PHARMACEUTICAL **PHYSICIAN**

IN THIS ISSUE:

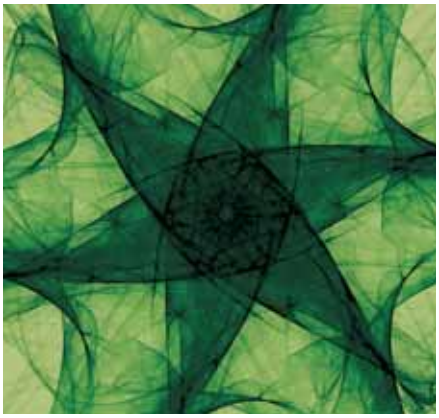
REGULATORY ROUND UP

Special features

Good science: The new role of Medical Affairs in an outcomes-focused world

Great innovation needs great leadership

Burn Out? ... Not Me, I'm Immune!



MAY 2017 **VOLUME 27 | Nº3**

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Head of Medical Affairs UK/ Ire – General Medicine/ Fertility Global Biotech – leadership role	W London	PP 6862
Associate Medical Director Oncology EMEA Global Pharma – Significant launch activity	Surrey	PP 6879
Senior Medical Manager Oncology EMEA Fast growing Global Biotech	W London	PP 6874
Global Medical Manager – Neurology International Pharma – Parkinson's	Berkshire	PP 6713
Global Medical Advisor – GI Specialty Pharma	Middlesex	PP 6696
Medical Manager UK Biologics Dermatology Global Pharma – launch and line management	Berkshire	PP 6748
Medical Manager UK Topical Dermatology UK/EU/Nordics Global Pharma – line management	Berkshire	PP 6810
Medical Advisor Ireland Biopharma	Dublin	PP 6875
Senior Medical Advisor UK – Hyperkalemia International Pharma	Surrey	PP 6801
Medical Advisor UK – Rare Diseases Biopharma – interesting portfolio	Buckinghamshire	PP 6864
Medical Director Clinical Development Global Biotech – Immuno-Oncology	Germany	PP 6861
Medical Director Clinical Research Research Organisation – Respiratory/ Infectious Diseases	Central London	PP 6882
Medical Director, Global Drug Safety Global Biopharma – Strategic focus	Germany	PP 6823
Senior Drug Safety Physicians – Oncology or Fertility Global Biopharma – Global remit and visibility	Germany	PP 6880
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Resourcing Solutions for Medical Affairs, Pharmacovigilance and Clinical Development

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Contents

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THE "RETRO" FEATURE has proved very popular with you: "Plus ca change mais plus ca meme chose", perhaps? It is fascinating re-reading opinion and 'state of the nation' from some time ago and contrasting with today's context. Lots to learn there. And thank you for the constructive feedback. With the various reports on the Bial Phase I unit crisis now freely available (and see a previous issue of PP for a commentary) it seems appropriate to look back at the TGN issues and for each of us to consider what we may have learned.

Your feedback also tells me that Regulatory Round Up continues to save you time and effort bringing together the key updates for the major agencies. Thank you to Anne Hetherington for tirelessly collating this for us. Change is the order of the day.

I am thrilled to be able to bring you a thought leader piece from the Accenture team on the role of medical affairs in an outcomes focused world. The world of medical affairs is changing rapidly too and the role descriptions have evolved very considerably from those of perhaps only 10 years ago. How are you future-proofing your career?

Continuing the leadership theme, Tarquin Bennett-Coles discusses the role of great leadership in innovation, looking at various settings and asking some key questions which may help you as you career plan.

Dovetailing well with that, Michael Atkins, a hugely experienced pharmaceutical physician who has enjoyed a variety of senior leadership roles in established pharma, considers what it takes to be the first medic in a company. Recommended reading for those of you contemplating this interesting environment.

Many of us try to be all things to all people- we like to make others 'happy'. This carries a cost and Catriona McMahon, a former UK medical director, discusses burn out and how we might consciously avoid it. For those of you who are nicely defended against the idea that 'it could be you', it really is worth the read.

Enjoy the spring.

Dr Madhu Davies

Dr Madhu Davies

REGULATORY ROUND UP

By Anne Hetherington, Senior Regulatory Consultant, Envigo Ltd.

HERE IS THE LATEST ROUND UP OF REGULATORY NEWS FROM THE LEADING AGENCIES, INCLUDING THE EUROPEAN MEDICINES AGENCY (EMA), THE MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA) AND THE FOOD AND DRUGS ADMINISTRATION (FDA). EMPHASIS IS PLACED ON THOSE NEW REGULATIONS WHICH IMPACT ON CLINICAL AREAS.

PLEASE CLICK ON THE LINKS BELOW TO TAKE YOU TO THE RELEVANT ITEM.

WE HOPE THAT YOU WILL FIND THIS DIGEST OF INTEREST. IF YOU HAVE ANY COMMENTS OR QUERIES PLEASE CONTACT US AT INFO@ENVIGO.CO.UK.

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Anne Hetherington

WORLD HEALTH ORGANISATION

- WHO launches global effort to halve medication-related errors in 5 years
  http://www.who.int/mediacentre/news/releases/2017/medication-related-errors/en/

EUROPEAN MEDICINES AGENCY (EMA)

News and press releases

- Medicine evaluation figures
  http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000256.jsp&mid=WC0b01ac058009fbb

- Conditional marketing authorisations give patients access to important new medicines earlier
  http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/01/news_detail_002680.jsp&mid=WC0b01ac058004d5c1

- Human medicines: highlights of 2016
  http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/01/news_detail_002678.jsp&mid=WC0b01ac058004d5c1

- First hormone replacement therapy for parathyroid disorder
  http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/02/news_detail_002700.jsp&mid=WC0b01ac058004d5c1

- Multiplicity issues in clinical trials
  http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001220.jsp&mid=WC0b01ac05807d91a4

Updates

- Post-orphan medicinal product designation procedures: guidance for sponsors
  http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500196994.pdf

- Report - Workshop on identifying opportunities for 'big data' in

medicines development and regulatory science
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/02/WC500221938.pdf

- Annual report on the use of the special contribution for orphan medicinal products
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/02/WC500221159.pdf

- Scientific guideline: Concept paper on the need to revise Condition – Specific guidance, Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man
http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500224997&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

- Scientific guideline: Guideline on clinical development of fixed combination medicinal products - Revision 2
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/03/WC500224836.pdf

- Regulatory and procedural guideline: Guidance on the format of the risk management plan (RMP) in the EU – in integrated format (Rev. 2), adopted
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/03/WC500224771.pdf

- Regulatory and procedural guideline: Guidelines on good pharmacovigilance practices (GVP): Introductory cover note, last updated with revision 2 of module V on risk management systems finalised post-public consultation, related revision 2 of module XVI and revision 2 of module II on PSMF
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/03/WC500224566.pdf

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA)

- New MedRegs blog
https://www.gov.uk/government/news/new-medregs-blog

FOOD AND DRUG ADMINISTRATION (FDA)

Guidance for Industry

- Considerations in Demonstrating Interchangeability With a Reference Product Guidance for Industry
https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm537135.pdf

SPECIAL FEATURE:
Good science:
The new role of Medical Affairs in an outcomes-focused world

By Elizabeth Coulton, James Crowley and Benjamin Rhee

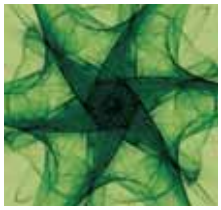
For years, pharmaceutical companies have deployed their Medical Affairs workforces to help physicians improve patient care through the safe and appropriate use of drugs. While these resources are considered valuable, customers rarely see them as critical to improving population health outcomes.

That's about to change.

Elizabeth Coulton

James Crowley

Benjamin Rhee



HEALTHCARE DISRUPTED

THE HEALTHCARE INDUSTRY is in the midst of massive change. Two primary trends are disrupting how scientific data and drug information are used and highlighting how the Medical Affairs workforce can be more valuable to healthcare delivery teams, from supporting administrators making policy decisions in boardrooms to supporting care teams making treatment decisions at the bedside.

Trend 1: Patient outcomes and population health

The healthcare industry is shifting its focus from volume to value. This transition is most evident in the move to measure and reimburse providers based on the quality, not the quantity, of care they deliver. Global healthcare reforms are accelerating this shift by introducing outcomes-based payment models and new care delivery models aimed at addressing population health issues. Socialized medicine systems in Europe, Japan and China are taking a lead in this regard, and are developing new approaches to increasing healthcare effectiveness and efficiency. In the United States, too, alternatives to the traditional fee- for-service model are on the rise.[1]

In this new environment, many more parties—from population health clinicians to pharmacists and administrators—are joining physicians in making decisions aimed at improving health outcomes. All of these stakeholders need to know more about the solutions, services and drugs (and the science behind them) that are available. Pharmaceutical companies, through their Medical Affairs workforces, are uniquely positioned to help.

Trend 2: Complexity of care

Scientific advances are making it possible for providers, researchers, clinicians and administrators to define, understand and treat diseases at a more granular level than ever before. In addition to making treatment paradigms more complex, these advances are producing more data than these stakeholders can effectively use. Information overload is likely to get much worse. Accenture research has found that more than 40 percent of life sciences companies surveyed expect to see their data volumes increase by at least 50 percent in the coming year.[2]

This is particularly concerning because as the healthcare industry shifts more of its attention and investments to improving patient outcomes, players within the industry are placing more emphasis on the reliability, rigor and relevance of the drug information that underpins so much of their decision-making. That information must be accurate and trustworthy. It must be discoverable. And it must be actionable. Often, it is none of the above. This presents a tremendous opportunity for Medical Affairs to serve as the source of information and insight to improve health outcomes.

MEDICAL AFFAIRS: STEWARDS OF PATIENT OUTCOMES

Against the backdrop of trends and challenges that are now affecting all players in the healthcare ecosystem, pharmaceutical Medical Affairs organizations have an unprecedented opportunity to play a much more

strategic role in the delivery of patient outcomes.

While regulatory restrictions will continue to define the nature of the relationships that Medical Affairs can have with customers, pharmaceutical companies can make those relationships broader, deeper and much more meaningful. To do so, Medical Affairs will need to re-imagine every aspect of their roles.

Who are the customers?

Medical Affairs professionals will continue to be a vital source of information for physicians looking to improve the health outcomes of their patients. But they will also drive solutions for a broader network of decision-makers and opinion leaders, including healthcare administrators and business managers, as well as pharmacy and therapeutic committee members at hospitals and health systems. Additionally, they will support other stakeholders such as population health managers, who work with hospitals and health systems to manage the healthcare outcomes and costs of specific patient populations.

What services can be provided?

Ensuring the safe and appropriate use of drugs has always been— and always will be—the most important role for Medical Affairs personnel. But they now have the opportunity to serve as trusted experts to their extended network of stakeholders. Further, Medical Affairs professionals can act as credible curators and connectors of information to treat information overload and help them make better decisions at the point of care. By helping capture, understand and use science from many sources, Medical Affairs can assume a prominent (and largely unfulfilled) role in minimizing complexity and improving patient outcomes and population health.

What skills will be needed?

To achieve a broader reach and greater impact, the Medical Affairs workforce will need deeper scientific knowledge in areas such as population health. Other skills will be equally critical.

- Collaboration skills will be important because Medical Affairs field personnel will need to interact with customers, internal teams, and internal and external experts in more responsive and personalized ways, connecting these healthcare ecosystem participants to the information that will lead to better health outcomes. They will need to work with experts inside and outside their organizations to build their knowledge of the complex science now underpinning drug development and the patient journey. They will need to engage with behavioral health researchers and health economists to understand and develop valuable insights into issues affecting population health. And they will need to interact with third-party specialists to understand how new technologies and solutions might be integrated into a broader plan for improving patient outcomes.

- Judgment skills will be increasingly important in an environment that is pivoting from volume to value. In many disease areas, for example, the definition of value is not yet clear. As the link between the science of medicine and the business of healthcare delivery, Medical Affairs professionals can serve a strategic role and help inform these value discussions by sharing the most relevant and trustworthy information with healthcare teams. Beyond curating and prioritizing information, these professionals will apply their judgment to determine the best way to help their customers define outcomes and understand the science behind the patient outcomes they seek.

STEWARDSHIP IN ACTION

One of the ways Medical Affairs professionals can serve as stewards of patient outcomes is by helping healthcare teams tackle issues that threaten to derail achieving the desired patient outcomes. Drug adherence is an example.

Pharmaceutical customers can now access mountains of information about why some patients fail to take their medications as prescribed. Similarly, digital technologies have produced a host of potential tools to improve adherence.

Unfortunately providers don't have the time to sift through these tools and materials to determine the right approach for their patients.

The Medical Affairs workforce can help. First, they can collect, aggregate, and determine the relevance of online and offline information related to adherence. They can add additional value by reviewing anecdotal evidence from their contacts in the field and scouring their own organizations' clinical trial data for insights and technical innovations that might inform adherence strategies. Armed with the most useful and objective findings, they can help their customers not only understand the barriers to patient adherence, but also devise solutions for overcoming them.

Continues on page 8 ▸▸

Continues from page 7

In the workforce of the future, Medical Affairs must:

Determine the relevance and trustworthiness of online and offline information

Search for insights that might inform adherence strategies

Compile data that help their customers understand patient adherence and devise solutions

How can we enable success for Medical Affairs?

Technical and analytical skills will become more important. Accenture research found that 79 percent of pharmaceutical companies intend to invest in capabilities that will streamline and automate some of their knowledge workers' more time- consuming tasks over the next three years.[3] That's encouraging. The challenge for leaders now will be to balance the technology investments made to support the Medical Affairs workforce with investments made for other workforces.

Technology investments for Medical Affairs—both internal operations groups and field teams—should be focused on the things that will allow these resources to deliver more personalized and more strategic services. Such investments might include solutions aimed at minimizing administrative burdens, analytics capabilities that reveal insights into customer needs and preferences, digital monitoring solutions that enable the mining of new evidence sources, or systems designed to help aggregate insights and information for quicker customer visit preparation. Pharmaceutical companies will need to train internal and field personnel on how to use these new technologies for maximum effect.

THE DIGITAL WORLD OFFERS NEW SOURCES OF EVIDENCE

According to Accenture research, 57 percent of US consumers accessed a website for medical information last year. One in five (21 percent) used social media for that purpose. And 12 percent turned to online communities.[4] While the quality of information retrieved from online sources is often general in nature and sometimes questionable,[5] patients are using their digital findings to ask their doctors and providers more specific questions. That, in turn, changes the types of information pharmaceutical customers seek.

Pharmaceutical companies may want to invest in digital monitoring solutions that allow Medical Affairs to uncover new sources of evidence. Healthcare consumers leave a digital footprint with their online queries and conversations, which means pharmaceutical companies can analyze the behaviors, opinions and concerns that patients demonstrate online. By applying those insights, as well as their judgment skills to identify the trustworthiness and relevance of sources, Medical Affairs

can better predict the types of questions patients will ask of their physicians—and the types of questions that pharmaceutical customers may ask of Medical Affairs.

Last year, US consumers went online for medical information:

57% Accessed a website

21% Used social media

12% Used online communities

SHAPING THE FUTURE OF HEALTH

We believe the opportunity to refocus and enable the Medical Affairs workforce is one of many that will emerge for Medical Affairs organizations in the coming years. To ensure that Medical Affairs continues to deliver the services and solutions that meet customers' growing expectations and demands, pharmaceutical leaders should:

- Rally support across the organization for a new Medical Affairs vision.
- Constantly evaluate their medical strategies, as well as the roles and resources they will need in the future.
- Invest in the skills, technologies and training that will ultimately bring that vision to life.
- Measure the effectiveness of Medical Affairs efforts so that the services, channels and tools that are available to customers can be continually refined and improved.

Science does not stand still.

Neither can pharmaceutical manufacturers' Medical Affairs organizations. It's not too early for pharmaceutical leaders to start thinking about how they can position their Medical Affairs organizations to have an even greater impact on the healthcare ecosystems they serve. Refining the role of Medical Affairs from disease and product specialists to curators and connectors of outcomes-focused information is a first step in that journey.

The second step is equally important. It calls for leaders to honestly assess their workforce's capacity to make the transition. Do they have the right number of customer-facing and operational resources to deliver against the new Medical Affairs imperative? Do they have the right talent and skill sets to address the growing B2B nature of customer interactions? And how will Medical Affairs measure its success?

Join the conversation

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@Accenture-Strategy

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Continues on page 10 ▸▸

Continues from page 9

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Accenture Life Sciences Blog

Accenture experts share insights and opinions on opportunities and challenges in the pharmaceutical and medical technology industry *ww.accenture.com/lifesciencesblo*.

| REFERENCES

1. Jeff Elton and Anne O'Riordan, Healthcare disrupted: Next generation business models and strategies, Wiley, 2016, pp. 12-18.
2. Accenture Technology Vision Research for Life Sciences, 2015.
3. Ibid
4. Accenture Consumer Survey on Patient Engagement, US findings, 2016.
5. Eric Topol, The patient will see you now: The future of medicine is in your hands, Basic Books, 2015, pp. 34-35.

SPECIAL FEATURE:

Why life sciences innovators need to build the right teams

An opinion piece

By Tarquin Bennett-Coles, Principal Consultant in the Life Sciences Practice, Carmichael Fisher

GREAT INNOVATION NEEDS GREAT LEADERSHIP.

THE LATE, GREAT Steve Jobs said: "Innovation distinguishes between a leader and a follower."

So, when it comes to spotting opportunities in the exciting cross-over fields of life sciences, technology, and consumer applications, the right leadership team is vital.

Businesses may be set up with an original goal in mind, such as developing new tools for cancer screening.

The potential applications for the technologies they innovate, however, could be far wider than the healthcare field.

Tarquin Bennett-Coles, Carmichael Fisher's Principal Consultant in Life Sciences Practice, says the need for some members of leadership teams with broader skills and experience is now being widely recognised by companies in this cross-over space.

The need for managerial agility in recognising skills gaps and plugging them with the right people is paramount for a successful business.

"Original teams may well be very focused on the healthcare benefits of their potential projects and have extensive experience in that field," he says.

"Their skills may be highly specialised.

"However, lucrative consumer applications could transform the future of a company. They could ensure its viability and its ability to carry out further research and development in important areas of life sciences.

"Failure to capitalise on these opportunities could have the opposite effect. Companies which fail to grasp them could be held back from performing important work.

"Leaders must be aware from the outset that there may be potential for the application of their technologies in different areas to those they initially target, and they must be open to the opportunities which arise. They must be open to changing direction.

"Then, people with the right kind of skills at every level must be brought in to develop these potentially lucrative consumer applications.

"As the project progresses, companies may need those with corporate skills or those experienced in the use of different technologies."

Many of the consumer markets which may use applications may be radically different to the field of life sciences.

"Leadership teams need people who understand these markets," Mr Bennett-Coles says.

"They also need those with excellent corporate skills. They will know whether companies need to be split and run separately to maximise the opportunities.

"There are also differences in timescales. In life sciences, teams might

Tarquin Bennett-Coles

SPECIAL FEATURE:
Why life sciences innovators need to build the right teams

An opinion piece

Continues from page 11

expect to see results after a five to twelve years development process.

"For those with experience of the consumer markets, they would perhaps be looking to develop a product or a service within 18 months.

"This speed is necessary to ensure the technology isn't overtaken or another team moves more quickly to bring something to market."

Two case studies show the importance of that approach:

How technology developed as a cancer diagnostic became a tool in the war on terror

TeraView Ltd, based in Cambridge, was originally set up as part of the Toshiba overseas research laboratories in the 1990s.

It began life as a way of researching cancer diagnostic tools using Terahertz light technology.

X-rays give us images of our bones. Terahertz T-rays allow us to see molecular structures.

TeraView uses T-ray light, which sits between microwaves and infrared, as a tool to carry out tests and inspections.

The T-rays allow the creation of 3D images.

Though the technology was originally developed as a tool in cancer diagnostics, it soon became obvious that it had several other applications which needed to be developed.

Alongside medical testing, TeraView's technology is used in the pharmaceutical, semi-conductor, and solar industries.

It is also used to test for explosives, noxious gases, and non-metallic weapons.

Technology which began as a medical diagnostic is now an important tool in security screening.

TeraView's CEO Don Arnone says: "These opportunities became apparent quite early on. We could see there was potential in three or four different markets and we pulled in people with experience of operating in those markets.

"We knew we needed a team with the right technical skills and an entrepreneurial flair and professionals with a good knowledge of those markets to commercialise the technologies we were producing.

"Initially, we brought people in on a consultancy basis, then on contract. As we moved forward, they stayed with us.

"We brought in people who understand markets in the USA and those who have experience in the automotive market.

"As the company grew and we faced different challenges, we needed a technological team which could help us deliver solutions fairly rapidly.

> "The need for managerial agility in recognising skills gaps and plugging them with the right people is paramount for a successful business."

"We also needed people who could develop and maintain customer relationships in our different markets.

"We've maintained a flat structure. We don't have a bunch of expensive executives or vice presidents, for example.

"As we have grown, we have grasped opportunities and our team has developed knowledge and skill in different markets.

"We developed a product for the inspection of microchips in mobile phones for Intel in 2008/9.

"Since then, the team has developed contacts and experience in the semi-conductor industry after working with Intel's engineers for eight years.

"As we've grown, our team has adapted to different markets and technologies, and there has been some convergence.

"However, there are still differences in markets which must be taken into account. Someone in sales in the semi-conductor market would not be particularly adaptable to selling in the automotive market, for example."

Understanding different markets is helping one company expand overseas

For innovative company Ieso Digital Health, building a team with an understanding of different healthcare marketplaces has been a key building block to success.

The Cambridgeshire company was launched in 2011. It delivers cognitive behavioural therapy (CBT) to patients through a ground-breaking online method.

Its Director Dr Andy Richards explains: "There's a well-known inhibition when a patient sees a therapist face-to-face. Freud recognised this. It takes several sessions to build a trust and honest dialogue.

"We deliver therapy online using a written method which helps our qualified therapists to develop trust with patients much more quickly than if they were physically seeing a therapist.

"Our system is highly secure and a written record of all sessions is kept - something which is useful to therapists and patients and allows improved protocols to be developed."

"Patients can access treatment via our online method more quickly than physically seeing a therapist, and out treatment has proved highly effective in many cases.

"We took the decision in the UK to work within the NHS, rather than privately, so our patients are referred to us by NHS trusts.

However, there is a growing market need for this approach overseas, and this is where the right leadership team has become an important element in Ieso Digital Health's growth.

Alongside skills in the commercial and technical fields, the company's team has needed market-specific knowledge.

Dr Richards says: "If you take the United States, the 'behavioural health' market is very underserved, but healthcare is delivered in a very different way than within the NHS including Medicaid and the private healthcare segments. So, we have needed senior people with experience and skills in those markets, we have 'aimed high'

"An additional key factor for us is regulation. It can be a complex area. In the USA, regulation varies from state to state, and in Europe from country to country

"We need people with a deep understanding of what's needed to operate in these markets.

"Without the right people in place, companies will make a lot of mistakes."

The opportunities in the cross-over space between therapy and technology are substantial.

With one in four of us likely to suffer from mental illness in our lives, and a growing focus on preventative medicine for mental health issues, world-wide demand for online therapy is only likely to grow.

For Mr Bennett-Coles, the lessons learned by companies like TeraView and Ieso Digital Health are vital for any forward-thinking business in the field of life sciences.

Without the right skills and the right entrepreneurial spirit, teams will fail to take advantage of opportunities for experimentation and growth, he says.

Future success starts with the visionary leadership to build those teams.

SPECIAL FEATURE: Burn Out?

... Not Me, I'm Immune!

By Dr Catriona McMahon

Dr Catriona McMahon is a seasoned pharmaceutical physician, ex Medical Director of AstraZeneca UK Ltd and now an Executive Coach, focusing on the needs of Healthcare and Life Science Professionals. She has a specialist interest in working with people returning to work after, or remaining at working during ill-health. For more information, visit www.te-aracoaching.co.uk

Dr Catriona McMahon

AND SO I thought ... until 2012, when I burnt out; acute on chronic stress, followed by clinical depression. Both had a significant impact on my performance … and my outlook on life. I recovered, slowly, and in doing so, found out so much about myself that I didn't know. And I discovered what it feels like to ask for help, to have that help refused and survive, and to receive genuine, compassionate assistance – three experiences that now shape my approach to my life and career.

As for many executives who experience stress and burn-out, the causes were many, originating from both my work and personal life. Some I couldn't have influenced, for example the severe pain from a frozen shoulder and subsequent surgery; but one that I might have, if I had been able to recognise it, was the development of workplace stress. Whilst it may not have been in my power to change the business asks, I now see that it was within my power to change how I was managing those projects and tasks … if I had recognised the slippery slope that I was on. I wonder now how many of my friends and colleagues saw the signs, how many of them tried to tell me? Did they not try, or did I not listen when they did? You'd think I'd remember…

If I were to ask you how confident you are that you are not in a state of sub-clinical stress, at risk of burn out, what would your answer be? Oh, no, not me, I thrive on this stuff (my old response); I don't know, I'm not sure what to look out for; or no, I'm good as I feel in control of how I carry out my responsibilities, have a great support system and know how to listen to those who care? I hope you fall into the latter category!

This article is an introduction to workplace stress, to burn-out. It is not a scientific review of the topic, but a personal reflection; and hopefully a conversation starter. We cannot manage mental health issues in the workplace by hiding them behind closed doors, no matter how much we are tempted to try.

Stress is an important cause of ill health in the workplace and can have significant impact on business productivity. But what is workplace stress, what is burn-out? The official definition of workplace stress is "a harmful reaction that people have to undue pressures and demands placed on them at work and includes stress, depression or anxiety[1]". Using this definition, workplace stress has an incidence rate of 6.9 per 1,000 UK workers in 2015/16, resulting in 11.7 million working days lost, equating to an average of 23.9 days lost per individual. In 2014/15, 35% of all work related ill health and 45% of all working days lost due to ill health were due to workplace stress[2]. So, this is a big problem; and there is some evidence that our training[3] and ways of working[4], [5], may place physicians at greater risk than some other professions. I wonder how relevant these data, gathered from physicians in clinical practice, are to us, physicians in Pharmaceutical Medicine? Subjectively, I recognise the discussion and they feel relevant to me.

However, I find the above definition challenging as I struggle to define

'undue'; none of my 2012 objectives were unreasonable; all were, in theory, achievable and I had the skills and capability to deliver. Knight, in a recent Harvard Business Review article, defines burn out as "the mental and physical exhaustion you experience when the demands of your work consistently exceed the amount of energy you have available[6]". This description I do recognise as relevant, reflecting the complexity of my own personal/work situation and the importance of energy; it also reflects the conversations that I have with pre-stress or stressed colleagues and clients.

> IF I WERE TO ASK YOU HOW CONFIDENT YOU ARE THAT YOU ARE NOT IN A STATE OF SUBCLINICAL STRESS, AT RISK OF BURN OUT, WHAT WOULD YOUR ANSWER BE?

In today's increasingly tough and fast-paced work environments, work regularly invades our homes - via our granting of discretionary hours, and our responsiveness (some would argue addiction) to remote and mobile technology. This in itself is not 'bad'; indeed, many of us choose to work this way. No, it is how we manage ourselves within our chosen patterns of work-life that has the greatest impact on our risk of stress; and for most of us, we get the balance right enough to ensure that our energies remain sufficient to meet the demands upon us, most of the time ...

So, how can we recognise when we are not getting the balance 'right enough' and/or we are failing to tick the 'most of the time' box? What should we be watching out for that could signal that our balance is at risk of going off balance? Could I have detected my stress before it reached the tipping point?

We all know the risk factors for workplace stress: lack of control within role, whether real or perceived; unclear role/project expectations; dysfunctional workplace dynamics; a mismatch in values; and frequent extremes of activity – from monotony to chaos. Similarly, we are aware of the importance of good social support and healthy work/life balance. Like you, I knew all of this, yet I still slipped into the chasm of stress. So what did I miss? Honestly? Nothing. It wasn't that I missed the signs; no, I saw the issues, the risks, and decided that they didn't apply to me; that I was strong, that I could cope, that I could make these situations work for me - and as a business executive, I believed that it was expected of me to manage the 'ambiguity', the 'challenges' facing me, often alone. This fog of high expectation very efficiently hid the chasm from my view.

So, I'd decided that the risk factors were not relevant to me – I was already half-blind; how about my recognition of the early signs? Lee, Medford and Halim[7] characterise burn out as emotional exhaustion, depersonalisation and a reduced sense of professional efficacy, with the first being considered the earliest and most important sign *(Table 1)*.

I can safely say that I experienced all three signs. I was aware that I was becoming less engaged with my role, with the exception of my continued passion for team and individual development. Importantly, I was no longer recognising many aspects of my role as a potential source of growth and development and was becoming unsure as to where I could add new and/or additional value. Looking back, I now see this perception resulted from a

TABLE 1: Adapted from Lee, Medford and Halim[5]

Features	Explanation
Emotional exhaustion	Emotional depletion from being overworked
Depersonalisation	A sense of being unfeeling towards colleagues or peers; often negative, callous and detached responses
Professional efficacy	A reduced sense of competence or achievement in one's work

Continues on page 16

SPECIAL FEATURE:
Burn Out?

... Not Me, I'm Immune!

Continues from page 15

combination of exhaustion, depersonalisation as I unconsciously tried to reduce demand upon me, and some, though initially limited, insight into the short-term consequences of my state. Unfortunately, it sometimes takes moments of crisis for true awareness develop – and this was the case for me.

So, with all of this in mind, how can you avoid developing workplace stress?

First, be open to the risk factors in your environment – I am sure that you do this for your colleagues and team members; remember that you deserve the same care and attention and do the same for yourself.

Listen carefully to the messages that your body/mind is sending you. Rest assured, if you miss the early signs, the gentle shot across the bows that you will experience, a stronger message will be sent as your body/mind finds a way to stop you! Hopefully it will only be a "cold" that takes a few weeks to shift …

Next, don't just hear the comments of colleagues, listen carefully. If you feel yourself getting defensive, pause and ask the question, why? Consider whether it is possible that their commentary is coming from a place of concern and caring, and not a place of criticism. Perhaps it is professional feedback; or perhaps they have more insight into your state than you have?

If you find yourself being impatient, short or sharp; if you find that your thinking is slowing down; if you feel unusual self-doubt; or if you realise that you are struggling - don't try and resolve these challenges by working harder. Find a trusted colleague and speak to them about what you are feeling. In this way, you will share, which will reduce your burden and will start to build a support system around you.

And don't manage a slipping performance on your own – work with your manager, a mentor or a coach; someone who can explore your experiences with you, help you broaden your perspective and identify how to regain and retain your balance.

Finally, consider professional (counselling or psychotherapeutic) help if you realise that you are on the wrong side of the tipping point – I promise you, the feelings of embarrassment or shame that you may experience as you ask will not remain, and, most importantly, do not define who you are in any way.

My journey to recovery is my own, and as my purpose for this article is to pre-empt burn-out, I will not go into further detail here – I am happy to share if anyone wants to contact me and ask more. But I do want to share what this experience has taught me. Whilst I would not wish burn-out on anyone, I find that I have a deep sense of acceptance and, perversely perhaps, joy that it happened to me – I am now aware of me and the world around me in a way that I was not before; and perhaps in a way that I wouldn't have discovered if life had stayed the same.

First, I now listen to my body/mind. I know that if I don't listen and pay due regard, it will find more impactful ways to slow me down!

Second, I appreciate that it is impossible to compartmentalise my home, family, personal and work lives away from each other. I exist in each one; in fact, often in more than one at any time. Work stressors affect home and family peace and vice versa. Now, rather than compartmentalise, I integrate.

Next, I engage with and listen to the council of others. I had an amazing councillor whilst I was at my lowest, and a great Executive Coach as I moved into recovery. Now, as a member of the 'helping profession' of Executive Coaching, I work with a Supervisor who co-creates with me an environment that encourages and supports reflection on my performance, whilst considering my

associated physical and mental health. I recognise that the supervision relationship is different from the manager-employee relationship, but I do believe that it is possible to develop a reflective relationship with your manager or a trusted colleague; and if not, then with a formal coach or mentor.

Fourth, I have stopped hiding behind 'doing', being busy all of the time, and now dedicate time to 'being', including having an active mindfulness practice. This has been a very challenging change for me, as like many people, the 'doing of stuff' has taken priority over my 'being' needs for a long time, and keeping busy was an important defense mechanism – it's much easier to keep going, than to stop, accept, inquire … and change if need be.

And critically, I now embrace the fact that I'm not omnipotent – I am as human as the rest of us, and accept that my intelligence, position and seniority in an organisation neither protect me nor make me immune to that simple, beautiful fact.

Workplace stress is not a sexy topic, but it is an all-pervading issue in today's high impact, fast pace corporate cultures; nobody is truly immune. Our individual health is critical to the healthy functioning of our organisations – whether they be our employers or our home/families. Look after yourself and stay well!

> "…NOW EMBRACE THE FACT THAT I'M NOT OMNIPOTENT – I AM AS HUMAN AS THE REST OF US…"

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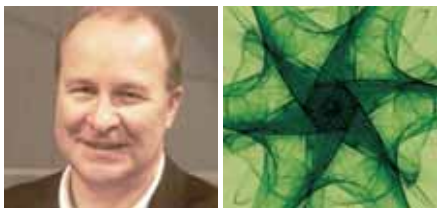
SPECIAL FEATURE:

First medic

By Dr Michael Atkins

Some guidance for a Medic Affairs medic entering a company that never had one



Dr Michael Atkins

I AM NOT talking about replacing an existing medic or acting as a consultant or interim, I am talking about a company that has NEVER had a pharmaceutical physician before and now needs one full time. It would be indiscreet to say from which companies I am sharing my experiences but experiences they were! Anyway, here are some points to think about.

This article does not discuss the role of the medic in Phase I or other aspects of R&D. It is likely (if needed) such individuals will already be in place.

- **Is it for you?** The first BIG question is whether you are right for the job and the job is right for you. The sort of companies needing a medic are likely to have been start-ups that have R&D experience and that's all. They may or may not have got as far as using regulatory professionals to begin a marketing authorisation process. The chances are that they have discovered new words like "Medical Affairs", marketing and sales.

In my opinion, you would be a very big step to be a "first medic" unless you are a final ABPI Code signature and a Medical Director (or at that level). If not, I believe you may struggle and be out of your depth and unhappy. First medics are the brave and the entrepreneurial. It carries risks (and great potential benefits). This role is not just a stepping stone on a pharmaceutical physician's path to other things. Immediate career prospects in this company are zero.

- **Due your "due diligence".** What has the company got and why do they need a Medical Affairs medic? What are their expectations of you? One company had the bizarre idea I could schmooze a competent authority to accept data I was lead to believe (before I joined) was "robust". It wasn't and I didn't.

It is likely the company will have few employees and even fewer who involved (if any) in medical affairs. Meet as many as you can and ask their views of the company and its people. Remember, with few key employees, if someone leaves or goes off sick or maternity/paternity leave, who is going to cover. You?

- **The "package".** You may be offered a low salary and generous share options ("scare options"?). This could be at the start of your billion dollar lifestyle but companies can falter and you may find you have taken a drop in salary from your previous job with that "golden carrot" they promised going mouldy after 2 years. Even more concerning (alarm bells) if you are asked to forgo a salary as part of the start-up/buy-in. I walked away from that particular "opportunity".

Don't expect all the normal big pharma trappings –car/car allowance, phone, computer, private health, holidays etc. Small companies may provide these but not at the level you may have been used to.

- **Resources.** Being the first and probably the only medic you may end up a one person band. No longer the luxury of Medical Information to check references or an administrator to help with your diary and travel

plans – you are on your own. For the right candidate, that will be exciting but for others it is becomes a stressful additional workload on all the other things they expect you to do - Phase III trials, key opinion engagement and management, setting up and running advisory boards, developing training slides on the Code and products… shall I go on? You cannot delegate. Who will cover for you on holidays? What about IT support?

Don't expect to be trained – you must take that in hand yourself to keep up to date for your own GMC status. That is why this role is unlike to suit anyone who is still in higher medical training. Your managing director will want you focussed on the tasks at hand – your training is not on his/her radar.

Many functions may be contracted in/out rather than on head count. That can pose challenges if such functions are not on site in terms of just popping to their office for a quick chat about a delicate issue.

Also, beware of promises that they want you to "build a medical department". It may well be true and a hook to get you in. However, will it be on Day 1 you find such plans are linked to revenue yet to come? Remember, most young biotech/pharma companies are on what is called a "cash burn" – they are spending to fund the projects yet to be commercially viable. What you might assume as a necessity, they see as a luxury.

Do they know what they don't know about the ABPI Code? Be prepared for creating Code compliant SOPs and for an uphill course when helping with sales force training versus the wide eyed wishes of the CEO to make money quickly. MSLs are not super reps to gain KOL access and talk off-label and their objectives must not be based on call rates. The CEO needs to understand and accept that. Hence, you must be both Code expert and a compliance manager - two hefty tasks. The battles I have had getting a dedicated Compliance Manager into a growing organisation are many. Want to see the scars?

- **Travel.** Not just in the UK, but what will be the requirements of seeing investigators/KOLs abroad and attending international conferences. You may be expected to man promotional stands as the resident medical expert. I was once asked to do just that in the first week of joining a small company as a first medic – in Singapore. Travel and work commitments may take their toll on home life and seeing your children grow. I got my British Airways Gold card in one month and after 8000 miles air travel. During that time, I once fell asleep in my own lecture. Travel can be tiring.

- **Are you tough minded?** Being the only medic will mean you making some big decisions without a mentor. Can you stand your ground? Can you negotiate? You will need to engager trust and respect and that is not done by just being nice and saying yes all the time.

- **Is it a therapy are you know?** – If your background is ophthalmology and a start-up company wants to launch a new product in glaucoma, this may be your chance to make a real impact. The company will want you to hit the ground running and that may include contact with your own precious KOL network.

- **Map out your tenure.** The CEO will want to see your plans mapped out according to his requirements. Be realistic. Rome was not built in a day.

- **Matrix management.** All your managing skills will be needed to guide the company along a Medical Affairs journey. Some concepts will be alien to them or (worst still) they think they know what is best. Explain your intended actions rather than defend them afterwards.

- **Become a Mr/Ms fix-it.** There is a great opportunity to shape a growing organisation as a medic. With your previous experience, you can show

> "Being the only medic will mean you making some big decisions without a mentor"

Continues on page 20 ▸▸

Continues from page 19

them how best to do it. They do not have to invent square wheels and waste time and resources in the process. However, you must not assume a mantle of infallibility. With your confidence, you can share areas of doubt and uncertainly whilst still suggesting options and the best course to take – that shows you are in control.

- **Things happen quickly.** In one role I recall suggesting to the Managing Director we should create a corporate brochure – nothing fancy, but to set out our stall. He smiled and said "it will be out of date in 6 weeks". Bad things can also happen quickly. Following a Board Room coup, a new CEO was put in place – one of the truly nastiest people I have ever had the misfortune to work under. I left soon afterwards.

- **Keep commination short and clear**
  - **Talk to people:** - Do you really need to send that email to one person and that person is sitting next to you?
  - **Emails:** - Short, relevant and few. Make sure you file them for easy retrieval.
  - **Meetings:**-Short, relevant, and few. The agenda and minutes should occupy just one page. Action points - clear, dated and named.
  - **Reports:** - Short, relevant, and few. Send a one page monthly report to your boss about what you have done, and ongoing issues. This also forms part of your CPD/revalidation file.

- **Gut instincts**

Having taken all into consideration, what do your instincts tell you about that job – are you excited or worried? For the right medic, being a first can be a life changing step. Go for it?

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RETRO FEATURE:
Pills, probabilities and precaution

Reprinted from January 2008

Professor Stephen Senn.

First published in PP in January 2008, given recent events, it bears re-reading and further consideration today.

Although you don't need statistics to tell you that something is wrong when faced with terrible outcomes, you need data, calculation and risk assessment, in short statistics, to help you plan so that things don't go wrong and you also need statistics to analyse the data when they go right.

Professor Senn

TRIALS AND TRIBULATIONS

ON 13 MARCH 2006 EIGHT HEALTHY young men entered a clinical trial of TeGenero's monoclonal antibody TGN1412. Within 16 hours at the most all six who had been given the active treatment were in intensive care at nearby Northwick Park Hospital and being treated for the symptoms of a severe 'cytokine storm'. These dramatic events received extensive news media coverage around the world and have probably changed for ever our attitude to running so-called 'first in man studies'.

The trial was planned to be a grouped escalation study with eight healthy volunteers in each step, six of whom were to be allocated the given dose of TGN1412 and two of whom would be given placebo. As it turned out, of course, there was no escalation: the trial was stopped at the first hurdle and in consequence its results can be summarised as in *Table 1* below.

Anyone with even an amateur knowledge of statistics, will recognise such a table as being a contingency table and know that where the frequencies are as low as this, a common analysis is Fisher's exact test. Actually, Fisher's exact test yields a very modest one-sided P-value of 0.0357, which is not significant by the conventional standards of drug-development, which requires a one-sided P-value of no more than 0.025 to declare significance in any given trial.

Clearly this common formal analysis does not begin to do justice to the evidence. I am convinced that every reader of Pharmaceutical Physician is convinced with me that TGN1412 caused the adverse events in this trial. What is the origin of our common conviction?

One explanation is that such an analysis takes no account of background knowledge that cytokine storms are extremely rare. The placebo group is a very small control group and if we base our knowledge of the probability of an adverse reaction in the absence of treatment on the results for the two subjects given placebo alone, then the uncertainty in estimating this background rate is so large that it translates into an uncertainty about the results of the trial. This is illustrated by *figure 1,* which shows the probability of the results of the trial as a function of a

| TABLE 1: Outcome of the TeGenero trial

		CYTOKINE STORM?		
		Yes	No	Total
Treatment	TGN1412	6	0	6
	Placebo	0	2	2
	Total	6	2	8

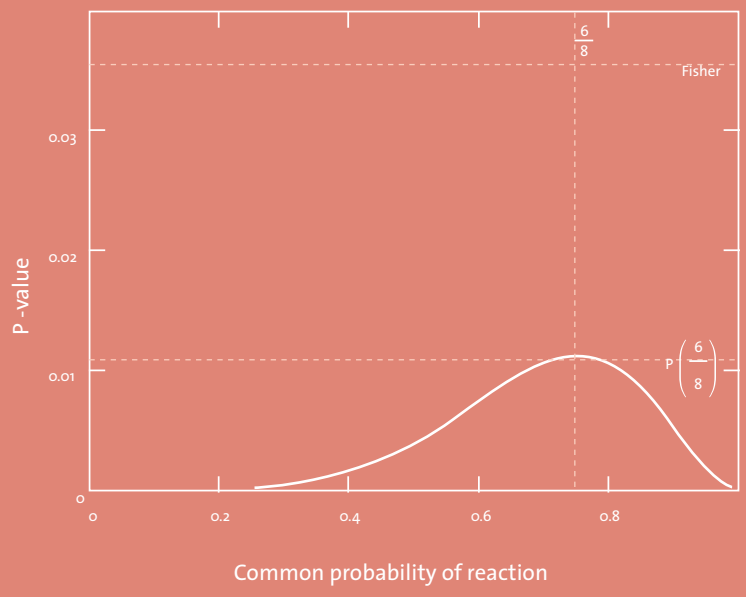
known background probability of adverse reaction.

Since the six to two split is the most extreme split possible, the probability of the table is actually the P-value. It can be seen that this P-value attains its maximum of just over 0.01 when the background probability of an adverse reaction is 6/8 = 0.75, this being the estimated value under the null hypothesis that there is no true difference between active treatment and placebo. More precisely, the P-value is 0.0111 and corresponds to Barnard's test. This value is lower than that given by Fisher's exact test because it does not treat the six to two split of adverse reactions as being a given. To use statistical jargon it does not condition on these values.

However, the point is, whether one uses Fisher's exact test or Barnard's test or some other common method of analysing contingency tables, it makes no difference. These conventional formal methods do not begin to do justice to the evidence. We all think that the appropriate probability is at the extreme left hand side of *figure 1.*

> "...THIS COMMON FORMAL ANALYSIS DOES NOT BEGIN TO DO JUSTICE TO THE EVIDENCE."

| FIGURE 1: P-value as a function of an assumed background risk of a severe adverse reaction



Other plausible information, of course, has to do with timing of events, and medical statisticians are beginning to develop methods that pay far more attention to timing as a means of analysing data[1].

Given that you don't need statistics to prove it, you might think that statistics had nothing to say about the design and analysis of such trials. However, the Royal Statistical Society (RSS) did not think so and in the summer of 2006 set up a working party under my chairmanship to see what could be done about improving such trials. The point, of course is, that although you don't need statistics to tell you that something is wrong when faced with such terrible outcomes, you need data, calculation and risk assessment, in short statistics, to help you plan so that things don't go wrong and you also need statistics to analyse the data when they go right.

Our working party, however, was not limited to statisticians (of which there were representatives from academia and the pharmaceutical industry) and we were joined by Dr Dipti Amin, a pharmaceutical physician with Quintiles and the eminent immunologist Prof Sir

Continues on page 24 ▸▸

RETRO FEATURE:
Pills, probabilities and precaution

Reprinted from January 2008

Continues from page 23

Peter Lachmann, FRS, FMedSci, emeritus professor at Cambridge. We reported on 13 March 2007, a year to the day after the trial of TGN1412, and our report is available from the RSS, in its journal[2] and also on its website.

DATA DIFFICULTIES

One of our first tasks was to try to establish what was known about the rate at which severe adverse reactions occurred in first-in-man studies. To this end we placed a freedom of information act request with the MHRA. Initially this was refused but eventually with the kind help of Dr Martyn Ward of the MHRA we were provided with the limited information that the MHRA had.

Table 2 summarises the phase 1 trials by type of investigational medicinal product (IMP), that is to say whether 'biological' or 'chemical', and by type of subject, patient or healthy volunteer, that has been authorised by MHRA during the period September 2004 to end of May 2006 inclusive.

Prior to the trial of TGN1412 these studies had yielded no adverse reactions of similar severity but theses data only represent a fraction of those that would be available had a policy of routinely logging such information been in place much earlier. Of course one can always regret that data were not routinely collected earlier but International Conference on Harmonisation (ICH) guidelines instructing sponsors regarding presentation of safety data date back to the mid 1990s and these of course reflect much earlier standards from the three ICH regions so that it is disappointing to find that more had not been undertaken by regulators.

Of course, hindsight is an exact science, and whatever the explanation of the difficulty with which one can obtain statistics on safety, a key recommendation of our report is that drug regulatory agencies should organise themselves to collect data on adverse reactions in phase I trials. This is a field in which data need to be pooled between sponsors and thus it seems logical that regulators should take a lead.

ACCEPTABLE RISKS

Of course, one wants not just to have reliable data on risk but to reduce that risk to an acceptable level. What is acceptable? Clearly to take the attitude that only zero risk is acceptable would mean that no phase I trials could ever be carried out. We felt that two matters need to be considered: that which is acceptable to the individual and that which is acceptable to society.

To understand the difference between the two suppose that we decided that no individual should run a risk of more than 1 in 2000 of a severe adverse reaction but that our best assessment of the risk for a given treatment was 1 in a 1000. This is too high to study. However, suppose that healthy volunteers are randomised with equal probability to either placebo or

| TABLE 2: Phase 1 trials authorized by the MHRA, September 2004 to end May 2006 by Investigational medicinal product (IMP)

	TYPE OF SUBJECT		
TYPE OF IMP	PATIENTS	HEALTHY VOLUNTEERS	TOTAL BOTH TYPE OF SUBJECT
Biological	26 (28%)	66 (72%)	92 (100%)
Chemical	82 (9%)	842 (91%)	924 (100%)
Total both types IMP	108 (11%)	908 (89%)	1016 (100%)

treatment. The risk is now 1 in 2000. Does this make it acceptable? We think not and one way of arguing why not is to say that the expected number of adverse reactions in a given trial is not reduced by adding subjects given placebo, although the risk to any subject is reduced.

However, this line of argument can also be turned the other way around. A much criticised feature of the trial of TGN1412 was that subjects were treated nearly simultaneously. Thus, a consequence was that six suffered adverse reactions rather than the one who might have had a sufficient dosing interval been observed. Such an approach would have been more cautious and more acceptable in terms of society's risk. Indeed on of the recommendation of our report is that a 'proper interval' for dosing subjects should be established for every treatment and observed when conducting first-in-man studies. However, even had this precaution been observed, somebody would still have to have been first, so that the risk to that individual is also important.

> "The risk is now 1 in 2000. Does this make it acceptable?"

DETERMINING RISK

Many readers will no doubt say that this is all very well but hopelessly academic. The risks can't be determined and if they could, no-one could agree what was acceptable. We think this is too pessimistic. Individuals take risks all the time and must make some sort of assessment of them and unique events are also insurable. Several of our recommendations address this issue.

First we, recommend that a separate document expressing a formal risk assessment be produced prior to first-in-man studies. We believe that the exercise of having to commit to paper calculations of risk, however imperfect, will help improve risk assessment.

We also recommend that insurance for such studies should be mandatory and effective. The TGN1412 study was insured but insurance has turned out to be inadequate. One of the reasons is that the design led to six simultaneous claims rather than one. Clearly somebody somewhere got the calculations wrong. Had they been available in a formal assessment it would be easier to eliminate such errors.

We also think that there should be a more frank exchange of information between all parties. The standard to be observed is that of 'open protocol hidden allocation'. That is to say all details of how the design will be run, including the allocation and randomisation scheme to be employed should be open to all, especially would-be subjects of the trial, and only where blinding is required should the actual allocation be concealed.

It may seem again that this is a trivial and obvious point but first this standard is regularly violated in clinical trials in all phases of development employing placebo run-ins[3, 4] and secondly the European Medicines Agency's (EMEA) own response to the TGN1412 story fails to address the issue of informed consent[5].

DESIGNING BETTER

Finally, it is perhaps worth mentioning that since first-in-man studies are run with the expectation, thank goodness, that severe adverse reaction will not occur they also have to be designed to deliver good information when things don't go wrong. It is important therefore, that designs and plans for analysis are good. This is precisely why it is not an excuse to say, that for data such as those provided by the trial of TGN1412 you don't need statistics. The point is that in embarking on such a trial you don't expect that something like that will happen but can never exclude that it might so that the only justification for such a risk being run is that the data will be collected and analysed in a way that is capable of yielding useful information when things don't go wrong

Here we feel that the drug developers could do much better. The protocol of TGN1412 was extremely hazy about exactly how whatever information it was designed to collect would be obtained and analysed. In this respect it is no different from scores of other trials being run. We make a number of recommendations about approaches to

Continues on page 26 ▸▸

RETRO FEATURE:
Pills, probabilities and precaution

Reprinted from January 2008

Continues from page 25

trial design and analysis depending on what effects can be assumed to be present or absent. Just to give a simple example, the fact that the allocation ratio of six to two active to placebo was proposed for dose escalation steps in the TGN1412 study only makes sense if placebo results are to be pooled at the end of the trial but this in itself only makes sense if first, trend effects are assumed to be small and second one is confident that the end of the trial will be reached. But this latter step is far from guaranteed, even when the outcome is not as catastrophic as was the case with this trial. We are not suggesting that assumptions about trend effects are not reasonable but we do feel that they should be addressed in any protocol. In fact, we are feel that it is time that we took the business of planning and analysing phase one studies as seriously as we do phase three studies.

This is not to say that the same techniques will be appropriate for phase I as for phase III studies but it is to say that the same degree of care and attention will be required. Unfortunately, it seems, whatever we have learned from the tragic events of March 2007, we are still in danger of falling short in the degree of scientific respect we accord first-in-man studies.

ACKNOWLEDGEMENT

I am extremely grateful to my colleagues on the working party for all their help in producing our report. This article reflects my personal views.

Stephen Senn is Professor of Statistics, University of Glasgow

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LETTERS:

Reprinted from March 2008

"MADAM, I WOULD LIKE TO ADD just one point to Stephen Senn's excellent account of the TGN1412 monoclonal antibody "first in man" study which went so badly wrong.

There are "obvious" uses of a monoclonal antibody where the anticipated effects result directly from agonism or antagonism of the antibody's ligand; or from antibody-mediated cell killing or phagocytosis. There are also "non-obvious" uses where the effects are the result of more complicated chains of events. These "non-obvious" applications are inherently more hazardous and they require more intensive preclinical study and an even more cautious introduction into human use than is required for "obvious" uses

TGN1412 is a "superagonist" antibody to CD28, a stimulatory receptor widely distributed on T-cells. The "obvious" function of this antibody would therefore be to give rise to widespread T-cell activation. The purpose for which it was being developed was however the selective activation of regulatory T-cells which inhibit effector T-cell activation. The mechanism proposed by the investigators for this selectivity is that initial stimulation of all CD28+ve T-cells causes effector T-cells to secrete IL-2. This then binds CD25 (an IL-2 receptor) on the regulatory T-cells which, together with the superagonist anti-CD28, gives them such a powerful activation stimulus that they can control the stimulated effector T-cells. This is an excellent example of a "non-obvious" application.

This mechanism must depend on the balance between the number of effector T-cells on the one hand and the number of CD25-positive regulatory T-cells on the other so that the amount of IL-2 produced is sufficient to stimulate the regulatory cells but not so large as to cause systemic toxic reactions, and that the number of regulatory T cells is sufficient then to control the activity of the effector T-cells. It would not be surprising that this balance is favourable in one species and not in another; and in a single species such as humans, it may be affected by age, sex, clinical status, the presence of infection or of an acute phase state or other factors. With hindsight it is clear enough that a more detailed preclinical analysis would have been a good idea.

It would however be unfortunate if the unhappy experience with an "unobvious" application were to place undue barriers in the way of developing "obvious" therapies with monoclonal antibodies and thereby delay the introduction of valuable therapies. TGN1412 itself might still find a useful role as a therapy for reversing T-cell failure in the elderly - which would be an "obvious" indication."

Sir Peter Lachmann, Sheila Joan Smith
Professor Emeritus of Immunology,
University of Cambridge

From: Professor Sir Peter Lachmann

Thursday, 24 Jan 2008

Subject: Pills, probabilities and precautions. Professor Senn, Pharmaceutical Physician 2008; 18:(5): P 6-10

From: Medicines and Healthcare products Regulatory Agency

NEW MHRA INSPECTORATE BLOG

From: Medicines and Healthcare products Regulatory Agency

THE MHRA INSPECTORATE blog is aimed at those organisations that are inspected by MHRA and need to keep up to date with the latest thinking and guidelines.
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It will give our inspectors a chance to speak directly to the organisations they inspect and get feedback from them on topics they would like to hear more about. Areas the blog will cover include:

- compliance management approaches
- data integrity
- preventing drug shortages
- significant findings from our inspections
- supporting innovation and our work with the MHRA Innovation Office
- upcoming learning opportunities

MHRA Inspectorate Group Manager Mark Birse speaking at an event

The first article, from Mark Birse, Group Manager of the Inspectorate at MHRA, introduces the exciting new platform and gives users an idea of what to expect from the blog. Mark says:

A large part of our role in the MHRA Inspectorate involves engaging with our many stakeholders. This new platform gives us an excellent opportunity to talk directly to those stakeholders in a less formal way and help them maintain compliance and engage with us on issues that are important to them.

It will also give stakeholders and opportunity to give us their thoughts and comments and will encourage a beneficial two-way conversation between us at MHRA and those working in industry and academia.