# PHARMACEUTICAL PHYSICIAN

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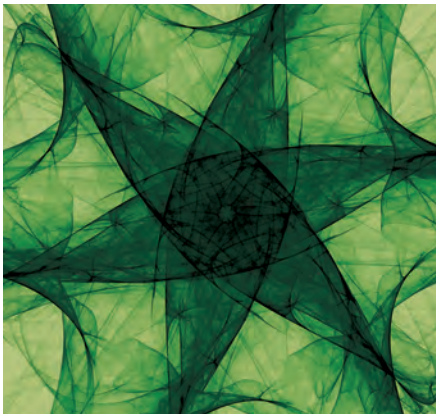

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AS WE PUT this issue to bed, it is incredible to reflect that BrAPP will be 60 years old in 2017. It seems only yesterday that we celebrated our golden anniversary. And then one thinks of all that has happened in the intervening decade; not to mention a very turbulent immediate past year! Whatever one's political leaning, 2016 cannot be said to be anything short of a sea change. And only the coming months and years will show whether it is merely a blip along the way or indeed a shift in world order.

To celebrate our Diamond Jubilee we will be running articles from the inception of the journal (in 1989) and if anyone has other items to contribute we will be pleased to receive and publish them. To start the ball rolling we have chosen a piece written by Dr Matthew Hickling, then a Medical Advisor at UCB, and published in January 2010 focussing on Drug Discovery. It is interesting to reflect what has and what has not changed over the period.

As ever, we are delighted to have the invaluable Regulatory RoundUp content from Anne Hetherington and when reading the article from Matt Edwards and Nicola Harding, you will note that Medical Affairs physicians are perceived to need a breadth of knowledge of all things regulatory to contribute significantly in today's industry. Regulatory Affairs and Pharmacovigilance disciplines and knowledge maybe under-valued by physicians working closer to the immediate market interface but an understanding and awareness of the current guidelines and modules (ICH and EMA et al) along with rest of the diverse aspects of our specialty will separate the successful from the "steady eddies" as Matt and Nicola call them.

2016 began with the pharma industry in the headlines and Dr Daryl Bendel offers a timely review of what happened – as far as we know- in the Rennes trial that cost the life of one volunteer in January. He asks "what can we learn" and in essence it seems we can only learn that caution is a valuable characteristic and that first-in-man studies remain a small step into the unknown.

Reflecting on the changing times in the industry, Dr Michael Atkins, provides a view of a "good" way to demerge. The key to this seems to be, remember there are people involved and people have feelings. Finally, Dr Matt Goodman co-founder of MapMyHealth gives us a thought-piece ahead of a two article series to follow in 2017 about the harnessing of digital therapeutics to help turn the tide of the diabetes epidemic.

I personally look forward to 2017 and hope for a peaceful and happy year. I wish all our readership the same.

PS Please let us have your contributions to what is YOUR journal. Email info@brapp.org

**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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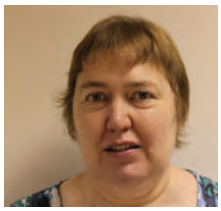


Anne Hetherington

## 1. EUROPEAN MEDICINES AGENCY (EMA)

### News and press releases

- First statistics on PRIME are released
  *http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/06/news_detail_002541.jsp&mid=WC0b01ac058004d5c1*

- Regulation of advanced therapy medicines
  *http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/06/news_detail_002543.jsp&mid=WC0b01ac058004d5c1*

- Proposals to revise guidance on first-in-human clinical trials
  *http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/07/news_detail_002572.jsp&mid=WC0b01ac058004d5c1*

- Annual activity report 2015
  *http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/07/WC500210118.pdf*

- Statement on the outcome of the UK referendum
  *http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/07/news_detail_002566.jsp&mid=WC0b01ac058004d5c1*

### Updates

- Periodic safety update reports
  *http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000361.jsp&mid=WC0b01ac058066f910*

- 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*

- Clinical Trial Regulation
  *http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp&mid=WC0b01ac05808768df*

- Q & As on how to express the frequency of adverse reactions within the product information *http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/07/WC500210919.pdf*

- Guideline on the clinical development of medicinal products for the treatment of HIV infection, adopted *http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500209918.pdf*

- Guideline on clinical evaluation of medicinal products used in weight management, adopted *http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500209942.pdf*

- Clinical investigation on medicinal products in the treatment of hypertension (updated) *http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001069.jsp&mid=WC0b01ac0580034cef*

- Clinical investigation of medicinal products in the treatment of lipid disorders (updated) *http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001073.jsp&mid=WC0b01ac0580034cef*

- Guideline on clinical investigation of medicinal products in the treatment of lipid disorders, adopted *http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500209944.pdf*

- Guideline on clinical investigation of medicinal products in the treatment of hypertension, adopted *http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500209943.pdf*

- Draft guideline on the clinical evaluation of direct acting antivirals for the treatment of chronic hepatitis *http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500209917&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc*

## 2. EUROPEAN COMMISSION

- Four public consultations on recommendations related to clinical trials are open from 1 June 2016 to 31 August 2016 *http://ec.europa.eu/health/human-use/clinical-trials/developments_en*

## 3. MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA)

- Statement on the outcome of the EU referendum *https://www.gov.uk/government/news/medicines-and-healthcare-products-regulatory-agency-statement-on-the-outcome-of-the-eu-referendum*

- Human Factors and Usability Engineering – Guidance for Medical Devices Including Drug-device Combination Products *https://www.gov.uk/government/news/human-factors-and-usability-engineering-guidance-for-medical-devices-including-drug-device-combination-products*

- Pharmacy dispensing models and displaying prices on medicines *https://www.gov.uk/government/consultations/pharmacy-dispensing-models-and-displaying-prices-on-medicines*

- MHRA GxP Data Integrity Definitions and Guidance for Industry *https://www.gov.uk/government/news/mhra-gxp-data-integrity-definitions-and-guidance-for-industry*

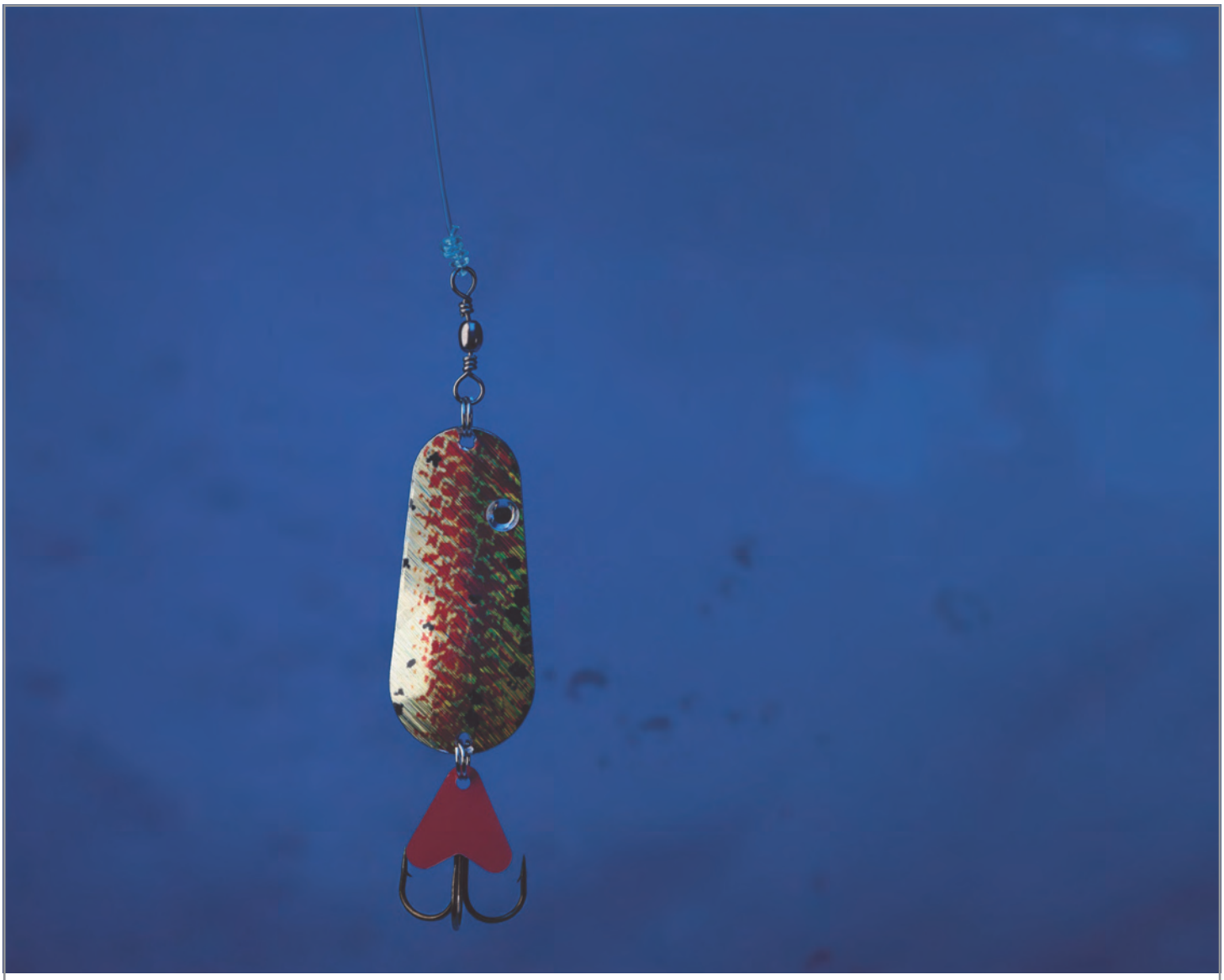
## 4. FOOD AND DRUGS ADMINISTRATION (FDA)

Guidance for Industry

- Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351261.pdf*

- Charging for Investigational Drugs Under an IND — Questions and Answers *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351264.pdf*

- Implementation of Acceptable Full-Length and Abbreviated Donor History Questionnaires and Accompanying Materials for Use in Screening Donors of Source Plasma *http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/UCM341088.pdf*



**SPECIAL FEATURE:**
# The French Drug Trial Disaster
## What can we learn?

*By Dr Daryl Bendel*


## SUMMARY
EARLY PHASE DRUG trials have a very good safety record. In January 2016, a healthy participant died and a number of other participants were hospitalised with drug-related CNS effects while participating in an early phase study of the drug BIA 10-2474 being conducted in France. This article discusses some of the key features of our understanding as to what might have gone wrong, the outcome of the main investigations and some of the proposals to further improve the safety record of early phase drug development.


## INTRODUCTION
Serious incidents in healthy participants in Phase 1 studies are thankfully extremely uncommon, with study related deaths in healthy participants being exceptionally rare.

In a systematic review of 475 trials enrolling 27,185 participants, there was a median [interquartile range IQR] of zero serious adverse events [0–0] and a median of zero severe adverse events [0–0] per 1000 treatment group participants/day of monitoring. The rate of mild and moderate adverse events was 1147.19 [651.52–1730.9] and 46.07 [17.80–77.19] per 1000 participants/adverse event monitoring day respectively [17].

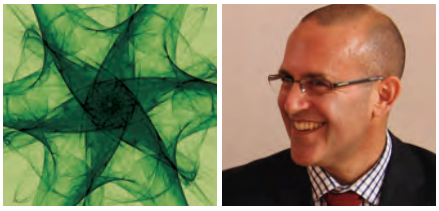
Following the TGN1412 trial, Sibille et al[18] noted that 15 deaths in healthy participants have been published during the last 30 years in Western countries, although probably 100,000 healthy participants are dosed every year. Furthermore, only three of the deaths were unavoidable.

The risk of a life-threatening adverse event in trials with monoclonal antibodies is more difficult to accurately establish. Tranter et al [19] reported an incidence of between 1:425 and 1:1700 life-threatening events, but all such events occurred in a single trial (TGN1412). Furthermore, it was difficult to establish the number of healthy participants exposed.

The death of a healthy participant and serious adverse reactions in four other participants in study BIA-102474-101 (BIA) of study drug BIA 10-2474 was an unprecedented event. Although parallels will be sought between the BIA trial and the TGN1412 trial 10 years earlier, they couldn't in fact be more different.

TGN1412 supports the old maxim, all drugs are poisons, it's just a matter of dose. Starting at a dose of 1/1000th of that used in the TGN trial and escalating to 1/14th of the dose, Tyrsin et al [20] demonstrated the absence of proinflammatory cytokine release and transient IL-10 release at the highest dose indicative of desired selective activation of regulatory T-cells in healthy participants. The drug, rebranded as TAB08 is now in a Phase 1b trial in patients with rheumatoid arthritis. Following TGN1412, the EMA introduced EMEA/CHMP/SWP/ 28367/07 Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products [21], which was predominantly applied in the BIA trial.

## BIA-102474-101
Unfortunately minimal source data regarding BIA 10-2474 is available in the public domain. L'Agence nationale de



Daryl Bendel

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sécurité du médicament et des produits de santé (ANSM) released the study protocol (BIA-102474-101)[22] which provides detailed information regarding the study design but only basic information of the study drug pharmacology and toxicology. Unfortunately the involved parties have chosen to withhold the investigator brochure (IB) and clinical trial data, citing commercial confidentiality[31]. A detailed chronology of events has been provided by the ANSM[23]. Much of our understanding of the events is obtained from the Scientific Committee Specialized Temporary (CSST)[24] and General Inspectorate of Social Affairs (IGAS)[25] reports, bodies that were established to investigate scientific (CSST) and compliance (IGAS) aspects of the trial.

BIA 10-2474 is a long acting reversible inhibitor of the serine hydrolase fatty acid amide hydrolase (FAAH) that increases the level of the endocannabinoid anandamide in the central and peripheral nervous systems. This class of drugs were being developed for a range of conditions such as pain, vomiting, anxiety, mood disorders, Parkinson's disease, Huntington's disease and various cardiovascular conditions. A number of drugs from this class had been safely through phase 1 trials and into early clinical development; although they had been largely discontinued due to lack of efficacy[22, 24].

Although BIA10-2474 was stated as being reversible, in humans there is almost complete enzyme inhibition after 24 hours, even with plasma concentrations below the limit of quantification. It was reported that there is a steep dose response curve between zero and maximal enzyme inhibition. Potency was reported as being at least 100 fold less than for other FAAH inhibitors. On the available data the specificity of BIA 10-2474 is unclear as it is not specified which targets were evaluated – there are about 300 targets in the serine hydrolase family. Nine human metabolites had been identified, with three of them having similar potency to the parent. Metabolic pathways or potential for polymorphism was not reported[24].

The toxicology programme that was undertaken was interesting in that 13 week studies were conducted in mice, dogs and monkeys and 26 week studies were conducted in rats. Additionally, reproductive and developmental toxicity studies were done in rats and rabbits. No justification has been provided for such extensive use of animals, and in particular, non-human primates prior to going into Phase 1 human studies. This level of toxicological investigation prior to going into man for a non-novel compound is highly unusual. The CSST report noted the IB had translation imperfections and transcription errors, particularly in the tables and figures that generated ambiguities and difficulties in understanding[24].

No end-organ toxicity was reported and calculations of the starting and maximal dose from 0.25mg to 100mg in humans were appropriately justified. Whilst easy to find minor comments on the protocol in hindsight, on balance this was an appropriately designed and commonly used first-in-man programme that included the single (SAD) and multiple (MAD) ascending dose elements, a food effect and a proposed pharmacodynamic group. One point in the protocol that stands out states that if the maximum tolerated dose (MTD) is not reached after completing the planned sequential groups, additional groups can be included to a maximum of 8 groups. Planned dose levels were up to the NOAEL which is acceptable. Under certain circumstances going beyond NOAEL could also be justified. However the proposed rate of escalation and basis for decision was not described in the protocol.

## CHRONOLOGY OF EVENTS

The study schedule described in *Table 1* has been adapted from the ANSM publication of the chronology of events[23].

It has been reported that the study progressed without significant event, through the all the SAD cohorts (0.25mg to 100mg, n = 48 on active treatment), food-effect cohort (40mg, n = 12) and MAD cohorts M1 to M4 (2.5mg daily to 20mg daily, cumulative dose of 200mg, n = 24 on active treatment). For MAD cohorts M1 to M4 dose escalation doubled. For MAD cohort M5 participants were dosed at 50mg, which was a 2.5 fold increment over the previous level. Usually the rate of dose escalation reduces as exposure levels reach toxicological limits.

Cohort M5 (50mg per day) started dosing on 6th January 2016 and on the evening of the fifth day of dosing (10th January 2016), the first participant was hospitalised (cumulative dose 250mg). Reports vary as to the nature of his condition at this time, and indeed by the time the remainder of the cohort was dosed the following morning (day 6), following which the trial was halted and the remaining 5 participants who received active treatment were hospitalised (cumulative dose 300mg). Symptoms included headache in 5 participants including very severe 'thunderclap' in one, cerebellar signs in 3 participants, reduced consciousness including coma in the deceased participant and memory disorders in two participants. The CNS was the only system affected. One participant had non-specific changes to the cerebrospinal fluid. MRI findings included bilateral and symmetrical oedema, haemorrhage and gliosis in the hippocampus, thalamus and cortex, suggestive of a metabolic/toxic process [24].

Pharmacokinetic data in animals was unremarkable whereas in humans, there was a dose-related increase in elimination half-life and consequently exposure, possibly due to saturation of elimination mechanisms. Interindividual variability of pharmacokinetic

**TABLE 1:** Study Schedule BIA-102474-101

| | Cohort | Dose | Increment | Participants Active/Placebo | Days since prior dose level |
|---|---|---|---|---|---|
| **Part 1 SAD** | | | | | |
| 09 July 2015 | S1 | 0.25mg | N/A | 1/1 | Sentinel Group |
| 10 July 2015 | S1 | 0.25mg | N/A | 5/1 | 24 hours after first 2 subjects |
| 11 August 2015 | S2 | 1.25mg | 5 | 6/2 | 31 days after S1 |
| 19 August 2015 | S3 | 2.5mg | 2 | 6/2 | 8 days after S2 |
| 26 August 2015 | S4 | 5 mg | 2 | 6/2 | 7 days after S3 |
| 3 September 2015 | S5 | 10mg | 2 | 6/2 | 8 days after S4 |
| 16 September 2015 | S6 | 20mg | 2 | 6/2 | 13 days after S5 |
| 30 September 2015 | S7 | 40mg | 2 | 6/2 | 14 days after S6 |
| 9 October 2015 | S8 | 100mg | 2.5 | 6/2 | 9 days after S7 |
| | | | | | |
| 21 October 2015 | F1 TP1 | 40mg fasted | N/A | 12/0 | N/A |
| 10 November 2015 | F1 TP2 | 40 mg fed | N/A | 12/0 | N/A |
| | | | | | |
| 06 October to 15 October 2015 | M1 | 2.5 mg daily * 10 | N/A | 6/2 | In parallel with SAD, 20 fold safety margin |
| 28 October to 06 November 2015 | M2 | 5 mg daily * 10 | 2 | 6/2 | 13 days after last dose M1 |
| 17 November to 26 November 2015 | M3 | 10mg daily * 10 | 2 | 6/2 | 11 days after last dose M2 |
| 9 December to 18 December 2015 | M4 | 20 mg daily * 10 | 2 | 6/2 | 13 days after last dose M3 |
| 6 January 2016 to 11 January 2016 | M5 | 50mg daily * 10 | 2.5 | 6/2 | 19 days after last dose M4 |

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Continues from page 9

parameters increased with dose, and at dose level M5, trough levels continued to rise through dose 5 and dose 6. Variability in some of the human metabolites differed to that expected from animal studies. It was reported that the onset of FAAH inhibition starts at about 1.25mg and is almost complete at 5mg [24].

## PROPOSED MECHANISMS OF TOXICITY

The CSST, in their report evaluated the causality of these adverse events and concluded that with almost certainty, this was related to the administration of BIA-10-2474 [24].

Although no comparative enzyme and receptor binding assays were reported in the protocol, an in silico study performed by Ekins [27] predicted that BIA 10-2474 would bind to other targets as well as FAAH. It is possible that the toxicity seen was due to off-target effects seen suddenly at high cumulative dose [24, 26].

Other groups have shown using an automated computer-based proteome-docking approach that BIA 10-2474 interacts with some proteins that have been implicated in causing brain/intracerebral hemorrhages [28].

## CONCLUSIONS OF CSST AND IGAS AND RECOMMENDATIONS

Overall the CSST reported that that study was conducted and approved in accordance with the Regulations in effect at the time. Recommendations made included [24];

i. there should be sufficient preclinical data predictive of clinical utility to justify the investigation of the drug in man;

ii. comprehensive neuropsychiatric screening should be included in Phase 1 studies for CNS drugs;

iii. for first in human studies, protocols should allow doses to be adjusted based on emerging data, and in particular, extrapolation should be made from data from the most sensitive participant and not merely the cohort average. Pharmacodynamic data should be used and consideration given as to the justification for significantly exceeding the maximal pharmacological effect.

iv. that further staggering of dosing is proposed for the MAD part of the study;

v. that dose escalation strategies should involve common sense in addition to the usual pharmacological and regulatory considerations;

vi. that there is greater transparency and data sharing between Agencies for Phase 1 data.

The main findings and conclusions of the IGAS report cited three major finding in relation to Biotrial, the Phase 1 unit who conducted the study, namely; that [25];

- The study should have been stopped after the first participant had been hospitalised and the remaining participants should not have been dosed on day 6;

- All other participants should have been notified and asked to reconsent before continuing participation in the study; and

- The incident should have been reported immediately to ANSM and not four days later.

Biotrial has rejected these findings on a number of grounds, the details of which are provided on its website [29].

Furthermore, it was noted that a number of the protocol provisions were too vague, that the eligibility criteria should have been more explicit regarding substance use habits of the volunteers and that there was no legal

requirement for the sponsor to disclose all pre-clinical data to the ANSM [25].

The EMA has recently issued a concept paper for the revision of the existing Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products' (EMEA/CHMP/SWP/28367/07) [21, 30], which recognises that many first in human studies are integrated protocols involving a number of parts.

## DISCUSSION AND CONCLUSIONS

Despite two high profile tragedies in early drug development in the last decade, the safety record of Phase 1 trials is overall very good with the overall risks approaching those of normal daily life. There will always be an element of risk associated with drug development and in particular early phase drug development. Most Phase 1 trials are conducted in healthy participants who have no opportunity for clinical benefit; the risks must be mitigated and balanced accordingly.

Our ability to learn and develop suitable risk mitigation strategies from BIA-10-2474 is significantly undermined by the choice of those involved to hide behind commercial confidentiality in not releasing the IB and clinical trial data [31]. Of the three main parties involved in this tragedy, BIAL, ANSM and Biotrial, only Biotrial as the economically and politically weakest party has a legitimate claim to non disclosure. Both ANSM and BIAL, parties potentially subject to criticism, could have chosen full disclosure and transparency.

The standout feature of the IGAS report is the fact that this tragedy happened, despite the Regulations being followed. It is notable that there was no legal requirement for the sponsor to disclose all pre-clinical data to the ANSM [25] which must once again raise the issue of transparency. Will we ever know what was not disclosed and what the relevance of that non disclosure was? Without the benefit of hindsight, the IGAS criticisms of Biotrial don't amount to much and had no role in the cause of this tragedy. Reconsenting participants for example needs ethical approval of the revised consent form, something that cannot be achieved overnight.

The CSST report provides evidence that this tragedy was almost certainly related to BIA-10-2474 [24], and likely due to off-target effects. Various hypotheses have been proposed as to how this may have happened and how the dose response curve could have been so steep. At this stage there are no definitive answers.

> "The standout feature of the IGAS report is the fact that this tragedy happened, despite the Regulations being followed."

With the benefit of hindsight, there are clues indicating that BIA-10-2474 may be a problematic compound. In general, factors such as low potency, poor specificity, limited or incomplete receptor binding assays, numerous metabolites, and somewhat counter-intuitively, the absence of any toxicological findings are signals for potential problems. In this case, the unusual and extensive toxicology programme must have raised some questions. Once human data became available, the suggestion of non-linearity in exposure would suggest a more cautious approach to dose escalation is required.

The absence of reported toxicological findings provides a good justification to proceed cautiously, particularly as evidence emerges that human pharmacokinetics are non-linear and approaching the NOAEL. It is difficult to understand the rationale for the 2.5–fold final dose increment and it is difficult to understand why ANSM approved this. To illustrate this point, when the first participant was hospitalised, the investigator quite understandably considered this to be an unexpected, unrelated event in a participant based on the absence of toxicology findings and absence of significant adverse events in the preceding human data. Furthermore, some minor events that were reported in lower dose levels (blurred vision, diplopia of short duration less than 30 minutes) would, in the absence of toxicology findings, likely be considered unrelated. Had the toxicology studies for example pointed to the pathology that materialised in

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humans, these minor events would have been viewed differently, dose escalation would likely have preceded more cautiously and different action would likely have been taken following the presentation of the first participant.

The study protocol as approved by ANSM and the Ethics Committee allowed for dose escalation up to the maximum tolerated dose (MTD). The MTD is the dose below that which provides intolerable effects. Clearly, and as is evidenced in this case, not knowing the nature of the intolerable effects, how to identify them early, their treatment or reversibility, dose level of onset or dose response, means that such a study cannot be safely conducted. MTD studies as commonly done in Phase 1 cancer trials should not be done in healthy participants unless there is a good scientific rationale and almost certain knowledge that the intended intolerable effects can be easily managed and will not lead to irreversible harm.

From the data provided, it appears that the likely clinically effective dose would be around 1.25mg to 5mg. This could have been established *in vitro* prior to study start and confirmed during the study by activity of FAAH.

Clause 16 of the current version of the Declarations of Helsinki states that medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

It is difficult to see any importance in defining MTD and minimal importance in exceeding the maximal clinical dose by at least 10-fold; in the absence of any toxicology signal it is not possible to properly evaluate the risks.

The CSST make the recommendation (v) that for dose escalation strategies in first in human and Phase 1 studies, that common sense should also be applied. Perhaps we have become too engrossed in following the rules that we lose sight of why we are doing it.

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**SPECIAL FEATURE:**
# Personal Profile Analysis.

## Recruiting for the future of medical affairs

*By Matt Edwards (Consultant) and Nicola Harding (Partner), the RSA Group*

Matt Edwards

Nicola Harding

## 1. INTRODUCTION

THE ROLE OF medical affairs in the pharmaceutical industry is changing. In 2014, a report by McKinsey & Company on this key profession predicted that, "a new set of competencies [would be] required [by staff] to navigate the future healthcare landscape across the globe"[1].

New technology, such as social media, has placed more clinical decision-making in the hands of patients while rising R&D and medical costs have led to demands for greater transparency and more evidence of cost effectiveness. To navigate this new landscape, medical affairs professionals need the customer skills of a salesperson, the strategic thinking of a marketeer, and a high-level understanding of the clinical, legal and regulatory environments.

Yet recruiting people with such a wide range of talents is a tough challenge. Part of the solution for hiring managers could be personal profiling, such as that carried out by RSA Consulting on its shortlisted candidates. A recent study by the company suggests pharma companies may benefit from the use of behavioural profiling - which has become part of the executive search process – as the next generation of medical affairs professionals may share many of the key behavioural traits.

## 2. THE MEDICAL AFFAIRS CHALLENGE

Medical affairs plays a key role in pharmaceutical companies. The function originally emerged in response to regulators wanting to separate the medical and commercial arms of organisations. Today it acts as a bridge between these functions, and as a conduit of information to and from the market.

Medical affairs professionals traditionally used data analysis and education to support late-stage development of pharmaceuticals and marketed products. These were technical roles that relied on strong understanding of the cinical data. A new hire, for example, might only be expected to provide healthcare providers with off-label data about safety and efficacy of a product.

Today, the role of medical affairs has changed and will continue to do so. There are three main trends:

I. Pharmaceutical R&D costs have risen over last five years while productivity has fallen. According to a report by Deloitte, returns on investment have more than halved since 2010, with the cost to develop a drug rising by about a third[2,3]. Companies increasingly need detailed analysis and input from medical affairs throughout the drug development process on product characteristics, market risks and unmet medical needs.

II. Medical affairs professionals need to work with a wider range of data and influence a larger variety of audiences than ever before. Rising healthcare costs in the US and Europe have led to widespread reforms in the provision of services:

   a. Some pharmaceutical decision-making is shifting from physicians to a wide range of other stakeholders;

b. Healthcare reforms have led to greater demands for transparency in the relationships between pharmaceutical companies and decision-makers;

c. New types of medical data are required to provide evidence before new treatments are adopted by healthcare organisations.

III. Patients have more desire for control over their own treatment, aided by the reach and influence of social media and a shifting focus to patient-centred care. Medical affairs professionals need to provide scientific data in an easy-to-understand form, and may need to work closely with patient advocacy groups. The latter requires stringent codes of conduct and transparent practices.

III. Persuasive - to demonstrate to internal stakeholders how they add value, and to be advocators, educating healthcare providers and other external stakeholders;

IV. Technically skilled - to understand the medical and regulatory framework of pharmaceutical products. They require a different skill set from clinical development, as medical affairs has less focus on processes and mechanisms.

For pharmaceutical companies to succeed, they must build new skills and talent in their medical affairs function. This involves training existing employees and helping them adapt their work styles but – more importantly – making hiring decisions with the future of medical affairs in mind.

> "The changing role of medical affairs means that professionals need to offer a wider range of skills than in the past."

## 3. PROFILE OF A PROFESSIONAL

The changing role of medical affairs means that professionals need to offer a wider range of skills than in the past. They must be:

I. Flexible and adaptable to deal with a broad-ranging role, and able to thrive on uncertainty.

II. Creative thinkers with excellent communication skills;

### 3.1 ANALYSING BEHAVIOURAL TRAITS

Behavioural profiling is a key tool in executive search. It's used to identify candidate strengths and areas to probe during interview. Sometimes profiling is combined with other tools, such as roleplay or aptitude tests. In medical affairs, such tools can be critical. Not only to avoid expensive hiring mistakes in the short term, but to help companies adapt their hiring practices to deal with long-term changes in healthcare.

We use in-depth behavioural profiling to identify the most suitable candidates for a given role – in an impartial, constructive way. This evidence-based approach helps the consultancy learn and adapt to the changing needs of the pharmaceutical industry.

Among the profiling techniques used is Personal Profile Analysis (PPA), a psychological tool registered with the British Psychological Society (BPS)[4]. PPA is based on DISC theory, a widely-used method for understanding work-based behavioural preferences.

DISC is based on a theory of human consciousness published by W.M. Marston in a book called Emotions of Normal People in 1928. A contemporary of Carl Jung, he developed his ideas after studying the behaviours of thousands of people. Marston's insight was that behaviour is affected by how people perceive themselves, other people, and their surroundings.

The PPA measures four behavioural traits: Dominance (D), Influence (I), Steadiness (S) and Compliance (C). These give an insight into how

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individuals see themselves in the workplace. For example, Dominant behaviours are direct, assertive and ambitious because they perceive themselves to have the power to shape events.

## 3.2 THE PPA IN PRACTICE

For executive search, we use the PPA developed by Thomas International. This tool is a 'forced choice' (ipsative) inferencing method. Candidates are expected to select desirable adjectives that they believe describe them, rather than ranking (e.g. 'strongly agree') the extent to which they agree with a statement.

To complete the PPA, candidates choose two traits from a block of four – one 'most like' and one 'least like' them. This process is repeated 24 times, giving 48 choices from a total of 96 words. The forced choice method removes the option of giving neutral responses, such as 'neither agree nor disagree'.

Assessment results are compared to the candidate's other responses and not scores from a comparison group. Behavioural traits selected as 'most like' the candidate are combined together to measure their 'work mask' – how they perceive themselves at work. Traits they 'least like' are used to assess their behaviour under pressure. Self-image combines work mask and behaviour under pressure.

Candidates' behavioural profiles are scored both against the brief for the role and against every other candidate on the short list using data driven comparative analysis. However, results from PPA are a guide only. They are not the only, or even the main, determinant of hiring decisions. Rather we combine them with other executive search tools, including further psychometric tests that look at an individual's potential to succeed, along with deep experience of the needs of the pharmaceutical industry and individual company cultures.

## 4. RECRUITING THE NEXT GENERATION

We wanted to understand typical PPA profiles for today's medical affairs professionals. These reveal behaviours that staff may adopt in the workplace, which will change dependent on the company culture and over time. A theoretical PPA profile for medical affairs, given recent changes in the role, will have:

I. High Influence (I) to influence external stakeholders and endorse their value to internal ones;

II. Not too much Compliance (C) as this can stifle creativity, although they need enough to ensure that whilst having the ability to push boundaries they remain "within the rules";

III. Relatively low Steadiness (S) as medical affairs involves a lot of variety;

IV. Enough Dominance (D) to drive events and to make things happen.

We tested how closely this profile mapped the behavioural traits of medical affairs professionals using results from 105 candidates shortlisted by the consultancy. They all had significant careers in medical affairs, and completed their PPA between 2014 and 2016. The data were collated by Thomas International.

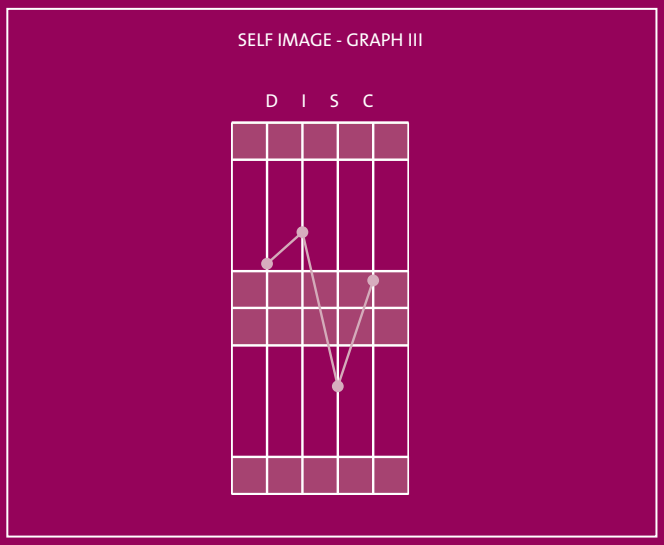
## 4.1 READING A BEHAVIOURAL PROFILE

There are no 'right' or 'wrong' results from a PPA. Each letter (e.g. I, D) is simply a different way of approaching challenges in the workplace. Leaders, for example, are typically perceived as having dominant behaviours, but some of the greatest leaders in history have been also high on compliance. An example is Air Chief Marshall Hugh Dowding, nicknamed 'stuffy' by his men, whose meticulous planning is credited with defeating Hitler's plan to invade Britain during the Second World War.

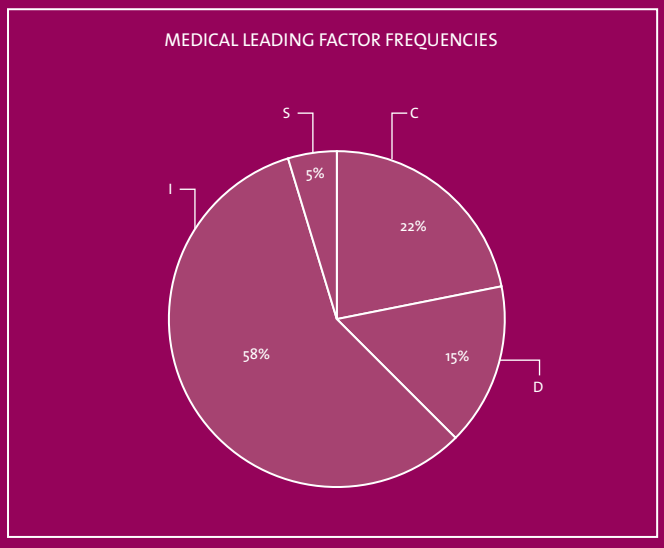
*Figure 1* shows an example PPA profile. The graph is read from top to bottom, with results above the shaded area being 'working strengths' and those below it being 'support factors'. This candidate has 'I' as their leading factor, and 'D' then 'C' as working strengths. 'S' is a supporting factor. Typically, an individual has up to three working strengths, but never four, as the factors conflict with each other.

Behaviourally, if they were a leader, the graph indicates that they would be a 'people person'. They would demonstrate behavioural traits high on assertiveness and persuasion due to their high 'D' and 'I' scores, using facts to get their messages across. They would also demonstrate good levels of compliance.

**| FIGURE 1:** Example PPA Profile




**| FIGURE 2:** Leading factors in the behaviour of medical affairs candidates




## 4.2 BEHAVIOURAL TRAITS FOR MEDICAL AFFAIRS

The main behavioural traits displayed by the candidates is shown in *Figure 2*. As predicted by theory, more than half had 'Influencing' in their personal profile. These professionals were keen to invest in new relationships, explore fresh ideas and begin new projects – key traits when liaising with stakeholders and for building trust.

Candidates for medical affairs roles were unlikely to have 'Steadiness' as a working strength. Reserved and cautious personalities are less suitable for a broad-ranging job that requires medical communication and education skills.

*Figure 3* shows the working strengths of the candidates. Nearly a quarter had high 'ID' showing they were persuasive, dynamic and able to thrive in a varied and fast-changing workplace. None of the candidates were pure 'S' and few were pure 'C' – medical affairs is no

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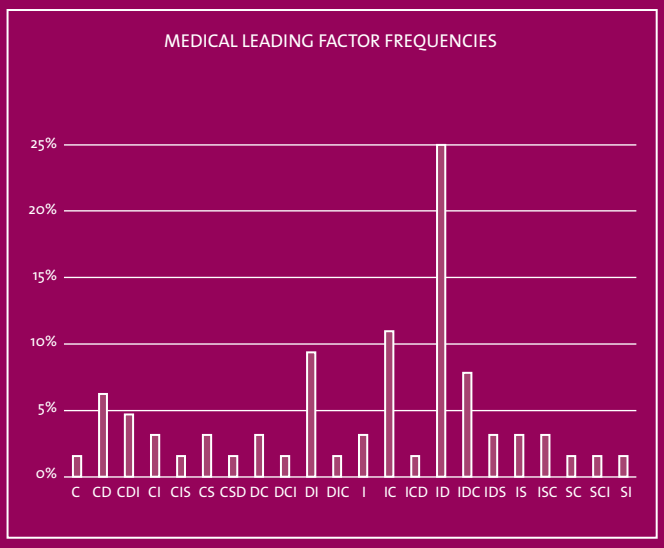
longer a 'steady eddie' role for technical specialists.

Many of the candidates had Compliance as a working strength. This is unsurprising as medical affairs professionals need to adhere to stringent codes of conduct, especially when dealing with patient groups or healthcare regulators. One of the factors left unexplored in this data is whether PPA profiles vary with the age of the candidates. Medical affairs professionals tend to move away from compliance-based towards strategic roles as they progress in their career, and their 'C' would be expected to fall as a result.

## 5. CONCLUSION

Medical affairs is changing and companies need to respond by recruiting the best candidates. PPA is a useful evidence-based tool to support the recruitment of talent able to respond to the new challenges that will have to be faced up to and beyond 2020. As with every psychometric assessment, these statistics aren't sufficient to base recruitment decisions on, but need to be combined with deep knowledge of the industry and personnel as found at specialist talent consultancies.

**| FIGURE 2:** Leading factors in the behaviour of medical affairs candidates

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# SPECIAL FEATURE: "Who gets the cat?"

## ...an amicable divorce model of a company demerger

*By Dr Michael Atkins*

A DEMERGER (LIKE a divorce) is never easy. A successful outcome is a separation of both parties with minimal expense, disruption, and drain on resources, whilst dividing up and maintaining appropriate staff, equipment, motivation, customer allegiances, and moving on to successful future business outcomes (win: win).

### "WHY ARE WE SPLITTING UP?"

Grounds for a company demerger must be clear and may be for one or more of the following reasons:

- The business has successfully evolved in different directions, such that staying as one company no longer makes good business sense.
- The business has formed formal alliances with external partners such that it makes more business sense than staying as a single company.
- The company has just got too big to logistically stay as one. This may be especially true where a company wants to get back to "its roots".
- "Hostile" reasons*:
    - o Personality clashes at the most senior level (especially family-owned companies).
    - o One part of the company is failing whilst another part is successful.
    - o Actions taken by appointed company liquidators.

**This article does not address hostile demergers or those forced by bankruptcy/insolvency.*

### "OH MY GOODNESS - THE SHOCK!"

Once the decision is made at a senior level, a communication ("comms") strategy must be the first priority. That does not mean the announcement of a demerger is first item to be actioned. Indeed, months of confidential planning are often required before the announcement is made as this information will have a significant impact on people. The challenge lies in engaging staff in the pre-announcement planning phase and containing confidentiality. Expect leaks and be prepared to announce early if needs be. Rumours breed demotivation and stress and will reduce productivity. Internal politics may escalate.

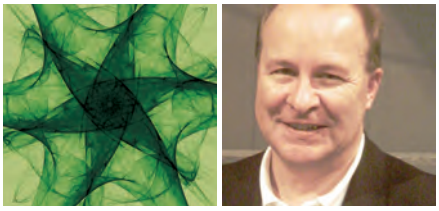
When sent out, typical "comms" rules should apply to include the why, when, how, what and who. Avoid jargon and keep it simple. Anticipate questions, like:-

- Why is it happening?
- When will it all happen?
- What happens with future jobs?
- What about redundancy (and outplacement support) and then my holidays still due and my pension?
- What is the location of the new businesses?

### "I CAN'T THINK STRAIGHT"

Not only are there the issues of staff stress and demotivation, a demerger may engender moods of "I don't care anymore" in some and "I can't think straight" in others – either way, ongoing

THIS ARTICLE EXPLORES AN "IDEAL" SCENARIO FOR AN EFFECTIVE DEMERGER, BASED ON A DIVORCE MODEL.



Michael Atkins

**SPECIAL FEATURE:**
**"Who gets the cat?"**

...an amicable divorce model of a company demerger

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work may lose momentum, compliance with key processes may slip, and more mistakes made than usual. This is a key time for senior management to predict these and plan. Staff should be given a bit more time and space. This is probably a bad time to start major projects. Current work to be handed over to new company entities should be professionally sorted out. Set deadlines not to begin any new activities. Recognise people's motivation when working on a task that will be irrelevant to the demerged company entity they are going to. Are there jobs that staff are doing now that represent a conflict of interests when they move on to a new demerger company entity or outplacement to another company? Is there a role for contract staff to help out?

## "LISTEN TO ME !"

It is common in mainland Europe is to have "work council" – staff representatives from all levels and functions. This council may already exist – if not, form one to ask advice and give information, some of which may be for the council's ears only at that time. Workers should use their council representative to voice general issues and concerns back to senior management and get answers. Human Resources must take a lead in counselling individuals– people's emotions are going to be exposed. Probably the biggest fear is " I will be without a job with no money coming in !"

## "WHERE WILL I LIVE? "

New jobs will be created and old ones disappear. Staff may want to go with one new demerger company and not the other. Some may be made redundant. Some positions may be left unfilled. Will voluntary redundancy be desirable/available? Watch out that all elements of employment law are followed. Be prepared for individuals mounting legal challenges to decisions made about their future. Provide advice on job applications, CVs, and outplacement. Organise staff interviews for jobs with the new company entities with care.

## "WHO GETS THE CAT?"

There are many, many legal and financial implications of a demerger. Internal experts should form a task force to plan. Dividing company resources must be rational and fair. Disputes must be avoided but that does not mean arguments will not ensue with internal stakeholders. External advice will almost certainly be required. A demerger is not inexpensive.

From information on servers/emails to paper records – who will take ownership of what post demerger? How can you access old data? Will an independent body be needed to manage data confidentiality post demerger? Can a less legalistic, amicable approach be taken (at least in the short term) post-demerger to iron out teething problems?

## "SHOULD I THROW OUT THE WEDDING DRESS ?"

A demerger is an ideal time to discard unwanted stuff. However, great care needs to be taken as some items may need to be retained. Think twice before throwing documents away. Seek legal advice - this relates not only to paper copies but to emails. Consider:

- Who needs access to what? Pre-demerger, partition the documents into each companies' responsibility.
- What needs to be kept at hand or what should be archived?
- Are archived materials properly labelled/catalogued for easy retrieval?
- How will documents needed by both companies post demerger be handled (especially those which are currently confidential)?
- Are there items of historical interest/value that should be put into a "museum"? Who should hold that once demerged?

- Can you shred unwanted items?

## "I FEEL REALLY HURT"

In any separation, there will be "winners and losers". The "winners" are seen to get the new top jobs or the redundancy packages they wanted; the "losers" are either offered jobs they don't want or unwanted redundancy. So, expect some unhappy people. How the company deals with the latter is a true mark of a caring employer. Make sure selection processes are seen to be and are fair. Offer good redundancy packages and support in finding new jobs for those who will not be staying.

There may be transition roles for those who have no new job to go to but can provide invaluable knowledge post-demerger whilst things settle in. Such jobs must be well remunerated to be attractive and must not compromise any redundancy packages.

Expect all the phases of bereavement (especially anger). It's OK to show sympathy and concern. Always respect emotions. Know your employment law and work to avoid industrial tribunals with disgruntled staff by doing the right things right first time. Retaining a sense of humour (even in the darkest times) can help.

One size never fits all, and be prepared to take exceptions where there are genuine hardships.

## AND FINALLY...

For a company that has been close and together a long time, staff may want a cheerio "wake"?

**SPECIAL FEATURE:**

**"Who gets the cat?"**

...an amicable divorce model of a company demerger

# RETRO FEATURE:
# What is Research and Development:
## What is drug discovery?

*By Dr Matthew Hickling, Medical Advisor UCB (now Medical Director at IPSEN UK)*

As part of BrAPP's 60th anniversary celebration we will be publishing a selection of articles from the extensive archive of Pharmaceutical Physician. We start the ball rolling with a piece from January 2010.

This article will outline some of the principles, strategies and activities required to progress early drug discovery projects.

Matthew Hickling

## INTRODUCTION

THE 'ART' AND 'SCIENCE' surrounding drug discovery and development can be unfamiliar to many physicians working in the clinic or in commercial functions of pharmaceutical companies. Yet even a basic understanding of this technically challenging and often complex process will ensure the right questions are asked at the right time when new projects are being adopted. The subsequent involvement of expert scientists and key opinion leaders (KOLs) in clinical development and product launch activities can also prove critical in the successful commercialisation of new therapeutics.

The role of physicians in research may be informal at the early stage and will vary depending upon the project. However their interaction with scientists from the onset of considering a new therapeutic project may help in advising on unmet clinical need, explaining clinical aspects of target diseases as well as helping identify KOLs who may then support projects as they progress.

More formal project interaction and involvement starts just before clinical development but having a thorough understanding of the key processes prior to this ensures critical issues can be addressed without delay. With the cost of developing new therapeutics exceeding 500 million pounds[1] and the time to market often spanning a decade, more needs to be done to shorten the learning curve. One solution is to ensure the cross fertilisation of ideas and expertise across the industry silos.

## NEW TARGET IDENTIFICATION

An important role for the physician in research could be supporting scientific colleagues in the exploration and rationalisation of new ideas on targets and indications. We easily forget that our breadth and depth of clinical experience is a valuable commodity to the research community who have never faced 'medicine in action'. The ability to translate clinical observations to altered pathological pathways or cellular activity to ultimately identify discrete targets requires cross discipline expertise at the research/early development interface. When proposing new targets for therapeutic intervention, a number of crucial factors need to be considered, these include:

### Relevance to human disease

Targets are often identified by producing mice lacking the target gene of interest and demonstrating a disease resistant phenotype. However closely the animal model resembles human disease there is a chance that the precise role of a given target may be different in mice and humans. Therefore clinical trials with a suitable therapeutic are often the only way to confirm the role of the target in human diseases. The presence of a target in human disease tissue can be confirmed using staining methods. However the functional effects of blocking or activating a given target may vary with interspecies differences in downstream signalling and function.

### Corporate strategy

Many good ideas fail at this hurdle; there may not be the capability or desire to venture into new therapeutic areas. Clear communication from the senior research management team is required to ensure that the efforts and enthusiasm

to drive research is not dissipated on targets not aligned with the corporate strategy.

### Commercial viability

Involving commercial colleagues at the onset of a research proposal should prevent nasty surprises when the likely cost of development dwarfs any possible return. This will often depend upon the indication, the cost and efficacy of current treatments as well as the likely therapeutic format. Orphan diseases may be attractive in terms of the likely accelerated development plans and favourable pricing strategies even though the patient group size may limit the overall return for a successful product. A successful launch in the orphan disease may however provide a route to accelerated development in more common diseases sharing common signalling pathways.

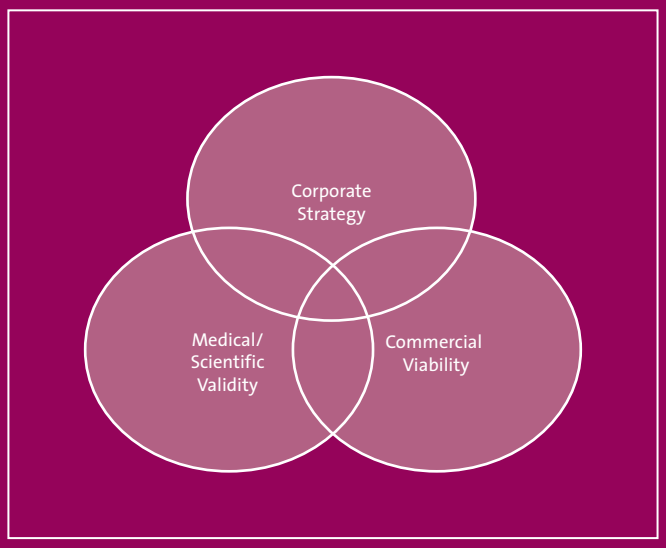
Alternatively, new formats for the treatment of common diseases like rheumatoid arthritis will require frank discussions on the competitor landscape as well as likely differentiating factors. The '10th in class' therapeutic will never pass the Technology Appraisal hurdle of the National Institute for Health and Clinical Excellence unless there are clear benefits in either safety, efficacy or cost. The predictions on cost balanced against the clinical benefit and commercial return are often hurdles new ideas fail to overcome.

However drug discovery is based upon innovation, searching for new modes of action and the modulation of alternative signalling pathways; therefore there will always be an element of uncertainty and risk with innovative targets. As an example, the success of the anti-TNFs came about from research into septic shock; it would have been unfortunate if this indication had not been investigated.

### Scientific validity

The problem (or benefit) of new targets is the degree of uncertainty on the value/rationale of the target. To clarify the main hurdles for new target progression, a Target Candidate Profile will be compiled that outlines in advance the critical decisions on progression, key experimental findings that will be required to gauge success as well as ideas on target diseases and patient populations. It is much better to kill a project early on, freeing up valuable time and resource for the next great idea, rather than see it progress into clinical development where millions of pounds are at stake. Even then, some element of project validation through preliminary research will be required to test the hypothesis.

**| FIGURE 1:** Interaction between medicine, science and commerce




## THE KEY ISSUES IN NEW TARGET IDENTIFICATION

Investment in clinical research requires patience, excellent project management and a bit of luck. Portfolio planning ensures that the company's therapeutic pipeline remains balanced, identifying deficits and bottlenecks where Business Development colleagues can scope possible licensing or collaborating opportunities. Although the journey of discovery may span several years, regular science meetings enable the discussion of project data as well as the consideration of the changing competitor landscape. This journey through research will often be mapped out with key decision points, indicating the level of resource and planning for each particular stage as well

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**RETRO FEATURE:**
**What is Research and Development:**

What is drug discovery?

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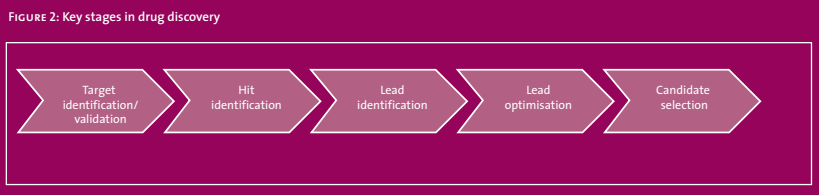
as those critical pieces of data that will 'kill' a project should they not be achieved.

## THE KEY STAGES IN DRUG DISCOVERY

Following Target identification, a hit is identified when a compound demonstrates favourable properties within a primary screening or binding assay. The hit will then be confirmed once the compound is shown to demonstrate a dose-response relationship in a secondary screening or cell based assay. Lead identification includes compounds or series that obey a number of criteria or standards for structure, pharmacology, pharmacokinetic / pharmacodynamic properties (PK/PD), toxicity and patents. Following further Lead optimisation, Candidate selection for preclinical development and clinical development will follow should the further assessment of PK/PD and safety pharmacology/toxicology be favourable.

**| FIGURE 2:** Key stages in drug discovery




## TO NBE OR NCE?

A typical new therapeutic, whether biological (NBE: New Biological Entity) or small molecule (NCE: New Chemical Entity), follows a similar path from Target identification to Candidate selection. NCEs however require a number of screening cascades to filter out molecules with unfavourable properties at different stages; NBEs such as monoclonal antibodies (mAb) have limited constructs which will require less manipulation. Once a new target is adopted, the choice/class of therapeutic will be considered; a decision again based upon corporate strategy, scientific rationale and in-house expertise. For example, intracellular targets will require passage across the cell membrane, favouring NCEs as NBEs such as mAbs have yet to be reliably used to target intracellular targets. However should a long biological effect be required, an NBE such as a mAb may be chosen given its likely half-life spanning days to weeks. Understanding the target, its location and down-stream signalling pathway effects are therefore crucial.

## ISSUES RELATING TO NCES

### Chemical starting points

When little is known about the target, a fragment screening approach may be considered. Large libraries of low molecular weight compounds can be assessed through using high throughput screening assays. Virtual screening utilising the computer simulation of known target and compound structures may help reduce the number of likely fragments for further consideration from millions to thousands. One major hurdle for fragment screening is the sensitivity of the associated screening assay; given the low potency of any fragment, will the effect be readily

detected and could the effects be off-target related?

### Structural biology and chemistry

Structural based drug design using software modelling in association with X-ray Crystallography and Nuclear Magnetic Resonance Spectroscopy can predict likely docking patterns of NCEs to binding sites. When combined with assays, the development of NCEs can be guided through functional readouts and computer predictions. This approach does however require detailed knowledge of the target as well as target protein synthesis; the availability of which can be a major stumbling block when it is difficult to synthesize.

### Is it druggable?

Traditional NCEs have often obeyed a number of key principles including the Lipinski rule of five:

- Molecular weight of < 500 Daltons
- CLogP < 5 an assessment of water solubility (octanol - water partition coefficient)
- Hydrogen-bond donors <5
- Hydrogen-bond acceptors <10

These basic rules help assess the ADME (Absorption, Distribution, Metabolism, Excretion) of the compound. The liberation of the therapeutic entity from different formulations will also be assessed. In-vitro and In-vivo assays assessing the PK/PD properties of compounds are essential to enable initial predications of dosing requirements for early clinical development. Compounds with adverse PK/PD profiles such as low bioavailability (essentially the amount of compound within the systemic system following ingestion, gastrointestinal absorption and first pass metabolism), poor distribution in target organ (e.g. crossing the blood-brain-barrier to target the central nervous system) or toxic effects (liver or other organs) need to be identified so that this series/class of compound within the program can be terminated as soon as the data becomes available.

### Simplifying synthesis

Often chemists will use inefficient routes to quickly synthesize compounds of interest. Once a number of likely candidates are shortlisted, work needs to be initiated to design the most efficient and stable synthetic routes to support both clinical development and eventually commercial production of approved therapeutics. One critical aspect will be to decide upon the form and delivery of the drug; confirmation of the likely indication is therefore needed.

## ISSUES RELATING TO NBES

NBEs encompass a number of different complex natural and synthetic proteins such as insulin, erythropoietin and somatotropin. Since the pioneering work of Kohler and Milstein which led to their award of the Nobel Prize in Physiology or Medicine[2] the development of mAbs has revolutionised medicine as well as the biopharmaceutical therapeutic field. Following identification of a target, there are a number of technical issues that require consideration for developing a mAb.

### Antibody generation and format

A number of different recombinant technologies exist for identifying and acquiring antibodies. Hybridomas pioneered the production of mAbs using myeloma cell lines and animal immunisation techniques. Phage display technology also enables the screening of DNA libraries for millions of different antibodies through the incorporation of different specific antigen binding domains into phage DNA that are then expressed through bacterial culture conditions. One critical issue that requires some thought is the exact format of the antibody therapeutic. Should the antibody be conjugated with a cytotoxic agent for a possible tumour target; will the recruitment of the host immune response confer a benefit through interaction with the Fc region and will the therapeutic benefit from a shorter half-life? These decisions will confirm whether a full construct or Fab (fragment antigen binding) will be the construct of choice.

### Protein engineering and humanisation

Following screening of suitable antibodies, selected antibodies can be isolated and sequenced. Using advances in molecular biology, both human and murine constructs (which can be humanised to reduce immunogenicity and improve PK/PD properties) form the basis of numerous treatments for chronic disease and cancer. Protein engineering enables the introduction of subtle changes in the construct; amino acid substitution may modify some of the biopharmaceutical properties.

### Protein expression

Following protein engineering, efficient processes for antibody production are required to allow for sufficient quantities of reliably expressed and stable product to be synthesised in order to support preclinical and clinical studies. Extensive analysis using technologies such as High Performance Liquid Chromatography (HPLC) ensures the stability and purity

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of the product. Both bacterial and mammalian cell lines can be used to produce the final therapeutic (depending upon the construct and other desired properties), often initially in small 1L flasks that can then be ultimately scaled up to produce quantities for product registration / market approval.

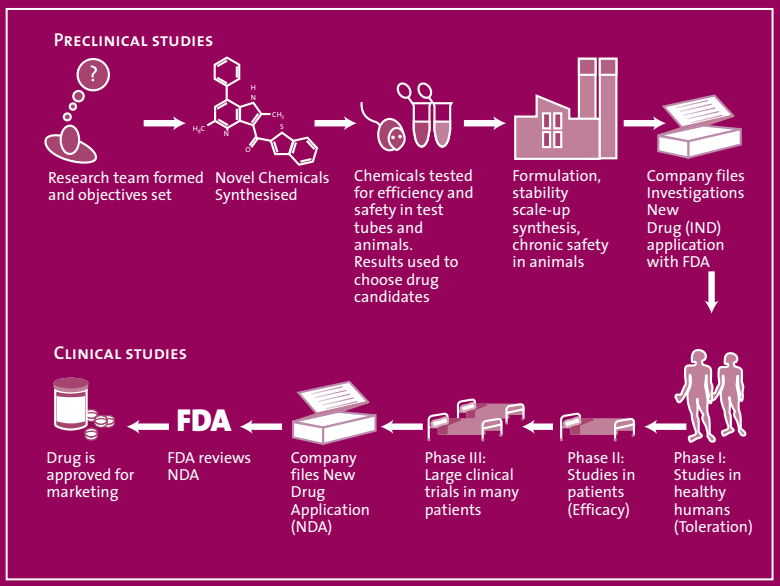
## DON'T FORGET THE PHARMACOLOGY

Following the identification of several lead compounds or antibody formats, pharmacological studies are required to assess therapeutic binding and effect. These extend from the development of screening assays that help determine the selectivity of the therapeutic through to those assessing changes in downstream signalling in cells derived from cell lines, animals and ultimately human donors / patients. The close (and early) collaboration with KOLs with an interest in the target / field is therefore essential in developing assays requiring patient derived samples.

The public debate over the use of animals in therapeutic research still remains a controversial issue; despite many advances in in-vitro and in-silico assay development, positive results in animal models of disease still provide confidence in both the target and the therapeutic being developed. Data from animal models is extremely important to help explore the full effects of pharmacological intervention and to identify pharmacological dosing regimens. One must be aware of interspecies differences in potency and pharmacokinetics which must be taken into account when determining FIH doses.

Numerous in-vitro and in-vivo studies are also performed to assess the safety of the therapeutic; often organised by colleagues working in pre-clinical development who specialise in toxicology. Exploratory studies will be performed early on to attain confidence in the safety profile. However, in

**| FIGURE 3:** The drug discovery process (Reproduced with kind permission from reference[3])



support of late stage research and in preparation for Investigation New Drug (IND: USA) applications, a range of studies will be performed under Good Laboratory Practice (GLP) conditions that are required for regulatory approval. In brief, these studies include those for genotoxicity, safety pharmacology as well as single dose, multiple dose and chronic toxicity studies that are performed at different stages of research and development, depending upon the risk profile of the therapeutic in question.

## PRECLINICAL PHARMACEUTICAL DEVELOPMENT

In parallel to candidate NCE or NBE Candidate selection activities, preparation for manufacture in sufficient quantities to support both preclinical safety studies and ultimately early phase clinical development should be underway. When and how colleagues in pharmaceutical development are involved in the project can be debated at length, my personal view would be as early as possible. A 'drug in a bottle' approach is often the simplest and quickest approach as it requires the least amount of development for early clinical studies. Essentially this is where the active compound is suspended in an oral solution. This will require specialist pharmacy support at the clinical site and further formulation resource will be required later on to support pivotal trials and ultimately product registration. How the therapeutic is to be delivered will depend upon the disease indication and target population, the choice of excipient (carrier substance) will also be decided once the delivery mechanism is chosen. One will have to consider the most efficient manufacturing process as well as assess chemical stability and consistency in physical, chiral and biopharmaceutical properties. Getting it wrong may mean more delays and wasted resource for completing additional bioequivalent studies that are required following an unexpected change in manufacturing process. Good Manufacturing Practice (GMP) will have to be implemented when preparing for clinical development.

## WHEN TO PATENT?

Extensive research into the literature as well as searches for patent applications will define the scope for work in a particular class of compounds, whether NCE or NBE. A crowded patent landscape may well 'kill' projects even if there is a positive scientific and commercial view on the target. Timing the patent filing is also crucial; given that patents in all commercially important territories are nowadays granted for 20 years. Filing the patent application too early when followed by many years of post filing development leads to a shorter time frame for market exclusivity and therefore loss in revenue following product approval. Alternatively filing too late may allow competitors an inside track on a novel target or compound. Often patent applications will be filed once several lead compounds have demonstrated promising results in a range of relevant in-vitro and in-vivo studies. Although seen as being a complex process to many, the basic principles are quite straightforward. Generally, for a patent application to succeed, the innovator should be able to demonstrate novelty (i.e. the molecule has never been published anywhere before) and inventive step (i.e. the structure or properties of the molecule are not obvious relative to the structurally closest 'prior art' molecule), as well as industrial applicability (although this is usually taken as read for a pharmaceutical molecule).

## CONCLUSION

The drug discovery process is subject to many scientific, commercial and corporate challenges. Medical research is a highly dynamic and competitive field that demands innovation, determination and some luck to enable the successful delivery of a new therapeutic into clinical development on time, within budget and of course before the competition!

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**PERSONAL VIEW:**
# Tackling the Diabetes Epidemic:
## with Digital Therapeutics

*By Dr. Matthew Goodman*

Matthew Goodman

AS THE GLOBAL leading cause of heart attacks, stroke, blindness and amputations, it's no exaggeration to say that diabetes threatens the lives of the people it affects. But it may surprise you to learn that the relentless rise of diabetes single-handedly has the potential to destroy healthcare systems and even undermine whole country economies if left to continue unabated.

The proportion of people now living with diabetes in the UK may be as high as 4 million, of which nearly all are type 2 diabetics. That number is set to rise to 5 million by 2025. The costs of this are staggering - estimates suggest that £10 billion per year is spent on diabetes in the NHS alone – that's £1 million an hour. Every hour. Of every hour of the year. And that number doesn't even touch on the indirect costs of diabetes - social care, time off work, family carers and a variety of other economically damaging effects.

With expenditure increasing every year to cover the rising numbers of diabetics, this is not just a huge burden to the healthcare systems, but a substantial risk to the already fragile wider economy of the UK overall. This isn't a healthcare issue anymore, but one of wider relevance to the entire country.

For an audience working in pharmaceuticals, you'll be disappointed to hear that it's widely accepted that the major part of the solution depends on improving 'self-management' – that is cultivating the skills in patients to better manage their lifestyle, and thereby improve the outcomes of their illness. Clinical studies support this notion – that better-informed, better-equipped patients tend to live longer, healthier lives, and suffer from fewer of the complications that diabetes can cause.

Innovators have recognized that there are opportunities to use technology to help manage diabetes. Indeed, affordable, portable devices let us organize all parts of our lives, from socializing to banking, conveniently and securely. These technologies offer the opportunity for us to transform the way we support self-management too. The benefits for patients are clear – the convenience of accessible support that can be relied upon at any time of the day, resulting in improved health and better outcomes. Equally, for healthcare providers, the unparalleled scalability and ability of technology to touch hard-to-reach populations, is attractive, not to mention the potential for tremendous cost-savings.

However this is not without its challenges. If it were as simple as creating 'demand-driven' technology products aimed at the healthcare market, then, like other consumer areas, this problem would have been solved a decade ago. Ironically this isn't about the technology at all, but about managing the integration of these new services into current healthcare systems, understanding the benefits and ensuring appropriate reimbursement, and navigating a nascent, but increasingly complex regulatory environment, including that of privacy and security concerns amongst users.

There's still a long way to go before we see the widespread use of digital therapeutics to improve health. But the 'push factor' of rapidly depleting NHS

healthcare budgets in the face of a national epidemic of diabetes, and the 'pull factors' of potentially huge and cost effective patient benefits are too strong to ignore.

The current way of delivering care is simply no longer sustainable – and without doubt technology will revolutionize healthcare. We have reached the tipping point where digital therapeutics move from being a futuristic showcase platform to an integrated healthcare solution used by patients and doctors alike.

*Dr. Matthew Goodman is a physician with a special interest in the application of technology to long-term conditions. He is Medical Director of Mapmyhealth, an Oxford, UK-based healthcare company that specializes in the delivery of digital therapeutics to healthcare providers in the NHS and beyond.*

*He also has experience as a pharmaceutical physician.*

*From: Medicines and Healthcare products Regulatory Agency*

Medicines & Healthcare products Regulatory Agency

## MHRA leading European action to reinforce market surveillance of medical devices to protect public health

The Medicines and Healthcare products Regulatory Agency (MHRA) has officially launched the Joint Action on Market Surveillance of Medical Devices.

Medical devices cover a wide range of products – from sticking plasters to hip replacements, from contact lenses to personal oxygen tanks and implanted pacemakers. These devices and others like them, can be found in every household across Europe, once they have been CE marked.

To make sure devices like these are acceptably safe and perform as intended, Competent Authorities need to have a strong programme of market surveillance.

On 19 October 2016, at the 39th meeting of the Competent Authorities for Medical Devices in Bratislava, Slovakia, MHRA officially launched the Joint Action on Market Surveillance of Medical Devices.

The project aims to reinforce the market surveillance system for medical devices by improving the coordination of activities by all member states of the European Union, and ensuring adequate communications and cooperation. These are crucial for success and effectiveness of the market surveillance in the field of medical devices.

The Joint Action supports the Consumers, Health, Agriculture and Food Executive Agency's (Chafea) programme of community action in the field of health to deliver against one of its objectives: to contribute to innovative, efficient and sustainable health systems.

Chafea is entrusted by the European Commission to implement the health programme and EU Members States involved in the programme – in January 2016.

John Wilkinson, MHRA's Director of Medical Devices, said:

We are pleased to be leading this important activity and look forward to working with our colleagues across the EU in delivering improvements to reinforce market surveillance.

### BACKGROUND

1. The Joint Action will be implemented through five work packages: MHRA leads on three (Coordination dissemination and evaluation), while two will be implemented and delivered by EU Member State partners: the Netherlands (manufacturers' inspection) and Ireland (clinical process and resource development). More information about the Joint Action can be found on the CAMD website

2. To report a suspected problem or incident with a medical device please visit the Yellow Card Scheme website.

3. MHRA is responsible for regulating all medicines and medical devices in the UK. All our work is underpinned by robust and fact-based judgements to ensure that the benefits justify any risks. MHRA is a centre of the Medicines and Healthcare products

Regulatory Agency which also includes the National Institute for Biological Standards and Control (NIBSC) and the Clinical Practice Research Datalink (CPRD). The Agency is an executive agency of the Department of Health.
www.mhra.gov.uk

*17 November 2016*

## New ICHP Managing Director appointed

IMPERIAL COLLEGE HEALTH Partners (ICHP) is delighted to announce that Dr Axel Heitmueller, who is currently acting Managing Director, has been appointed to the substantive position with immediate effect.

Axel was appointed by the Partnership Board following a robust search and selection process which attracted a number of high calibre candidates. Axel has an impressive track record spanning both senior positions in the NHS and government. In 2011 he was asked to lead the establishment of ICHP working alongside Lord Ara Darzi. He took up the substantive role of Director of Strategy and Commerce of ICHP in summer 2013.

As you know, ICHP, which is also licensed as one of the 15 Academic Health Science Networks in England, works with its partners to identify new innovations and best practice solutions to address system wide challenges and ensure safe, high quality and efficient services for patients.

In his new role at ICHP, Axel will lead the Partnership in helping to address some of the biggest health challenges facing the region. His focus will be on fostering collaboration and system leadership, and supporting the systematic uptake of best practice and innovation.

He will have a key role to play in North West London's health economy, working with our NHS and academic partners, industry, third sector, local government and patients and the public to deliver transformational change.

Axel takes over from Dr Adrian Bull who left the Partnership earlier this year to take up the role of CEO at East Sussex Healthcare NHS Trust.

Please join us in welcoming Axel into his new role.

Dr Axel Heitmueller