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# insight.

ISSUE ONE



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# In the issue.



Welcome to the first edition of Insight from Team Consulting, our regular magazine in which we will share ideas, thoughts and advice, while also hopefully sparking discussion or even a moment of inspiration.

This issue covers just a few of the many aspects of the medical sector which interest us as an organisation. We look back at the pioneering life of William Greatbatch, who sadly passed away recently, and forward to the further development of regenerative medicine. We review the strategies adopted by generic players in the dry powder inhaler sector, the design of safety-critical systems, and consider when and how to use computational fluid dynamics in device design. We've also invited Professor Brian D. Smith to contribute his thoughts on the future of the pharmaceutical industry, which makes for very interesting reading.

At Team we thrive on the sharing of insight – it strengthens and develops our understanding of the medical sector, and we hope that our new magazine extends this insight further, prompting useful discussion. Please contact any of our authors directly (emails can be found at the end of each article) to talk in more detail about any issue covered in this edition of the magazine, as we will be delighted to hear from you.

Neil Cooper, Editor

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## Team Consulting – Celebrating 25 years

November 11, 2011, represents a significant milestone for Team Consulting as we will be 25 years old (and you can read about our history on page 10). We've come a long way since we first set out, and today we are a business with an established reputation in a global market, and one of the first consultancies that companies turn to when developing a new medical device, or trouble-shooting a product or process. When I look back, I'm proud of what Team has achieved but above all I'm immensely proud of, and grateful to, all the people who have made Team what it is today – our clients, staff, associates and suppliers. I regard it as a privilege to have led the company for 20 of its 25 years, working with colleagues who are amongst the best in the business.

Looking ahead, we are really excited. We've strengthened and expanded our capabilities and recruited some great new people. As a result, we have built a platform from which we plan to grow – both significantly and sustainably – in order to meet the demands of an increasing number of clients.

If you would like to know more about our current developments and future plans, please do not hesitate to get in touch. We look forward to working with you.

With best wishes

Jerry Turner, CEO



# Parenteral drug delivery in the future: a view of developments, implications and opportunities



By Andy Fry

The focus of this year's PDA Conference is usability and compliance, issues which have been the subject of much discussion in recent years and which will continue to influence developments into the future. Good usability can enable patients to play a much bigger role in their therapeutic care, providing significantly increased convenience and a valid response to growing healthcare budgetary constraints.

But increased patient autonomy is acceptable only if therapeutic procedures are repeatable, reliable and effective. In the case of parenteral drug delivery, this level of performance will only be achieved if sufficient development effort is focussed on the delivery device; as PDA Europe senior vice president Georg Roessling has noted, stakeholders sometimes forget that the delivery device is the 'drug to patient interface', and therefore equally as important as the drug being delivered.

From a regulatory point of view, a 'usable' device is one which is easy to use correctly, difficult to use incorrectly, and therefore can improve compliance. As this imperative drives developments forward, effort will increasingly focus on those elements of designs which can be enhanced in order to improve usability while maintaining the parallel objectives of technical functionality and acceptable cost. Product design is therefore a sophisticated balancing act, demanding a thorough understanding of all the factors involved.

Naturally, the characteristics and demands of the therapy, such as dose size, viscosity and storage issues (such as refrigeration) guide choice of primary container and device mechanism, while dosing regimen and market size influence the manufacturing approach and hence cost of goods. The resulting product must however also reflect user needs. These include therapy-specific requirements and consideration of the cognitive burden imposed on the user, and of the environment in which the device will be used. All of this must take place within an increasingly stringent regulatory environment. 'Understanding' is the overarching requirement; understanding regulations, therapies, technologies, markets and manufacture, and of course perhaps the least predictable element, the user.

Moving forward, a number of technology developments are likely to prove influential. Pre-fillable glass syringes designed specifically for autoinjector use, for example, promise significantly better dimensional control and tighter tolerances than 'traditional' products. COC and COP pre-fillable syringes offer impressive levels of dimensional precision with good barrier performance and robustness without the tungsten contamination issues encountered with glass. New siliconisation inspection systems enable consistent syringe



lubrication and reduced silicone levels, while innovative new syringe treatment processes promise reduced friction without any silicone. These improvements will enable predictable engineering, capable manufacture and robust design for injection devices.

Parenteral delivery opportunities are expanding and the growing technology spectrum both supports and stimulates this expansion. For example, large volume delivery and high viscosity formulations enable reduced administration frequency, reduced discomfort and increased convenience. The ready to use needle-free devices can readily deliver high viscosity formulations, and electronically enabled delivery devices (EEDDs) include patch-pumps able to deliver several ml over 30 minutes or longer, and injectors which compute dose titrations, remind users to take therapy and automate the delivery.

For any therapy needing parenteral delivery, without a device there is no product. For a successful product the pharmaceutical, user, manufacturing and reliability requirements all have to be right – and that's the challenge we thrive on! ●

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# Standing on the shoulders of giants

Wilson Greatbatch sadly passed away on September 27, 2011. Unknown to many people, he is hailed as the inventor of the practical implanted pacemaker which, in 1983, was named by the National Society of Professional Engineers as one of the ten great engineering contributions made to society in the past 50 years.



By Dan Flicos

This is not surprising. It is estimated that worldwide three million patients have been fitted with a pacemaker, with over 600,000 more being fitted each year. The growing global market for pacemakers is worth over \$3bn and has spawned a number of international businesses such as Medtronic and St Jude Medical. As we look back at the history of the pacemaker's development, and glimpse into its future, we realise that we are standing on the shoulders of giants.

A pacemaker is an active implanted device that is used to treat conditions where the heart beats too slowly (bradycardia). By providing electrical stimulation, it ensures that the heart paces at the correct rate and is often the only and preferred method of treatment.

The remarkable story of the pacemaker really begins in Stockholm when, on October 8, 1958, Arne Larsson became the first person to have a pacemaker system implanted. His wife Else-Marie refused to believe that there was no cure for her husband – having heard of animal trials in cardiac pacing she persuaded Åke Senning and Rune Elmqvist to carry out the procedure on Arne. Åke was a surgeon at the Department of Thoracic Surgery, Karolinska Hospital, and Rune Elmqvist was an engineer at Elema-Schönander, a medical electronics firm. Rune constructed the first device in his kitchen and it lasted for three hours after implantation. The following day, a second device was implanted with more success. These devices were powered by nickel-cadmium (NiCad) cells, which were recharged by an inductive coil. Arne passed away from an unrelated condition in 2001, aged 86, having had 26 different pacemakers fitted in his lifetime – he outlived his surgeon Åke and the inventor Rune.

In 1956, across the other side of the world, recent Electrical Engineering graduate Wilson Greatbatch was working for Buffalo University on a device to measure heart rhythms. He realized that electrical impulses might be used to stimulate a failing heart and set about miniaturizing a device that was

then implanted in a dog. In 1958, Wilson left his job and set up in his garden shed with \$2,000 of his savings. Collaborating with William Hardwick at the Buffalo Veterans' Affairs Hospital, in 1960 a device was implanted in a 77 year old man who subsequently survived for 18 months. Within a year, nine more patients had received devices including two children. The pacemakers were manufactured by Medtronic under license and, unlike the Swedish device, the Wilson Greatbatch pacemaker used primary (non-rechargeable) mercury cells, which had a limited life. Perhaps the greatest breakthrough that Wilson made was to recognize the potential of new lithium-iodine battery technology which promised a higher energy density and lower self-discharge characteristics. Introduced into pacemakers in 1971, the new battery technology offered implanted life times of over ten years.

Greatbatch Inc remains a leading supplier of batteries and pacemaker technology to this day, and the development of the pacemaker has also prompted further innovations in materials, signal processing, communications and electronics. Other implanted devices, such as the Implantable Cardiac Defibrillator (ICD), take their inspiration and heritage from pacemakers. However, there is much yet to do in implanted device innovation, and especially regarding miniaturization, longer battery life, increased functionality and less invasive procedures.

From the first pacemakers – invented in garden sheds and constructed in kitchens – a whole industry was spawned which changed literally millions of lives. As engineers we are inspired by the likes of Wilson Greatbatch and Rune Elmqvist and we marvel at brave patient pioneers such as Arne Larsson. It is clear that innovation thrives where there is an urgent need and where clinical, scientific and engineering experts can work together. It's why we are drawn to the medical devices industry although most of us mortals merely get to stand on the shoulders of giants. Wilson Greatbatch we salute you – may you rest in peace. ●

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# Developing a strategy for generic inhalers



By David Harris and Stewart Fox

According to BCC Research, the global market for the treatment of asthma and COPD is estimated to be worth \$31bn by the end of 2014. With key drugs and delivery devices soon to come off-patent, the race is on to take a share of this highly profitable market – but should pharmaceutical companies copy successful products or create something new?



Unfortunately for the world's population, inhaler use continues to grow. Rapid industrialisation (especially in BRIC countries), together with better access to healthcare, has led to a continuous rise in asthma diagnoses and resulted in a global market currently worth over \$26bn a year. Pharmaceutical companies around the world, especially the generic players, are looking for ways to address this market, and one route is to capitalise on long established therapies, now off-patent.

This is certainly the case for the DPI (dry powder inhaler), a sector currently dominated by GSK's Advair Diskus (right), often used by patients who find it difficult to use a pMDI device (pressurized metered dose inhaler). Although more expensive – and therefore less frequently prescribed than the pMDI – Advair has become the therapy of choice for millions of patients around the world, generating a staggering \$7bn of revenue in 2009 for GSK.

Key patents relating to Advair have started to expire, opening the market to a host of new competitors. Not surprisingly, many of these have been waiting for this moment for many years, with device replication a common response strategy. Given the investment GSK made in developing Advair, and the proven success of the product, replication seems the most obvious way to quickly enter a highly profitable market, but one which is also driven almost exclusively by price. If the copy is the same in every aspect except cost, then market share is virtually guaranteed.

But some competitors have chosen not to replicate but to innovate instead. By comparison, innovation – higher risk and higher cost – seems almost inappropriate, given that most users are happy with what they already have. But some companies are innovating, and innovating successfully, challenging the almost automatic assumption that replication is the best route forward.

### Replication for fast market share

Replicating off-patent therapies to create cheaper, 'own' or 'no brand' alternatives has a long and well-established history. Although studies show<sup>1</sup> that a recognised brand can improve therapeutic effect, there is still a large market share to be had when patient choice is driven primarily by price, especially in sectors such as tablet-based analgesics.

The relative ease with which many generic drugs have entered specific markets has perhaps developed a false assumption that all generic equivalents are 'simple' to create, especially when formulations are well documented, and off-the-shelf packaging systems ready to buy. But recreating a device as complex as a DPI requires much greater and wider ranging expertise, and it is becoming clear that R&D teams can underestimate the challenge involved.

In particular, many companies fail to appreciate the importance of the delivery device, seeing it as just another form of 'packaging'. The replication of a DPI, however, requires an understanding of the complex interactions between device

and formulation, and of areas such as fluid dynamics and aerosol science, often beyond the scope of most in-house R&D teams. DPI design tolerances are critical, given the nature of its operation and its small size; poorly designed copies can exhibit undetected faults such as air leaks or poor powder aerosolisation characteristics, significantly affecting efficacy and success in the clinic. Price may be a driving factor, but the device still has to work just as well as the branded equivalent. In addition, the regulators now require evidence that devices are safe to use: this means that it cannot be assured that a device based on outmoded functionality will meet current regulatory requirements.



The important interaction between the DPI powder formulation and the delivery device is also frequently misunderstood. DPI formulations typically comprise active pharmaceutical ingredients (APIs) and lactose carrier particles in a mixture which has to remain homogenous when stored or transported, as any vibration can cause preferential segregation, compromising dose content uniformity throughout the life of the inhaler. For Advair, GSK developed a highly sophisticated packaging system which loads and seals single doses of the compound in a specially designed, foil-sealed blister pack. The packaging process is so precise that even though no headspace exists within each compartment, the compound is not compacted – simply held securely. This prevents movement, and therefore minimises segregation, but also means that when the Diskus device removes the foil seal, the compound is moved only by the inhaled breath and at the minimum flow rate to ensure an efficient dose. If packed too tightly, the compound may form a solid lump, too loosely and the active compound may separate from the lactose carrier. In both cases, the dose would be delivered incorrectly and given that each dose is already only 25 – 30% efficient, getting this right is crucial. This attention to detail by GSK is one of the many reasons why Advair has been so successful – and why generic alternatives may fail to replicate the performance.

A final hurdle for a replicated product is to show that it is 'substitutable' – that the instructions given for the original device can be used with the new. In the case of Advair, with elements of the Diskus still protected by design rights, >

achieving this level of reproduction is, again, a serious challenge. Not impossible, but rarely achievable without some expert input across the R&D process.

### Innovating for future growth

When successful, copying is undoubtedly a much quicker route to market. Clinical trials are shorter, saving significant time and money, and market success is guaranteed if the product operates correctly and is priced aggressively. However, any product chosen purely on price is always vulnerable to competition from alternatives developed in just the same way. Replication can certainly generate short-term profits, but is perhaps a less appealing longer-term strategy.

An alternative was demonstrated in 2010, when one of the leading Indian pharmaceutical companies, Sun Pharma, announced the imminent launch of a brand new DPI design, developed to work with a generic version of the Advair formulation. Sun worked with external design houses to create a device which may not be cheaper than a Diskus copy, but which offers much better value for money. Sun's strategy was to offer an improvement over the market-leading Diskus inhaler, both in terms of performance and features.



For example, the Sun device offers improved efficacy and cannot be activated unless the user inhales correctly, minimising waste and ensuring correct delivery. A dose counter comes with a lens to help the partially sighted, and an additional low dose indicator informs blind users when the device is nearing the end of its therapy. Overall, the device is sleeker, more attractive, simpler to use and more intuitive – and it even glows in the dark.

Undoubtedly, Sun's decision was not without risk. The process to develop a new DPI is expensive and must take place in a highly competitive space; around 400 patents have been filed in the last year related to DPI technologies, indicating the level of activity in this area. In addition, we would approximate, based on data that we have seen and anecdotal

evidence, that currently, the accepted success rate for new inhaler devices reaching the market is only around 10%, further underlining the challenges inherent in this sector.

But a crucial feature of the Sun device – and a compelling argument in favour of innovation – is that it is specifically designed to adapt to both current and future formulations which could be developed by Sun. This means that users familiar with the Sun device can stay with the same technology as drugs improve. This future-proofing also addresses a number of regulatory issues associated with DPI design. For example, many current devices would not meet regulatory approval if they were designed today. By starting from scratch, Sun has created a device which meets and exceeds current standards and guidelines, is better for patients, and which should also generate a bigger, and more sustainable return on the original investment required to innovate. However, it must also be said that the Sun device still leaves room for further, more radical innovation.

### Deciding on a future strategy

The response to off-patent DPI therapies is teaching the industry many useful – and possibly uncomfortable – lessons, and one of the most important is never to underestimate the complexity of an established design. Effective replication requires an understanding of all the many reasons why the therapy has proved so successful, and access to the full range of skills and technologies needed to create a viable product is essential.

Replication, however, is certainly one of the best strategies for short-term income generation. For many companies it will still make better economic sense to invest in getting a copy right, thereby securing their share of such a huge market, than to create a brand new device which carries with it a much higher level of risk.

But Sun Pharma's experience shows that innovation is not as unrealistic as may first seem, and in fact offers many opportunities for better product design, enhanced performance, greater clinician and patient support, and – crucially – future potential. ●

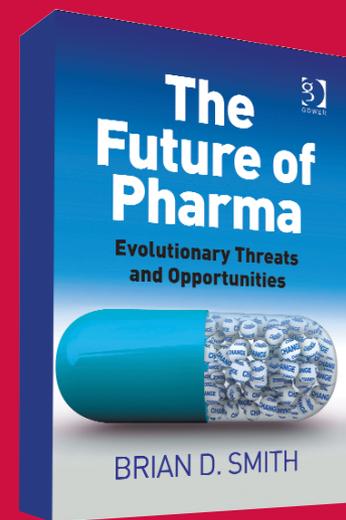
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# Speciation, sex and death



By Brian D. Smith

Having just published a three year research project and an 80,000 word book on the subject, I am often asked, by pharma executives too impatient to read the whole story, "So, in a nutshell, what is the Future of Pharma?" Hiding my amusement that such a huge subject can be compressed into a sound bite, my usual reply is "Speciation, Sex and Death". Of course, my slightly flippant answer begets a puzzled look so, if you have the patience, here's the 500 word version.

Although everyone connected to the industry agrees that we're in the midst of massive, generational change, no-one has yet painted the big, over-arching picture of how pharma will look in, say 10 or 20 years. If we want to do this with any sort of scientific basis, as opposed to merely speculating, we need a robust explanation of how industries change over time. Fortunately, Darwin gave us that explanation 150 years ago. We're all familiar with it as a tool biologists use to explain how ecosystems change, but evolution is in fact a general theory for describing the behaviour of any complex, adaptive system. Ecosystems and industries differ only in details; the general principles are the same.

Apply evolutionary theory to pharma and it predicts that business models will adapt to fit the changes in the market environment. More specifically it predicts that the three present 'species' of pharma company – big pharma, speciality pharma and generics – will become extinct and be succeeded by seven new species of business model, each one superbly adapted to a particular sub-habitat of the pharma market. So that's the speciation part.

The biological comparison goes a lot further. Those companies that survive (and most won't, the research suggests), will do so by acquiring new DNA and new traits or, in corporate terms, new capabilities. Some of these will be obvious

– building economic value propositions, for example – whilst others are less so – such as working in a virtual network structure. Firms will acquire these new capabilities from other firms, sometimes by acquisition and merger, sometimes via consultants and business schools. This swapping of DNA is of course the business equivalent of sex.

And the death part? Well, most pharma companies are poor at acquiring capabilities from outside of the industry. By and large, they prefer to swap genes within the industry pool. Academics have a term for this – mimetic isomorphism – and it is the equivalent of having sex with your cousin, with similar results. Firms that fail to acquire new capability 'genes' will fail to adapt to the market changes wrought by technology, demographics, globalisation, economics and politics. And as Darwin famously said, it is not the strongest of the species that survives, nor the most intelligent. It is the one that is the most adaptable to change. ●

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*Professor Brian D. Smith is the author of 'The Future of Pharma: Evolutionary Threats and Opportunities'. It is available from Amazon or, as a personally signed and dedicated copy, at [www.pragmedic.com](http://www.pragmedic.com)*

# A brief history of Team



An interview with  
founder Andy Fry and  
CEO Jerry Turner



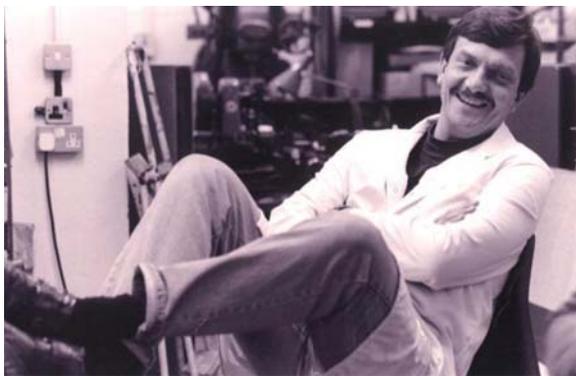
Team HQ: a wonderful 13th century barn  
in the Cambridgeshire countryside



By Neil Cooper

Twenty-five years ago, five colleagues who had worked together at PA Consulting decided to set up their own product development and engineering company. The focus, according to Andy Fry the only remaining founder still involved with Team, was to target the tranche of companies put off by the rates charged by larger consultancies but still in need of a high end technical service. The founders settled on the name 'Team Consulting' as it embodied the aspirational culture of the fledgling firm, one of combined wisdom, teamwork and collective expertise.

During 1986, the founding five resigned from their existing jobs and on November 11, 1986 the company was officially incorporated. Team's first office was an inauspicious cottage on the High Street in the small Hertfordshire village of Barkway. By the beginning of 1989, Team had expanded, albeit slightly, to six full timers and two associates, and had moved into a larger property literally just up the road at 102 High Street.



Jerry Turner, circa 1991

Following the move, Team recruited Jerry Turner as a senior consultant: "Andy and I had known each other from our student days and he called to see if I wanted to go back into engineering," he remembers. "At the time I was completing a company rescue but I was keen to return to my mechanical engineering roots."

For the next two years Team's reputation grew and the consultancy started winning projects in a wide range of areas, including a hydraulic power system for a commercial lawnmower, a tuna canning machine, robotic keyboard test equipment for IBM, and a variety of projects in the automotive sector. As the nineties dawned however, the British economy struggled as the country lurched into a deep recession. The impact on Team was bigger than anybody had expected. "It was the toughest time we've ever known," says Andy. "Our clients were either going out of business, keeping R&D in-house or putting it on the backburner. It was a trying time, especially in 1991."

Ninety-one was also the year when Jerry was made Managing Director: "Three or four months after I took over as MD we –

Andy, fellow founder Peter Sharpe and I – sat down and talked about the type of company we wanted to be. Successful, of course, but we all wanted Team to be a company that treated people with respect and did not follow the typical style of management that we had seen elsewhere," comments Jerry. "We wanted to build a company based around a set of values that we all held and, crucially, we decided to focus the company on the medical sector as this was a sector where companies were used to outsourcing R&D. This strategy also gave us the opportunity to develop products that could make a real difference to people's lives."

But as 1991 went on the situation got tougher and tougher and by October the company had just a few projects left. "Before Andy asked me to join Team I had worked in a variety of roles including sales and marketing," says Jerry. "The others had great skills in their respective engineering fields but it was felt that I had the commercial skills to lead the company through its tough patch. I believe that we learn a tremendous amount dealing with difficult situations, but at that time it felt like there was a real chance that we wouldn't make it." One remaining project was to develop an assembly machine for disposable hygiene wear for the catering industry. Everybody knew that delivering a good job and getting the machine running to the client's specification would win the next crucial phase of the project, and keep everybody employed. If not, it would be the end of the company that everyone had worked so hard to build and grow. The project turned out to have a profound impact on the company and the people involved.

"We were really struggling to get the machine performing as we wanted and in the build up to the pivotal client meeting we just couldn't get it fully working. The night before the meeting four of us stayed late pitching in and trying to fix the problems," recalls Andy. "We all knew the consequences if we failed and as the night wore on, and our efforts bore no fruit, our spirits started to fall. At about midnight, Peter Sharpe placed his hands on the machine and prayed. We all did the same."

"What followed was amazing," adds Jerry. "We turned the machine back on and it worked, exactly as we had built it to. And it kept working. At this point, we turned it off and went home to rest. We didn't risk further test runs – in the morning, when the client turned it on, it simply ran as intended and >

we were congratulated on our efforts. This proved to be a significant turning point in our fortunes."

Following the successful test the client immediately signed up to the next phase, which kept Team going for an essential few months, seeing the company ride out the economic storm and land its first full inhaler development project. From this point on Team has never looked back, working hard over 20 years to build a deserved reputation with pharmaceutical companies and growing the business each year.



*Cokenach, Team's home for 10 years*

On contemplating the significance of that time, Andy concludes: "I wouldn't want to go through something like that again, and wouldn't wish it on our closest competitors, but we came out of that situation with a strong belief in ourselves and what we could do."

In 1994, as the UK economy recovered, Team relocated again to the south wing of Cokenach, a stately home in Barkway village. By now Team employed 15 people (many of whom are still with Team today) and had established a strong reputation in the medical sector. In order to consolidate its position, Team set about developing specific tools including risk analysis based around FMEA (Failure Mode and Effect Analysis) techniques proven in the automotive industry.

For the next ten years, Team continued to grow in size and stature and focused the business fully on the global medical and pharmaceutical sector, developing a large number of inhalers and injectors for an increasing number of pharmaceutical clients. Team also expanded its skill base by recruiting more industrial designers, usability specialists, and mechanical and electro-mechanical engineers. Then, in 2004, the stately home was unexpectedly sold to a new owner who wanted to use the whole site. Team set about finding a new home, never expecting to find anything that could match the beautiful Cokenach estate, but timing was kind and later that year the company moved into a thoughtfully renovated 13th century barn in the village of Ickleton, which is still the company's home today.

So how different is Team in 2011 compared to 1986? "We started off trying to apply our engineering skills and creativity to any problem that our clients encountered; now, we are focused on medical," says Andy Fry. "It is where we have a unique position and it is also where we can all work for clients from around the world on products that will enhance people's lives. This represents a big sector shift from when we started, but what hasn't changed is our focus on integrity, creativity and excellence, which is still engrained in our culture and drives our business today."

"I think that the spirit of 1991 is also still evident today," adds Jerry. "We still work hard and we place a lot of emphasis on our relationships with our clients allowing us to work together for the greater good. As an indication of our strength, the recent global recession has had little impact on our business; this has much to do with the long-term perspective of the sector in which we work, but is also a result of the strong relationships we have established with our clients. They trust us and as a result they regularly come to us."



*Jerry and Andy, circa 1997*

Celebrating Team's silver anniversary on November 11th this year provides the perfect opportunity to reflect on the company's success and history, and its unique culture and values. Cheers! ●

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# The future of regenerative medicine – an engineering and product development perspective



By Stuart Kay

There is recognition internationally amongst stakeholders in the regenerative medicine (RM) sector that the commercialisation of novel therapeutic interventions requires expedient development if they are to be provided by healthcare system and providers within the existing infrastructure.



*For Orthomimetics (now part of Tigenix), we designed an arthroscopic surgical toolset for a regenerative scaffold*

A number of key issues need to be addressed by the RM industry collectively in order for RM to go mainstream, including: demonstrating efficacy, understanding the biology, that products are dynamic rather than static, rate of tissue sourcing, regulatory pathway, avoidance of animal-based products, reimbursement, manufacturing scale, IP protection and many more. This list represents just a few of the barriers standing in the way of some truly remarkable innovations. From a purely engineering and product development perspective, and having worked in this space for the last decade, we have identified two critical themes where engineers can make a significant contribution to overcoming the key constraining R&D and production bottlenecks: standards and cost-of-goods.

## The development, introduction and adoption of industry standards

Regulatory guidance covering the development of RM therapies exists; however, there is room for considerable subjectivity in the interpretation of these guidelines by sector stakeholders across different territories. The development and introduction of formal standards across common research, development, and production processes provides a basis for best practice, and thus aligns and potentially expedites the commercialization of therapies. It is not so much about restrictive rules; instead, it is about the development of common, validated methods and solutions that contribute to quality, safety, and performance.

## The need for a significant reduction in the anticipated 'cost of goods' associated with RM interventions

Until the balance of health economic benefit and cost of goods can compete favourably with conventional biopharmaceutical therapies, RM will remain a niche option divorced from mainstream healthcare reimbursement systems.

Whether it is the delivery of an implant or cell therapy through a retro-injection delivery device, or scale-out manufacture in a 'cGMP-in-a-box' system with integrated PAT, the enabling technologies need to be developed in tandem with the science. By applying the same product development and engineering principles that are so useful during the development of many other medical devices, we can ensure that the science can be translated into a robust, capable and cost-effective product. There is also the additional benefit of creating intellectual property in the non-cell-based parts of the device, which has been highlighted by the recent judgement from the European Union's Grand Court in *Brüstle v Greenpeace* which ruled that stem cells from human embryos cannot be patented. This means that the commercial IP value in such interventions now lies in the processing equipment and devices.

## Building investor confidence

By addressing complete product design, manufacture and manner of use at an early stage, many non-value-added parts and procedures can be minimised or eliminated. An efficient and lean product that delivers a novel therapy, coupled with scalable manufacturing, provides an attractive investment target, whether you are looking for external funding or an increased slice of an internal R&D budget.

Over the last decade there have been a number of economic casualties in the RM industry – sometimes due to treatment costs, sometimes due to cash flow issues during extended regulatory approval time – and this economic pressure has been exacerbated by international austerity tightening the purse strings.

We believe that the resolution of these two key themes will serve to build investor confidence in RM interventions, which will in turn facilitate widespread introduction of RM therapies into existing healthcare markets. ●

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# Against all the mods...



By Grant Smetham

Faced with the prospect of designing a new inhaler where 80% of the parts and surfaces are already defined, you would think there was limited design scope. But in fact, this is not such an unusual situation for a designer to find themselves in, and it presents some interesting challenges.

Before launching any redesign project, a lot of thinking needs to go on in order to understand the technology, its users, and manufacturing and client requirements, whilst adhering to tight constraints. This holistic approach ensures the design effort is targeted where it is needed to achieve the optimal 'whole product experience'.

One of our clients recently asked us to re-skin a successful inhaler which had been on the market for several years. The key constraint was to ensure that the air path and dose presentation within the device remained exactly the same and would be unaffected by any external alterations - including plastic wall sections and tool split lines. However, as the inhaler was a flagship product, it was also a requirement that brand values were embodied in the visual language of

the design, and the overall product aesthetic was brought up to date. Bearing in mind the long lead-times for introducing the inhaler onto the market, the resulting design also had to be timeless and not simply aligned with the latest fashion.

Team's approach to the project identified product landscape, user expectations and client values as key areas for analysis. As it was considered advantageous for the design to be discrete, not drawing unnecessary attention or broadcasting a patient's condition, we looked for a design that would blend into the user's environment, project a positive image about their health, and underline a pro-active approach to managing wellbeing, in a similar way to taking vitamin pills or exercising.

Building on this, we considered a range of products and lifestyles that reflected positive, healthy living. Three themes were identified - nature (organic), active (sporty), and nurture (health spa). A number of design concepts were presented for each theme, giving the client the opportunity to assess which approach most closely mapped onto their brand objectives and vision. It was decided that the health spa aesthetic reinforced the values that they wanted to convey and this was progressed into the final design.

The predominantly plain white appearance of the resulting inhaler established its clinical pedigree, and provided an uncluttered canvas for small, focused areas of accent colour. These areas of colour gave life to the design, and provided opportunities for strong interaction cues when used to highlight the operating buttons. Colour also opened up the possibility of linking the design with a corporate colour scheme and brand identity. By incorporating a translucent area in the design, a level of openness and honesty about the product was suggested, subconsciously reinforcing the user's positive perception of both the therapy and the pharma company behind it.

When trying to enhance aesthetics, there is often a real tension between reinforcing the perceived quality of a device and disposable product cues. The inclusion of an area of tinted translucent plastic not only reduced the visual bulk of the device, but also helped lower the perceived value; this is important for disposable products as users are conscious of both plastic waste and the intrinsic value of the products they are throwing away. Clearly size and weight play a significant role in determining user concerns about waste, and this is a constant challenge. Fortunately, this particular device was already extremely compact, and could be used multiple times, so was therefore less dependent on some of the more subtle masking techniques.

As is typical with many, if not most, of our projects, industrial design input was not confined to how the device looked. Another very important aspect of this brief was to address an identified usability issue. Despite being on the market for several years, there was an unacceptable handling issue associated with loading the device. The original design, whilst technically efficient, was unintuitive for a significant proportion of users as the method of access did not conform to established mental models of how similar shaped objects behave, and the design lacked the necessary visual and physical cues to combat and redirect the user's expectations. The shape, proportions and size of any product, combined with the position of split lines and reinforced by experiences with other similar products, should naturally suggest correct use. In this case, the device's geometry, aesthetic and cues suggested the access component should either be pulled-off or hinged out of the way, neither of which were correct. This was evident during user handling studies when it was also observed that users, confronted with an interaction that did not conform to their expectations, would apply excessive force resulting in a damaged or broken device.

To address this problem we needed to identify the most obvious interaction appropriate to the function of the device within the design constraints. The requirement was for all

parts of the device to be permanently attached. Having considered a number of options, and supported by observations from the earlier user study, a hinged component emerged as the most obvious and intuitive solution. However, before designing the component in detail we needed to take a step back. For the design to be successful the user had to correctly orientate the device before any other operation was undertaken. To do this we needed to communicate which face was the front. From a design perspective this is like a pre-emptive strike, trying to ensure users start the process from the correct position so that everything else falls into place. To achieve this, several elements were introduced into the design. The form was intentionally asymmetrical so that the cap could obviously only fit one way; this asymmetry also helped provide a tactile cue enabling users, through experienced learning, to orientate the device without looking directly at it. The relatively large plain cap provided an ideal face on which to print a logo, visually reinforcing the front of the device. This strategy built on learnt behaviour, such as users' expectation of the direction in which a door handle or tap will turn, and this behaviour can become automatic provided there are sufficient cues. In the case of an inhaler, users typically use the device frequently and over a long period of time, enabling designs to exploit experienced learning rather than use exaggerated cues to primarily cater for novice users.

Having considered the basic orientation of the device, the next issue was how to communicate the hinged articulation. Given the objective of minimising the number of finger grip adjustments required to complete the tasks, the design intent was to persuade the user to hold the device between the thumb and forefinger throughout the loading and inhalation process. This ruled out the option of hinging components on one side or the other as this would make it biased to left or right-handed people. The design was therefore developed with a front to back hinge. By deliberately making the hinge visible, it provided an affirmative cue to the user that the design was intended to hinge and in a particular direction. Assuming the pre-emptive orientation cues have worked, the hinge opening front to back is intuitive, and this, in turn, makes it is easy to load the device and check whether all the drug had been fully delivered post-inhalation, and all achieved from the front of the device without changing grip.

This example does not focus on the additional elements of the brief - requirements to ensure the minimum number of parts, appropriateness for volume manufacture and assembly, and regulatory compliance - but does illustrate that even within an apparently very constrained brief, there is plenty of scope for improvement and enhancement. The right industrial design input can significantly increase the chances of developing a product that works as it should, is handled as expected, reinforces brand values, and looks elegant, practical and desirable. ●

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## Designing safety-critical devices – understanding user error to meet user needs



By Sebastien  
Couvelier Mussalian

Given the ubiquity of electronic devices in every aspect of daily life, users look for the same functionality in medical devices, even those which are safety-critical. But as added technology can also increase the risk of human error, careful design is required to ensure patients remain safe no matter how a device is used.

Safety-critical devices are those which can cause serious harm to a patient – even death – if used incorrectly, and range in scope and complexity from a robot-controlled surgical tool to an insulin pump. As more and more therapies, devices and interventions migrate from hospital clinic to doctor's surgery – and then into the home – safety-critical devices are increasingly being used by both trained medical staff and patients.

Recent developments in electronics are accelerating progress in this sector, allowing much more sophisticated functionality to be incorporated even into hand-held or body worn devices. From a clinician's point of view, electronics make devices much more intelligent, efficient and effective, providing greater levels of control and accuracy. The opportunity to log data across a huge range of parameters leads to a much better understanding of ongoing therapeutic use and efficacy, and can also be used to monitor user compliance and ease medical practitioner workload, improving efficiency even further.

### Increasing user sophistication

Such impressive functionality is paralleled across a wide range of consumer products and as a result users across the healthcare spectrum – from hospital consultant to house-bound patient – are increasingly technologically sophisticated. They now expect to see functionality such as touch screen operation or wireless connectivity on medical devices, features which undoubtedly improve user experience and user acceptance, driving market share for devices that meet user expectations in a desirable package.

But the use of electronics in safety-critical device design demands specialist expertise, and a thorough risk analysis, especially as some of these risks can have far more serious consequences than in similar non-critical devices. For example, electronic devices need power sources and as a power failure in a safety-critical device could result in death, battery technology has to be understood and contingencies identified if and when power is unavailable. Many devices now use wireless technology to enable continuous patient monitoring or data flow, irrespective of location. But what happens if the device enters a Wi-Fi blackspot – how will a loss of data transmission affect function? There are also risks when increasing functionality within the same device, especially when some functions are controlled by SOUPs – software of unknown provenance. Although using pre-written code is a perfectly valid strategy, especially for well established or proven functions, there can be unexpected consequences when different SOUPs work together, and these need to be identified and any adverse effects isolated.

### Controlling user error

But over and above the many technological risks, the primary cause of electronic device malfunction is user error. An essential step in risk assessment is therefore to understand all the different ways users could interact with a device, and the associated risks. For example, it is highly unlikely – although not impossible – that a safety-critical device is exposed to extreme climatic conditions for any length of time; it is highly likely, however, that a user will push the wrong button when

operating the device, and this risk increases dramatically as more functionality is provided, giving the user – to put it simply – more buttons to press.

This risk analysis soon shows that the GUI (graphical user interface) is one of the most important aspects of safety-critical device design. At one level, it must satisfy a whole raft of user demands while remaining relatively easy to understand and operate, especially when used by patients or staff with limited clinical or technical knowledge. Functionality must be clear, responses or results presented unambiguously, and the device must continue to work despite the many different patterns of operation users can adopt (as it's not unusual for users to persistently operate a device incorrectly if the right result is eventually achieved). Understanding users is always important in device design, but in a safety-critical context it becomes an imperative, especially if impressive functionality actually makes the device more confusing, thereby almost guaranteeing human error.

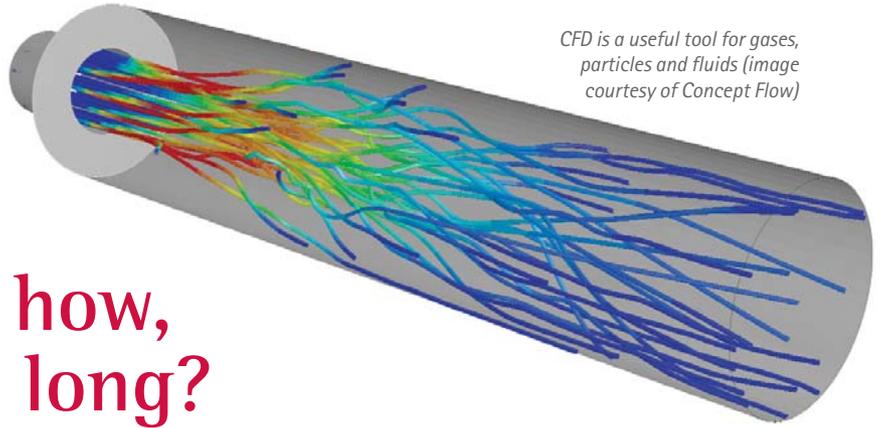
At Team Consulting, we have responded to this issue by creating a design methodology which separates the GUI into two distinct function types – safety-critical medical functions and user-focused functions.

Safety-critical functions control aspects such as essential power and memory, crucial sensor operation, and vital outputs, such as drug delivery, pacemaker operation or location tracking. User-focused functions encompass all the non-critical added extras – extended data management, wireless connectivity, touch screen displays and so on.

Safety-critical functions are controlled by a minimum of unambiguous buttons, which only the most determined operator could by-pass to compromise patient safety, and these buttons are completely separated from user-focused functions. If wireless connectivity is lost, for example, or the touch screen fails to work, the safety-critical functions will not be affected, and nor will the patient. The result is a device which features all the functionality which users want, but which also protects them from potential errors.

As with all device design, many stages exist between concept and delivery, not least testing and regulatory approval. But by placing the user at the heart of the development process from the outset, the resulting safety-critical device will meet user expectations more effectively and in so doing, make faster progress towards regulatory approval. This in turn means a faster return on investment, but also – most importantly – results in a device better able to maintain patient safety during operation. ●

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CFD is a useful tool for gases, particles and fluids (image courtesy of Concept Flow)

# CFD: When, how, and for how long?



By Philip Canner

When determining the performance boundaries of a design, or even if just looking at the feasibility of a concept, a certain level of analysis needs to take place. When it comes to a fluid handling device, which in the medical world could be anything from a pen injector to a blood analysis machine, the triangle of physical testing, 'heavy' analysis (in the form of Computational Fluid Dynamics or CFD), plus math modelling, can be a very powerful analytical combination. However, it is essential to understand both the benefits and limitations of the tools at your disposal.

CFD can help you test the effects of a number of design changes without having to prototype and test all the variations in reality. By comparing a real-world test to the CFD and math models, you can validate the accuracy of those models, and from there run a series of virtual experiments.

With CFD you can also determine the critical parameters, dimensions and geometries, by altering them in the CFD model and observing the effects. This can help real-world experiment design, by helping you decide which parameters to experiment with, and which aren't important to the performance of your fluid system. You can then run these experiments in the virtual world first, to see if they are likely to teach you anything. Taguchi style experiments reveal a great deal about a design with minimal testing, maximising the learning-to-cost ratio; CFD can help you determine which parameters to put into your Taguchi experiment.

However, you do not have to commit to modelling the entire fluid system in CFD. By taking bite-size chunks of the system, maybe just modelling the area of particular interest (such as a specific orifice or chamber), you can learn all that is needed. Math modelling can then be used to model the rest of the system. Keep a track on CFD modelling, and know when to stop; this will probably be driven by budget, but know when your results are 'good enough', and do not get stuck in analysis paralysis.

Before embarking on CFD, it is important to know what to expect from it, and whether it could help you or not. Too many assumptions in the modelling may invalidate the results, and

it is possible to spend a lot of time and money fully modelling an entire system, without learning anything useful about the design.

Also ensure that you understand the limits of CFD. For example, if the fluid is not well understood then you will get inaccurate predictions from the CFD model.

A good relationship with a CFD service provider can help ensure success. CFD experts can advise on how well a system can be modelled, and which elements of a system to focus on – in other words, how best to spend your money. The provider can also highlight what to expect from the analysis, and what it can be used for.

CFD is a powerful tool that can save weeks of time in the lab and can teach you about the critical parameters of your system. However, it does have its limitations, and it can be costly. You have to make a decision as to whether a full – or even a partial – understanding of the system is critical enough to warrant spending the time, effort and money on CFD. Finding a highly capable CFD service provider can help you make that decision and then keep the analysis on the right track. ●

*Another article from Philip on 'Strategies for designing a reliable, repeatable fluid handling system' is due to appear in the November/December issue of European Medical Device Technology (EMDT).*

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## Did you see us?

### World Pre-filled Syringes Summit

*Washington, 26-28 September 2011*

- Andy Fry and Colin Mathews ran a workshop on auto-injectors

### Mobile Healthcare Industry Summit

*Brussels, 20-21 September 2011*

- Sebastien Cuvelier Mussalian presented a master class on the integration of wireless technology

### IPAC-RS 2011 Conference

*Rockville, 29-31 March 2011*

- Julian Dixon presented on human factors and the design of inhalation devices

## Do you want to meet?

### PDA Universe of Pre-filled Syringes

*Basel, 8-9 November 2011*

- Andy Fry is delivering a keynote and moderating one of the sessions. We also have a stand

### DDL22

*Edinburgh, 7-9 December 2011*

- David Harris is presenting and we also have a stand

### Pre-filled Syringes

*London, 19-20 January 2012*

- Colin Mathews and Andy Fry are delivering a workshop on auto-injectors

### Pharmapack

*Paris, 15-16 February 2012*

- We will have a stand

## Did you read?

### PDA Letter, October 2011

- Andy Fry on device usability

### GEN, September 2011

- Stuart Kay on regenerative medicine standards

### Med-Tech Innovation, September 2011

- Chris Hurlstone on design verification

### PMPS, August 2011

- Stuart Kay on risk-based DFMA

### On Drug Delivery, July 2011

- Andy Fry on advanced injection devices

### American Pharmaceutical Review, April 2011

- Andy Fry was part of a panel discussing current pre-filled injection trends



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