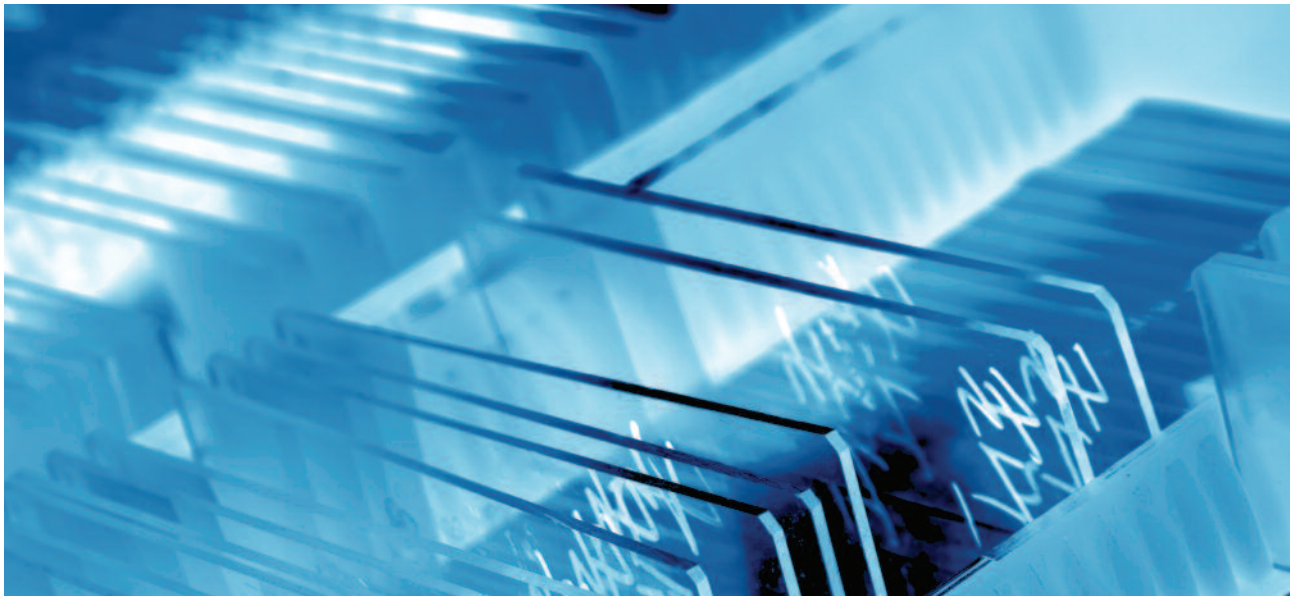
RISK FOCUS

LIFE SCIENCE BULLETIN MAY 2015

New Drug Applications – Reducing the time to market and the impact on the insurance industry

2014 proved to be a productive year for both the pharmaceutical industry and the US Food and Drug Administration (FDA). In total 41 new drugs were approved, providing a much needed upturn in a decade of moderate and sustained decline evidenced by an average of 26.8 approvals per year from 2005 to 2014 versus an average of 31 in the preceding decade.



Almost 10 years ago JLT Specialty (JLT) released a bulletin examining how criticism of the FDA's drug approval process prior to 2005 pushed the FDA to focus on the management of risk within their industry. This focus culminated in the creation of the Drug Safety Oversight Board and Guidance for Industry Development and Use of Risk Minimization Action Plans.

At the time we were of the opinion that approvals may decline due to additional risk mitigation information requested by the FDA. Whilst the approvals did drop as predicted it wasn't necessarily due to the bureaucratic hurdles being put in place.

The additional safety requirements introduced in 2005 may have hampered approvals but in reality it was just the implementation of another layer of complexity in an organisation that, by the admission of previous FDA commissioner Dr. Andrew von Eschenbach, was already struggling with red tape. In 2012 he stated for the Wall Street Journal that "…patients…shouldn't have to wait years while the FDA asks the company to complete laborious clinical trials proving efficacy. Instead, after proof of

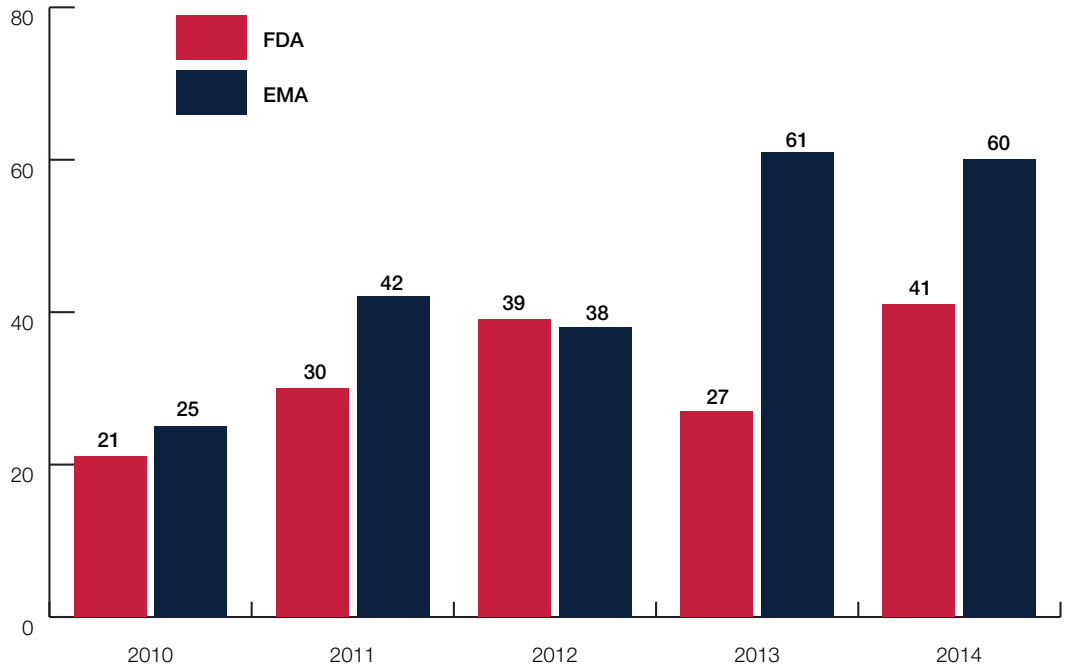
concept and safety testing, the product could be approved for marketing with every eligible patient entered in a registry so the company and the FDA can establish efficacy through post-market studies[1]."

It is also widely acknowledged that the pharmaceutical industry felt the impact of the most recent global economic turndown. This was not only from internal pressures of prioritising cash flow away from research and development, but volatility from external factors such as buyers who were facing unprecedented pressures on expenditure. The purpose of this bulletin is to examine why the pharmaceutical industry is now experiencing the latest upwards trend in approvals and what the impact on the product liability insurance market may be.

WHAT HAS CAUSED THE HIGHEST LEVEL OF APPROVALS IN 18 YEARS?

One way to frame this discussion is to examine it from the view of the four stakeholders, who by design or necessity have all been pushing towards freeing up a process that can take 10 years or more to complete. This lag comes at a cost not only to patients but the pharmaceutical companies themselves. Depending on which source you look at drug development can range anywhere from GBP 1.15 billion[2] to USD 5 billion[3]. Though the figures vary wildly between articles, one thing they all agree on is that the costs represent an enormous financial burden to any pharmaceutical organisation involved in drug development stages.

FDA vs European Medicines Agency (EMA) Drug Approvals (ex. generics)



1. http://www.policymed.com/2012/04/former-fda-commissioner-calls-for-updated-systems-and-more-education-for-fda.html
2. http://www.bbc.co.uk/news/health-27130098
3. http://www.forbes.com/sites/matthewherper/2013/08/11/how-the-staggering-cost-of-inventing-new-drugs-is-shaping-the-future-of-medicine/

STAKEHOLDER 1 – THE FOOD AND DRUG ADMINISTRATION

A recent report from PWC entitled "The FDA and Industry: A recipe for collaborating in the New Health Economy"[4] provides evidence that the FDA is deploying a more collegiate approach when dealing with the industry and it seems to be having a positive effect. According to their research 78% of Executives surveyed cited that the improved frequency and quality of communication as "…the most important things the FDA has done to improve its relationship with the Industry". It should not perhaps be surprising that this dialogue has had such an effect but yet it is a simple relatively cost effective process that can reduce conflict and help move towards a common goal.

This communicative approach is probably at its most visible when the FDA is woven into the drug development process right from the preclinical stage through their Expedited Programs for Serious Conditions[5]. This collaborative approach has begun to yield some significant results. A Johnson and Johnson drug, Imbruvica®, managed to go from Phase I to commercialisation in 4.5 years, less than half the timeline experienced on an industry average. The costs for the development of Imbruvica® are unknown but if you calculate drug development costs including the man hours taken it is certain there are savings made. It is also reasonable to assume that with the FDA being so familiar with the drug through its development that it continues to be successful at gaining authorisation for new indications.

Integral and key to the success of so many approvals is the accelerated process in the FDA's Expedited Programs. As stated above, Imbruvica® came through this process as did many others in 2014. There are now four routes to gain quicker approval through the FDA:

- Fast track
- Breakthrough therapy
- Accelerated approval
- Priority review / priority review voucher.

Each of these programs has its own qualifying criteria but the common thread is a drug that intends to or does treat a serious condition and demonstrates the potential to address unmet medical needs or show an improvement over existing therapies. The only curve ball in the above is when a pharmaceutical company gains access to a priority review voucher, they do need to meet the criteria of treating tropical diseases but you do not have to receive them directly from the FDA and in fact they have changed hands recently between pharmaceutical companies for up to USD 125 million.

4. *http://www.pwc.com/us/en/health-industries/health-research-institute/hri-pharma-life-sciences-fda.jhtml*
5. *http://www.fda.gov/downloads/Drugs/Guidance ComplianceRegulatoryInformation/Guidances/UCM358301.pdf*

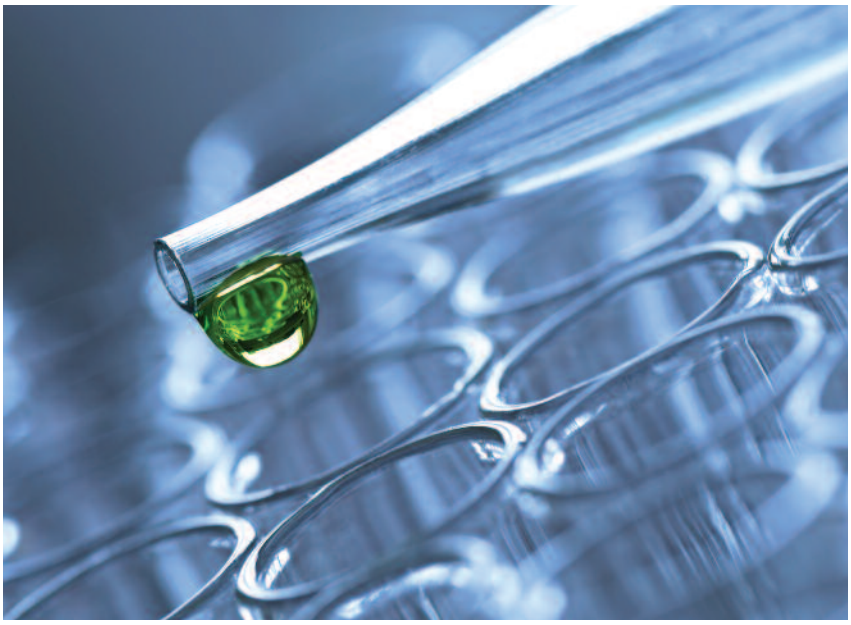
STAKEHOLDER 2 – THE PATIENT (AND PATIENTS' NEEDS)

Summarising the FDA's approvals in 2014 Janet Woodcock MD, Director for the Center for Drug Evaluation and Research, highlighted the focus that last year's approvals had on the patient population. Half of the approvals received priority review as they had demonstrable improvements over existing therapies, there were several new antibiotics and more orphan drugs were approved than ever before, further demonstrating the move away from blockbuster type treatments to more specialised medicines. It is also worth noting that the seven year marketing exclusivity authorised by the US Government will also have a significant bearing on the decision for pharmaceutical companies to pursue specialised medicines.

The major global health story in 2014 was the emerging threat of Ebola in West Africa. In response to the threat the FDA in the absence of any adequate, approved or available alternatives, invoked the Commissioners powers under section 564 of the Federal Food, Drug, and Cosmetic Act, allowing for various unapproved treatments to be used to combat the virus. ZMapp and novel uses of plasma from patients who survived infection as well as forthcoming vaccines from GSK and others set interesting precedents and perhaps signal a new and more flexible approach to dealing with unmet medical needs that can be rolled out for other life threatening illnesses.

It is a certainty given current population levels, the globalisation of business and the ease of travel that epidemics and pandemics are more possible than ever before so to ease on restrictions on drug development in circumstances such as these will make the industry more agile and able to respond when needed.

Finally whilst the industry is driving their business towards the unmet medical needs of patients, we cannot ignore the power that the patients themselves are beginning to harness. Patient and charity funded clinical trials particularly in the oncology sector are becoming more frequent. It is also hard to ignore the impact of social media simplifying the patient pressure group movement, allowing for a very vocal and direct questioning of Government policy such as the NICE approved drug review in the UK or even direct lobbying of pharmaceutical companies themselves. It is very easy for these types of situations to gain traction or be mishandled so the industry will need to move with the time to handle these issues compassionately and effectively.



STAKEHOLDER 3 – GOVERNMENT

The US Government has given both a direct and indirect impact on the speed of approval. Over the last 10 years Government funding for the FDA has decreased and as spending reduced it was in turn made whole by the pharmaceutical industry increasing their proportion. The Prescription Drug User Fee Act (PDUFA) is a huge source of revenue to the FDA and this is being supported by other schemes such as priority review. This makes the pharmaceutical industry the more powerful stakeholder and may give cause for concern around its independence from the industry but perhaps it forces the FDA to be more collegiate listening to their concerns and implement changes to process in order to speed up approvals.

The Government, whilst reducing their financial relationship with the FDA, has proposed new legislation to assist the industry and patient groups. The American Cures Act introduced to the Senate in March 2014 establishes a Biomedical Research Fund to be administered by the Treasury with expanded and sustained investment in biomedical research with a 5% increase on spending year on year.

The Promise for Antibiotics and Therapeutics for Health Act introduced to the Senate by Sens. Bennet (D) and Hatch (R) in December 2014 has been designed to allow for drugs to be studied in smaller clinical trials and approved for the limited patients that need the treatment. The argument is that current legislation demands for large clinical trials for antibiotics but the patient populations with untreatable infections are unsustainably small. Cited in recent blog for the Wall Street Journal[6] Allan Coukell, senior director for health programs at The Pew Charitable Trusts, stated that "Our analysis of the antibiotic pipeline shows about 38 new drugs in some stage of clinical testing…" encouraging signs perhaps that the PATH Act need serious attention drawn to it.

Finally Congress noting that legislation has not been keeping up with developments in technology and advancement in science, has set up the 21st Century Cures Initiative. This has been designed to ask questions and listen to the concerns of patients and the industry in order to assist in the discovery, development and delivery of new treatments, ensuring that the legislature does not become a barrier to innovation. Though this initiative has yet to directly yield results it is a step in the right direction.

6. http://blogs.wsj.com/pharmalot/2015/01/16/u-s-senators-re-introduce-a-bill-to-speed-approval-of-antibiotics/

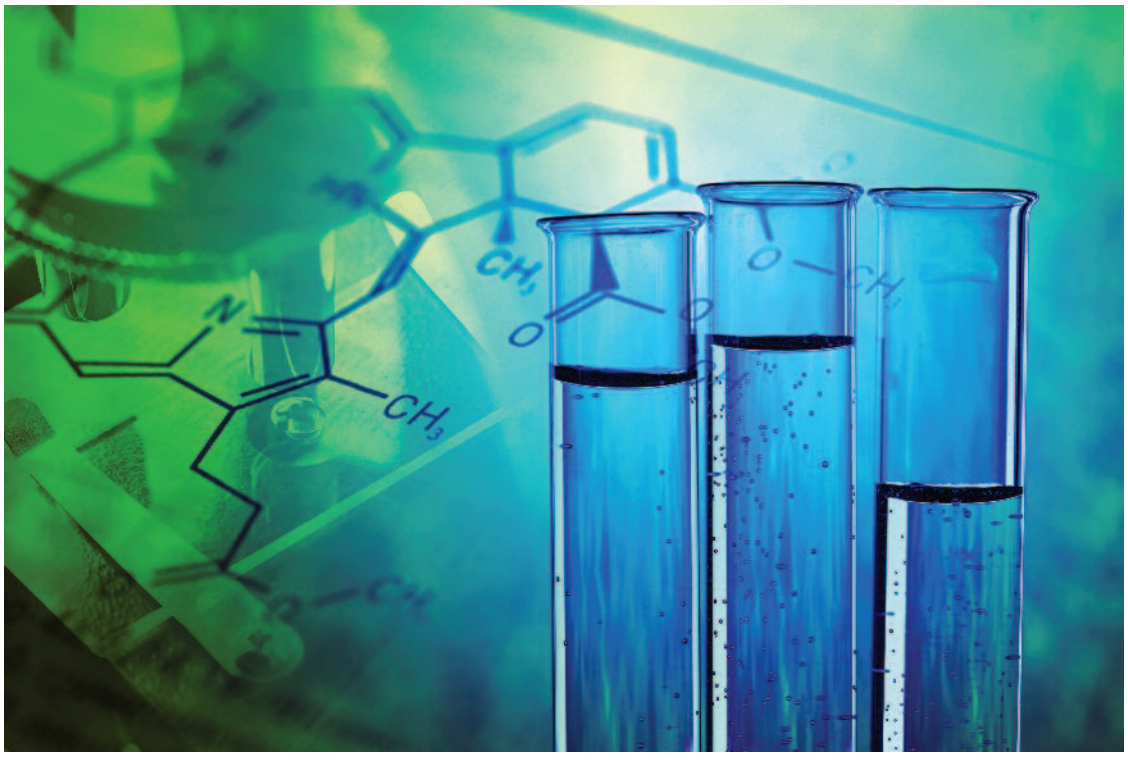
STAKEHOLDER 4 – THE LIFE SCIENCE INDUSTRY

The financial impact of the industry on their regulator cannot be ignored. As we highlighted above, Government funding to the FDA has been in steady decline and PDUFA funding has increased over 30-fold since 1993. This funding will have two effects: one is that essential investment is being provided to the regulator, plus it will allow, even on an implied basis, the industry a seat at the head of the table when it comes to decision making for the future. Although a positive step, it needs to be handled appropriately to ensure that the regulator remains independent and able to make decisions that protect the patient.

The ability and ingenuity of the industry to respond to the medical needs of patients continues to impress. You need only look at the headlines in recent months to see that not only does it continue to move at breakneck speed in some unusual directions but there are now "game changing" innovations such as CRISPR-Cas9 helping research move further, faster and potentially cheaper than ever before. Other areas that have caught the imagination include but are definitely not limited to:

- Rapid blood sample testing
- Electronic noses to detect early stage cancer
- Needleless vaccinations
- Stool transplants to fight C-Difficile
- 3D Printing
- Integration of medical treatment and phone applications *(https://www.jltspecialty.com/our-insights/thought-leadership/life-science/life-science-bulletin-july-2014)*
- Personalised medicines
- Cancer immunotherapy.

All four of these stakeholders together are driving forth the pharmaceutical industry but what impact might this have on the product liability insurance market?



Impact on the insurance industry

Impacted by significant losses due to pharmaceutical product liability cases, particularly in the US, buyers of the cover had been forced to rethink risk transfer strategies in order to plug the gaps that the burned insurance market was leaving them with. This could have been through significantly increased self-insured retentions moving insurers to more cat loss positions, or the move to stop buying insurance altogether as it was no longer economically viable or it was unavailable to do so on terms that were broad enough.

During the interim the marketplace stayed static. Any significant trends were dealt with by revised exclusion criteria. Generally insurers with a long term view on the industry swallowed hard and stuck with their reduced client base.

More recently however in the light of a soft market and a more opportunistic approach to underwriting risks the product liability insurance marketplace is gaining some buoyancy. The US domestic market is strong with new entrants providing additional capacity and the rest of the world is following suit. We believe that this revived marketplace is well positioned to take advantage of the progressive approach to drug approval and significant changes to the focus of the industry and that protecting the balance sheet with adequate cover will become a cost effective proposition.

An indirect consequence of the priority review system is that there is less of an aggregated risk for insurers. The patient bases when dealing with orphan diseases and infectious diseases are markedly less than was focused on during the 90's. The business models are changing and it represents a new underwriting environment for insurers. Personalised medicine will further reduce that exposure.

Orphan disease status drugs are given patent protection for a period of seven years, as a consequence generic pharmaceutical companies will need to focus on other low hanging fruit before getting an opportunity to begin manufacturing. Even when they do get the opportunity once the drug comes off patent the reduced patient base described previously will impact their business decision making, for example will there be enough volume of patients to warrant the investment in production? Again we anticipate a reduction in exposure to insurers because of this.

The main focus of orphan drug manufacturers is generally on life threatening and/or debilitating illnesses, which they hope to cure or help sufferers manage symptoms. Without being

cavalier about the serious conditions these patient groups live with, we anticipate that the more critical the disease the more acceptable potential side effects might be in exchange for a better quality of life, therefore reducing the chance of future claims.

There must still be caution though. The speed with which the pharmaceutical industry has moved in the last decade through scientific breakthroughs and competition has created a significant problem for the FDA and will no doubt cause issues with insurers. The FDA's current Commissioner Margaret Hamburg when speaking to Congress in 2010 confessed that "The FDA is relying on 20th century regulatory science to evaluate 21st century medical products."[7]

Insurers will arguably combat these developments in one of three ways. An uncertain insurer will walk away from a development until it has matured sufficiently in order to gain proper underwriting information. The opportunistic insurer will welcome an uncertain risk to a balanced book in consideration of the appropriate premium and the cutting edge insurer will employ internal or external consultants or pharmacologists to help them assess the risk and accept it, reject it or accept on specifically tailored terms based on their findings.

7. http://www.fda.gov/downloads/AboutFDA/Reports ManualsForms/Reports/BudgetReports/UCM205623.pdf

JLT Specialty Limited provides insurance broking, risk management and claims consulting services to large and international companies. Our success comes from focusing on sectors where we know we can make the greatest difference – using insight, intelligence and imagination to provide expert advice and robust - often unique - solutions. We build partner teams to work side-by-side with you, our network and the market to deliver responses which are carefully considered from all angles.

For more than a decade we have been the leading liability broker for larger life science companies, working with the majority of the leading players in the sector, from pharmaceutical and agricultural to chemical and research institutes.

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CONCLUSION

What has become clear over the last three or four years is that the shift in focus of life sciences companies to cater for orphan diseases presents a new and exciting era in the development of medicine and an opportunity for the insurance industry to respond to. The hope is that the FDA continues with their new drug approvals as in 2014. At 21 April 2015 approvals stand at 34 so it is highly likely that the 41 approvals will be surpassed this year.

The general consensus of the London life science insurance market is that they welcome almost all new drugs and therapies, should they have the ability to underwrite them. The orphan disease sector is particularly attractive to them and if they have the opportunity to underwrite the business they have a significant appetite for it. The patient numbers are much smaller and focussed and their current experience shows that claims activity is not alarming. The major hurdle the London marketplace has is getting to underwrite the business in the first place. If the company is domiciled in the US they will more than likely not underwrite the business, irrespective of how attractive on paper it may be. Additionally, companies which have stopped buying product liability insurance are prolific in this sector; and coupled with the recent mergers and acquisitions activity, the pool of insurable prospects is not as healthy as insurers would like it to be.

If the hurdle of company domicile can be overcome then our experience shows when it comes to batching language provisions, policy terms and conditions and consistency of cover, underwriting pharmaceutical risks in Europe and in particular London can work in the favour of the Insured.

Insurers' keenness to underwrite these new drugs should be tempered slightly by some of the steps the FDA has or will be taking to push new drug approvals through more expeditiously. These quicker approvals should lead to greater post marketing surveillance studies, so an insured will need to make sure that their product liability policy is up to the task. If the cover is inadequate either discuss the matter with your insurer, broker or consider a standalone clinical trial policy to cover for the activity.

It is early days yet but a concern lingers over the safety of the expedited process. With less stringent requirements by the FDA put on patient numbers to prove efficacy and a greater reliance on the post marketing process to examine safety, will the drugs be more harmful to patients? Moreover with drugs coming to market and not being taken under trial conditions there is a high probability that eventually claims will start to filter through. As this happens, it will be interesting if the FDA themselves are targeted more by plaintiff attorneys, alleging liability due to reducing the parameters involved in the research and development phase of the drug development process that led to the injury to the patients.