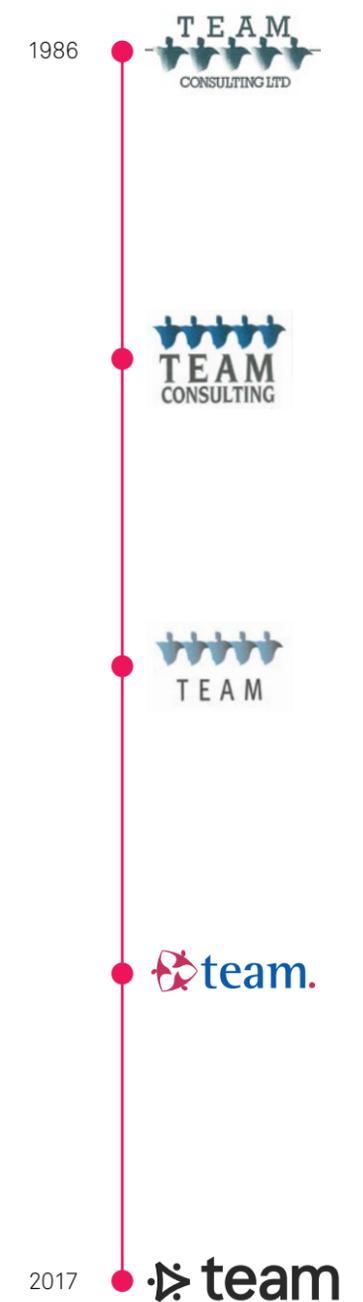
**Looking forward**



Our vision is for Team to be known as a talented and committed group of people helping our clients develop the very best medical devices. Above all, new logo or not, we will continually strive to be the company of choice for clients and staff alike, working in partnership to deliver exceptional quality work.

We are clear with our branding and our vision.  
We are Team Consulting.

### Through the years





**Curse of Friday 13th?**  
A paper published in the British Medical Journal in 1993 examined whether Friday the 13th is bad for your health. The researchers found that, despite there being fewer vehicles on the road on Friday the 13th, there were more injuries from transport accidents. However, whilst emergency admissions due to accident or poisoning were found to be higher on Friday the 13th than on Friday the 6th, the differences were not statistically significant.

**Fingers crossed!**

Crossing your fingers is a popular and enduring superstition to bring good luck or show support in many western countries. Pagans believed that the cross (made by two people crossing index fingers or their own index and middle fingers) was a powerful symbol and that at the intersection there was a concentration of good spirits. They could therefore wish on the mid-point of the cross to fulfil their wishes and fight off evil spirits. But beware: in Vietnam, crossing your fingers is seen as an obscene gesture!

# Unlucky for some!

**Is bad luck created through oversight? Issue 13 of *Insight* – is it unlucky, a disaster? Jess, Matt and Chris look at bad luck.**

**By Jess Fox,  
Matt Chandler and  
Chris Hurstone**



**Race number '13'**  
Professional cyclists are a superstitious bunch, perhaps with good reason, as so many aspects of bike racing are out of a rider's control. The tragic events on Friday the 13th July 1967 during the 13th stage of the Tour de France when Tommy Simpson died on the ascent of Mont Ventoux have done little to reduce superstitions in the peloton. To try and ward off bad karma, if given the race number 13, riders will often wear it upside down.

**Unlucky for some**

In many countries, the number 13 is commonly associated with bad luck, but it isn't the only 'unlucky' number. In China, the pronunciation of '4' is similar to that of 'death' or 'decease'. Many buildings do not have any floors starting with 4, and patients avoid having surgery on a date containing a 4. VIXI (an anagram of '17' in Roman numerals) is Latin for 'I have lived' and is commonly found on headstones in Italy. Consequently, the number 17 is unlucky and is associated with tempting death. Alitalia misses out row 17 on its aircraft.

**Omen-ous thunderstorms**

Ancient cultures believed that thunder and lightning were messages from the gods. The Romans feared thunder and believed that hearing it on your right side was bad luck. Depending on which day of the week thunder was heard, it could signify anything from the death of a beggar to widespread death. In the Middle Ages it was thought that thunder signified demons in the sky and dark-ceremonies during thunderstorms, believing that evil spirits were close to the Earth. However, the Victorians believed that thunder at a funeral signified a soul being accepted into Heaven.



**Always check your units**

July 23rd 1983. An Air Canada Boeing 767 crash landed at an air force base/motor-racing track in Gimli, Manitoba, having glided down from 12,000 metres after running out of fuel. The main cause was that ground staff and the pilot used the wrong units when re-fuelling, calculating the fuel on board in pounds rather than kilograms and hence taking on 4,900 litres rather than the 20,000 they needed.

**They were unlucky for four reasons:**

Canada was new to the metric system and flight paperwork still featured imperial conversion factors: the 767 was only four months old and checklists were still in flux: fuel gauges were faulty; the 767 was the first plane to have a pilot and co-pilot, but no flight engineer, who normally checked the fuel. However, the captain was an experienced glider pilot, and all 61 passengers (plus motor racers) walked away uninjured!

**Killed by Code**

The Therac-25 was a computer-controlled radiation therapy machine that was withdrawn from the market in 1987 following an intensive investigation into over-dosage treatments, which led to the death of four patients and life-changing injuries to two others. Two software bugs were found to be the cause of the malfunctions, but perhaps more fundamentally, the hardware interlocks present in earlier systems had been replaced with computer control. The poor system design, minimal risk and fault analyses, and inadequate testing of the Therac-25 has had a significant influence on the design and development processes of medical devices today. ENHS

**Fluttering in the breeze**

The Tacoma Narrows Bridge collapse is particularly famous amongst engineers. The suspension bridge in Washington state opened in 1940 and collapsed spectacularly in the same year. Moderate winds (under 40mph/64km/hr) generated huge twisting oscillations in the bridge deck that ultimately tore it to pieces. The cause was a phenomenon called "aeroelastic flutter", in which aerodynamic forces generate and feed a resonant vibration in the structure.





We are recognised globally as experts in the design and development of medical devices. That's all we do and we are proud of this focus. It enables us to deliver real insight and expertise to our clients.

Commercially successful products need to be safe, easy to use and ultimately make people better. Our clients like our approach, which combines design, human factors, science and engineering from inspiration right through to industrialisation.

Everybody at Team is driven by the same desire, to make things better by working in collaboration with clients and each other. Whether 'things' means people or the products we work on, we apply the same commitment to do the best and be the best that we can.

This focus and desire is a powerful combination and one that highlights why our clients trust us over and over again.

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