

An Introduction to the Pharmaceutical Industry

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ABSTRACT

As the founder and director of a contract research organisation and a recruitment company, the co-founder of PhUSE and an active consultant to many biopharmaceutical clients globally, James uses his unique and privileged view to take a high level look at the global healthcare industry and excite the reader about the career possibilities in this dynamic and worthwhile field. The paper introduces the role of the health research industries and documents the macro market that the industry operates within and highlights some apparent trends, inviting the reader to consider possible future developments. The job roles and functions are then described with particular reference to software users and potential career paths. Leading on finally to a discussion on career management and the role of continuous professional development. Whilst the paper is written with a view to guiding new starters in the industry it is envisaged that it will be of interest to many experienced industry professionals also.

KEYWORDS

GLOBAL MARKET; DRUG REGULATION; THE CLINICAL TRIAL; THE CLINICAL DEVELOPMENT PROCESS

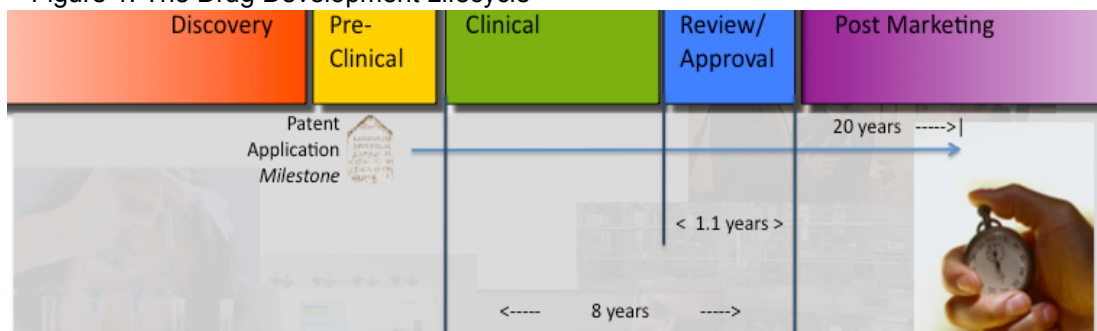
INTRODUCTION

This paper provides an overview to the reader and an insight into the nomenclature and resource links to further their research. It gives the reader a first hint at the extensive lexicon that has organically materialised around us and its little cousin the “TLA*”. *Three Letter Acronym.

DRUG DEVELOPMENT LIFE CYCLE

In order to best answer the question, “What is the healthcare industry?”, one good place to start is to answer, “What do we do?”. The we isn’t trivial to define in this derivative question but we shall explore that from many angles later on in the article. As an industry, we invent and manufacture products that aid in the diagnosis, treatment, and prevention of disease, illness, injury, and other physical and mental impairments in humans. The scope and magnitude of this endeavour is quite humbling. Many people that work in this industry are passionate and driven to improve humanity’s health and quality of life.

Figure 1: The Drug Development Lifecycle



The full spectrum of activities is displayed in the simple figure above. The size of each coloured box is arbitrary but aims to indicate a proportional magnitude of duration. It would be impossible to represent this accurately due to the range of variables that impact the duration but it gives an indication.

DISCOVERY

In terms of manpower, Discovery is the least intensive and to many professionals working in the later stages of this spectrum, is probably the most enigmatic. Many of the compounds that are marketed today

were the product of serendipitous discovery, such as the story of Alexander Fleming's discovery of penicillin or Albert Hofmann's discovery of the properties of LSD. Some products have been the progression from traditional remedies or isolation of their active ingredients, such as willow bark. It is widely reported that Hippocrates (460BC – 370BC) documented a powder made from willow bark as a remedy for headaches, pains and fevers. In the mid to late 19th century chemists synthesised an active ingredient called acetylsalicylic acid, then from 1899, Bayer AG marketed a drug called Aspirin made largely from this ingredient. In modern times discovery has been about understanding how disease and infection are controlled at a molecular and physiological level. The process of drug discovery, the identification and selection of candidate-remedies, still starts with exploration but today this is more likely to be in a computer model or laboratory rather than the rainforest.

PRE CLINICAL

A compound that surfaces from the drug discovery process is referred to as a New Chemical Entity (NCE). A corollary of this in Biotechnology is the New Biological Entity (NBE). The function of this stage of research is to fully explore toxicity, pharmacokinetics (PK) and pharmacodynamics (PD) or metabolism of this candidate-remedy before it is introduced to man, the so called (FHD) first human dose.

***Aside:** Many aspects of drug development, and now devices development also, are focused on satisfying the regulatory requirements of drug licensing authorities. In different regions there are specific procedures that must be followed to overcome each hurdle. The initial requirement is to seek authority to subject a human being to your compound or device. Ultimately it is the authority to sell your finished product in a particular region. In recent years there has been a further requirement to establish that your pharmaceutical, medical technology, or biotech product has both Clinical Effectiveness as well as Cost Effectiveness in addition to the standard three requirements of Safety, Efficacy and Quality. This hurdle has been referred to as the "fourth hurdle". Clinical effectiveness refers to a product demonstrating a clinically relevant benefit over and above the currently available alternatives, including no treatment. Cost effectiveness asks simply, is the product good value for money? The role of the regulatory authorities is described later in this article and the impact of the various hurdles discussed. In addition to the regulatory hurdles, there is a further constraint, one that drives the business model and provides fuel to the discovery and development engines. Its clock usually starts ticking during the pre-clinical stage.*

THE PATENT "CLOCK"

International patent legislation protects the invention and intellectual property rights of an inventor for a limited period of time. Whilst patent legislation is the domain of each nation state, significant international harmonization of patent term across national laws was established during the 1990s. The implementation of the World Trade Organization's (WTO) Agreement, Trade-Related aspects of Intellectual Property Rights (TRIPs), provides that "The term of protection available [for patents] shall not end before the expiration of a period of twenty years counted from the filing date." This filing of a patent starts the clock ticking on a 20 years window before anyone can produce a copy of your product, in the Pharmaceutical Industry it would be a generic drug.

CLINICAL

The manpower involved in the Clinical Research phase of the Research and Development (R&D) functions at healthcare companies is probably the greatest investment of money and effort within any organisation in this industry. This section of research is compartmentalised into Phases. Each phase has its own purpose and is aligned with business and regulatory requirements. To make the explanation simpler the following narrative will concentrate on the case of a pharmaceutical compound. Biotechnology products and to a lesser extent medical devices have a direct analogy but with some specific but important differences.

Phase I is the FHD phase. The subjects to be studied are often healthy volunteers, where this is appropriate, and the purpose is to assess the safety, tolerability, PK and PD of a compound. These studies are usually held under strict conditions in a special unit and typically involve up to 20 or so subjects. Often there is only an indication of the potential efficacy.

Phase II studies are carried out once the initial safety has been confirmed and typically involve 20+ up to 2 or 3 hundred subjects. Their purpose is to establish clear evidence of efficacy under strict guidelines as documented in a study protocol. Often this will involve dose escalation studies. Some companies split this in to Phase IIa for dosing studies and Phase IIb for efficacy studies but this is not universally practiced.

Once there is evidence of efficacy under controlled conditions and there is no evidence of unwanted or unexpected side effects or toxicities the company can then plan to move into **Phase III**. There are many different designs of clinical study but the gold standard, usually adopted in Phase III, is the Randomized Controlled Trial. These studies are typically 300+ up to thousands of patients depending on the characteristics of the illness, disease or intervention under study. Their size, complexity and importance to the regulatory process draws the majority of effort in to this pre-submission phase. Whilst it is not specifically mandated at any of the regulatory agencies, it is common practice to provide evidence of safety and efficacy from two trials in a submission dossier. Following satisfactory completion of the Phase III trials, the trial results are combined into a large document containing a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details, and shelf life. This collection of information is the *regulatory submission* that is provided for review to the appropriate regulatory authority in the required market or country.

Historically this has been by printing reams of output and analysis into documents and transporting by lorry to the offices of the agency. Increasingly the agencies have been actively encouraging electronic submissions. The FDA established the Electronic Submissions Public Docket number 92-0251 to provide a permanent location for a list of the Agency units that are prepared to receive electronic submissions, as well as a list of the specific types of regulatory records that can be accepted in electronic format (62 FR 13467, March 20, 1997). It was reported¹ recently that 40% of INDs submitted (Investigational New Drug) to the FDA in 2010 are using eCTD format (electronic common technical document) compared with 2.3% in 2005. Being granted marketing approval represents the end of this phase and in commercial terms the beginning of the opportunity to generate a financial return for the company by now selling the product. The time from patent registration, through Phases I, II and III and then through the regulatory agencies review cycle can vary considerably. Despite the fact that agencies such as the FDA have quickened their review and approval of new medicines, clinical development is taking longer in many instances, due to the complex nature of the diseases for which the new therapeutics are being created. Previously, the average time for the FDA (the Center for Drug Evaluation and Research at the Food and Drug Administration in the US) to approve new drugs was reported² as reducing to 1.1 years during the 2005–2007 period, but longer average clinical phase time means that combined clinical and approval time is approximately 8 years.

Global statistics are difficult to discover and report, largely due to the variances between agencies and therapeutic areas and the political and commercial sensitivity. However, it is true to say that a significant portion of the patent 20 year window is consumed in the clinical research area. Following the establishment of safe and effective procedures and after discharging the regulatory requirements, the single greatest effort of this industry is directed towards any endeavour that would reduce this period of zero revenue. As a consequence, in addition to being a highly controlled and disciplined area to work, for software scientists it is also an area of significant innovation and research. Along with the underlying health improvement imperative, this then leads to a climate for a very worthwhile and rewarding career.

PHASE IV

Also called post-marketing surveillance, phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after the company achieves an authorisation to market. Often required by regulatory authorities PMS studies may be carried out by the sponsor company for many reasons. These include finding a new market for the drug or testing for interactions with other drugs, or on certain population groups who are unlikely to subject themselves to trials. Leading up to the marketing of a treatment, by definition there has been a limited exposure to the compound, possibly fewer than 1 or 2 thousand patients with only a few years of exposure. The safety surveillance area is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the phase I-III clinical trials. Harmful effects discovered by phase IV trials may result in a drug being no longer sold, or restricted to certain uses: recent examples involve cerivastatin (brand names Baycol and Lipobay), troglitazone (Rezulin) and rofecoxib (Vioxx). Due

to the high profile and negative impact of this type of failure, significant effort and research is currently being directed towards pharmacovigilance throughout the industry. An early detection of a signal that the safety profile may be compromised, is not only a huge benefit to the patients' exposure to risk being minimised but also a huge benefit to the sponsor company who can divert those vital research funds elsewhere.

THE CLINICAL TRIAL

Throughout the various phases of clinical research the primary tool is the clinical trial. In his book³, Pocock uses this definition of a clinical trial: "...any form of planned experiment which involves patients and is designed to elucidate the most appropriate treatment of future patients with a given medical condition." It is not easy to determine when clinical trials began. Signatures of a clinical trial, a control group, were present as early as Lind⁴, 1753 in *A treatise of the scurvy*. Whether or not this is the de facto earliest trial, it shows that the methods and practice have been evolving over many years. In May 1980 the Journal of Controlled Clinical Trials was launched by the Society for Clinical Trials, indicating that the clinical trial was now an established academic and commercial tool. However over the ensuing 30 years, continued research and recurrent use has created a proliferation of variants to the basic trial. Whilst there is an established methodology available and routinely deployed in the practice of clinical research, there is still significant scope for academic research and methodology development, providing an opportunity for both the practical minded and the inquisitive research minded alike to prosper in a challenging career.

DRUG REGULATION

One of the most influential elements on this industry is the Regulatory Environment. A comprehensive review can be found in Drug Benefits and Risks: International Textbook of Clinical Pharmacology by Rago & Santoso⁵. Since ancient times mankind has produced remedies to improve health in an unregulated environment, operating to the general principle of caveat emptor. There are various key milestones to the introduction of state mandated regulation. Perhaps the first in the modern era was in 1937 when over 100 people in the United States died of diethylene glycol poisoning following the use of a sulfanilamide elixir, which used the chemical as a solvent without any safety testing. This triggered the introduction of The Federal Food, Drug and Cosmetic Act with the premarket notification requirement for new drugs in 1938. Following this tragedy, a catastrophe on a greater scale has influenced the development of medicines regulation far more than any event in history, the thalidomide disaster. Thalidomide first went on sale in West Germany in 1956. Between 1958 and 1960 it was introduced in 46 different countries worldwide resulting in an estimated 10,000 babies being born with deformities.

The global impact of the disaster was broad ranging. In the UK the regulatory system was reengineered, a Committee on the Safety of Drugs (CSD) was started in 1963 followed by a voluntary adverse drug reaction reporting system (Yellow Card Scheme) in 1964. In the United States, The Drug Amendments Act of 1962 was passed by Congress requiring the FDA to approve all new drug applications (NDA) and, for the first time, demanded that a new drug should be proven to be effective and safe. The FDA was also given the authority to require compliance with current Good Manufacturing Practices (GMP), to officially register drug establishments and implement other requirements. The EEC Directive 65/65/EEC on the approximation of provisions laid down by law, regulation and administrative action relating to medicinal products was also introduced following the thalidomide disaster. In the EU, regulatory harmonisation across the common market was identified as an aim. Following the introduction of two Council Directives in 1975, a sequence of steps lead directly to establishing the European Medicines Evaluation Agency (EMA) in 1993 and re-establishing the CPMP (Committee on Proprietary Medicinal Products) as a 'new' CPMP to formulate the opinion of the Agency on questions relating to the submission of applications and granting marketing authorisations in accordance with the centralised procedure. Whilst Europe was working towards a centralised procedure for regulatory submissions, there was a growing global awareness of the need for wider harmonisation. The three main regions, Japan, EU and US had preliminary discussions in 1989 that led to the establishment in 1990 of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). ICH standards and guidelines continue to be the bedrock of compliant working practices throughout the industry.

THE INDUSTRY

There are many ways of categorising or defining the Health Research Industries. The largest proportion

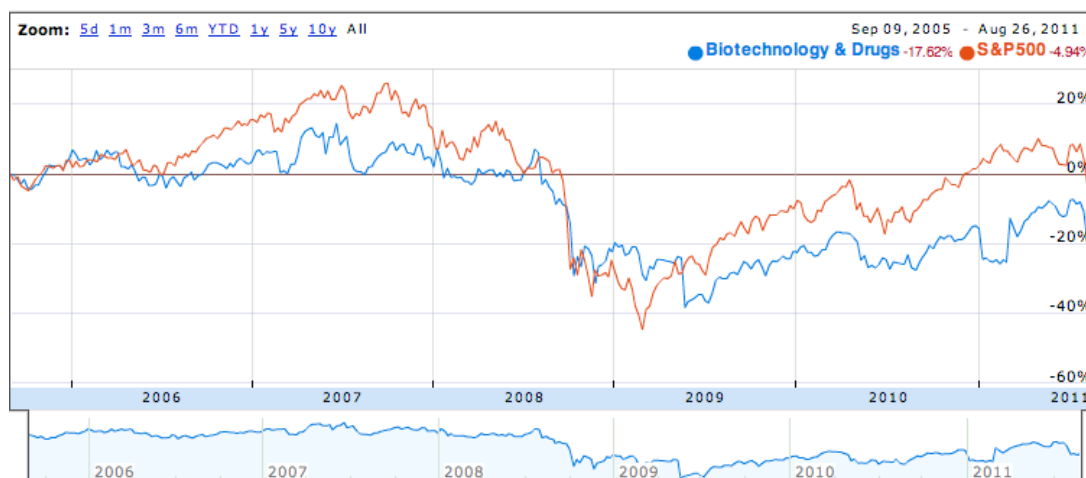
of this is the Pharmaceutical Industry. The OED defines pharmaceutical as “*a compound manufactured for use as a medicinal drug*”. The word drug is used for many substances that have a physiological effect on the body, so pharmaceutical is more precise than drug company. There are some adjunct industries that include, animal health, medical devices and biotechnology. The OED definition of biotechnology is “*the exploitation of biological processes for industrial and other purposes, especially the genetic manipulation of microorganisms for the production of antibiotics, hormones, etc..*”. Devices can be prosthetics, dressings, diagnostic tools etc. All of these companies, often referred to as sponsor companies, engage in the research and development of treatments for disease, physical impairment or illness, either drugs or devices or vaccines. The sponsor companies engage significant human resources in the pursuit of regulatory approval to market their products. Since the late 1980s an ever-increasing proportion of this work has been outsourced to Clinical Research Organisations (CROs). CROs provide additional staff and expertise to support the sponsor companies when they are deficient in either or both of these. For example, a sponsor company that has discovered, developed and marketed a treatment in the cardiovascular therapeutic area (TA) may engage the expertise of a CRO to aid in the research of a new compound that was in, say, the gastrointestinal TA. Alternatively, as a company scales up its R&D capability to cope with the growing resource requirements of each successive phase of research, it is often more desirable to outsource some studies. This in part will mitigate the risk to the company of a compound failure, being left with too many staff on their payroll. CROs can be better placed to be responsive to significant changes in demand for staff.

WORLD RANKING

According to the Forbes 2000 biggest companies⁶, when ranked by sales, Wal-Mart Stores is the largest company in the world. It has sales of \$421,800M and is reported to employ 2,100,000 staff. It beats oil and gas, insurance, banking and technology giants. The first pharmaceutical company appears at rank 93. Pfizer has sales of \$67,800M and employs 110,600 staff. In terms of sales that is 16% or approximately a sixth of Wal-Mart but in terms of staff it is 5% or around a twentieth. The largest Biotech company is at rank 533 in terms of sales. Amgen with sales of \$15,100M is 3.5% of Wal-mart and 22% of Pfizer. In terms of staff Amgen is less than 1% of Wal-mart and around 15% of Pfizer. The largest CRO is not as easy to report as the largest by many definitions is currently a private company. Quintiles has reported over 22,000 staff currently, with revenue (not sales) \$2,000M. Covance is the largest publicly traded CRO by reported sales \$2,108M with 10,528 employees. There are other CROs of this magnitude, for example PPD has reported 11,000 employees.

Figure 2 -Percentage Change in Stock Price of Biotechnology & Pharmaceutical Companies ⁷

[Healthcare > Biotechnology & Drugs](#)



The chart above shows the percentage change from the Q4 2005 stock price levels of the sector compared to the S&P 500 top performers. It gives an indication of the quality of the companies in this sector that they track very closely to the highest performers, at times out performing that list.

GLOBAL MARKET

Figure 3 - Global Pharmaceutical Market ⁸

ims Total Unaudited and Audited Global Pharmaceutical Market By Region

	2010			2009	2006-2010	2011 Forecast % Growth	2011-2015
	Mkt Size *US\$bn	Mkt Size **Const. US\$	% Growth **Const. US\$	% Growth **Const US\$	CAGR % **Const US\$	**Const US\$	CAGR % **Const US\$
Total unaudited and audited global market							
	\$856.4	\$874.6	4.1%	7.1%	6.2%	4 - 5%	3 - 6%
Total unaudited and audited global market by region							
North America	\$334.7	\$335.1	1.9%	5.4%	4.6%	2 - 3%	0 - 3%
Europe	\$245.3	\$253.2	2.4%	4.9%	5.6%	2 - 3%	2 - 5%
Asia/Africa/ Australia	\$126.5	\$129.7	14.0%	15.5%	14.5%	12 - 13%	11 - 14%
Japan	\$96.5	\$102.3	0.1%	7.6%	2.6%	5 - 6%	2 - 5%
Latin America	\$53.4	\$54.3	14.2%	10.3%	12.1%	11 - 12%	11 - 14%

Source: IMS Health Market Prognosis, March 2011

Notes on Numbers:

All forecasts are from IMS Market Prognosis International 2011-2015 which provides a view of the audited and unaudited market, using audited sales and adjusting for unaudited sales. The forecasts are based on the March 2011 Market Prognosis release; the next scheduled update is end of October 2011.

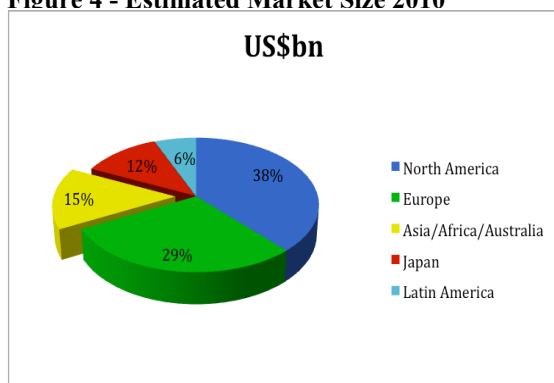
Includes IMS Audited and Unaudited markets

* US\$ uses actual quarterly exchange rates

** Constant \$ uses Q410 average exchange rates

The data from IMS⁸ presented in figure 3 is a representation of the global market as it stands today. An

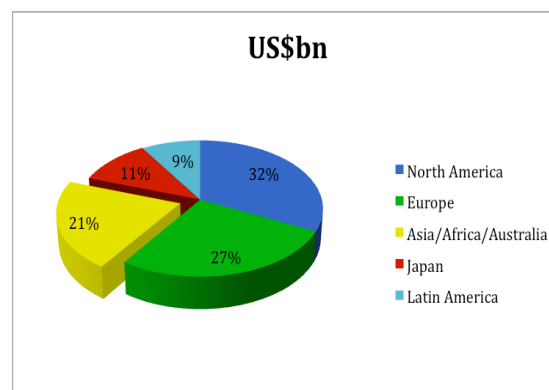
Figure 4 - Estimated Market Size 2010



estimated \$874.6bn was spent on Pharmaceuticals globally in 2010. Figure 4 shows the current proportions of each of the 5 major market categories. North America is still currently the largest market at 38%, with Europe not far behind with 29%. The most influential area of the modern industry has been China and India and their growth can be seen in the category Asia/Africa/Australia, currently 15% of the global market. Perhaps the most telling figure is the CAGR % figures. Using the mid point of this range for each category and projecting forward to 2015 the market could look quite different. The global spend will have reached around US\$1.1 trillion. The Asia/ Africa/Australia slice of the pie will have grown to around 21%. These figures are only a forecast and will be influenced by many unpredictable factors but they

give us a clue to one of the exigent influencing factors to pharmaceutical company strategy. A presence in China and India to research and develop western products for these rapidly growing new markets will be vital to the success of a global healthcare research organisation in the coming years. This is more significant than a manufacturing capability or a desire to employ low cost research and development staff. This tactic for maintaining costs has existed across many industries but the high levels of salary inflation in the East versus the very low current levels in the West suggest that this advantage will have evaporated before long. The advantage sought now is to engage in targeted research specifically to these markets. A natural result is that CROs must also grow in this region. Growth of indigenous CROs and the importing of western CROs is happening right now.

Figure 5 - Estimated Market Size 2015



This global presence and desire to collaborate on research within an organisation across many time zones provides our industry with some of its most exciting challenges. Globally available secure

databases and reporting environments are vital to maximise the productivity of these new firms that span the globe. Many people with a career in this industry enjoy the prospect of working closely with other cultures and can often travel to these locations to aid in the essential knowledge share required for a company to succeed.

THE CLINICAL DEVELOPMENT PROCESS

Figure 6 - Clinical Development Process⁹

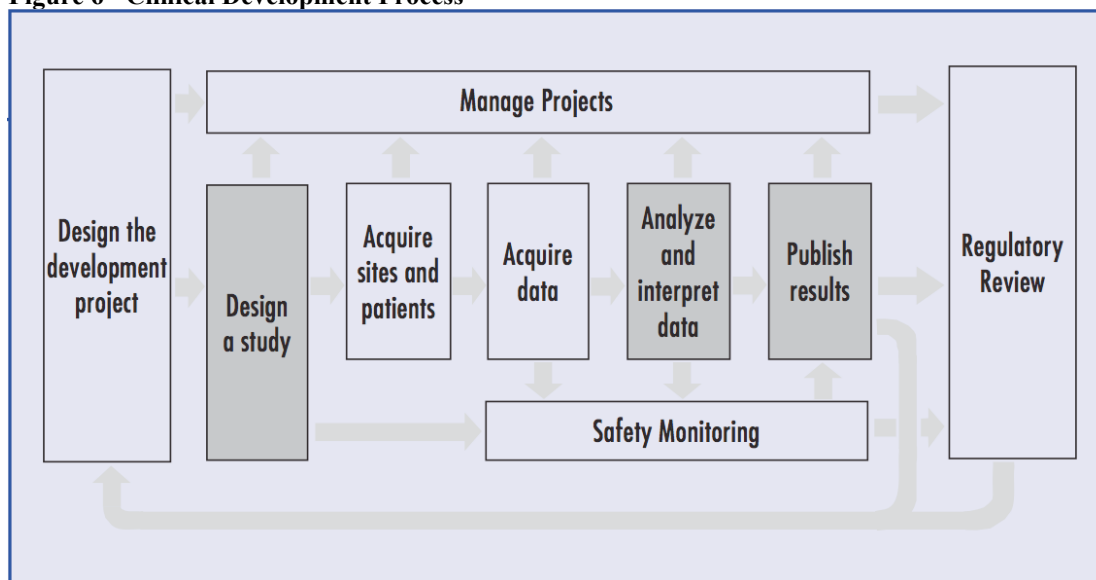


Figure 7 - Typical Organogram

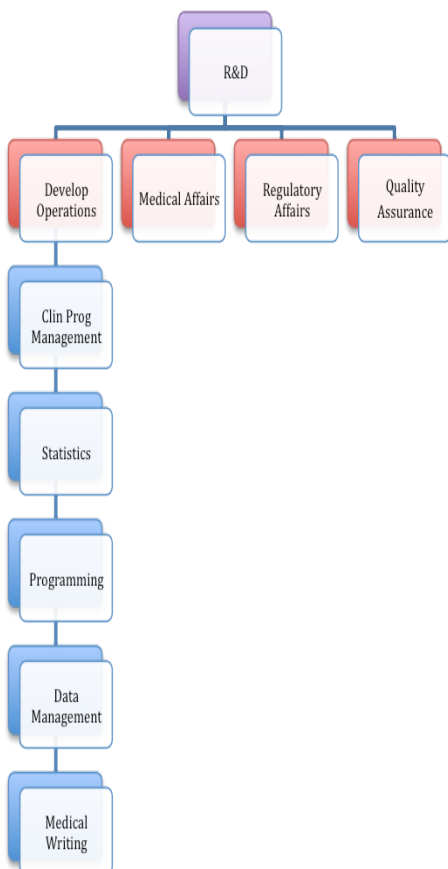


Figure 6 is a generic representation of the clinical development process. Each box either relies on data from prior processes or generates data that will be used later in the process. Necessarily, this requires integration of science, information technology, and statistical practice. Hopkins et al⁹ focus on the grey boxes in their article showing the areas that a Statistician is heavily involved with, indicating that managing the data pathway in clinical drug development should be a core competency among everyone involved with this process. Statisticians are just one profession, as with many jobs there are numerous names used by different companies, biometrician or analyst are two such alternatives for statistician. The profound changes happening in the ability to collect, store and process data are as overwhelming as they are an opportunity. The profession is balancing an awkward juxtaposition of traditional and established methodology and practice with voluminous and insightful data, this balance provides for a dynamic and exciting working environment as clinical researchers and analysts have to sift through the manifold new developments and applications and discern the real advances in the underlying cause.

Each company has its own particular structure and rather than try to reproduce a generic structure, figure7 represents a section of a typical organogram from a major organisation operating globally today. The diagram represents the departments in the R&D section of a mid-tier international pharmaceutical company, focusing

particularly in the departments that make up Development Operations, from Clinical Programme Management to Medical Writing. The number of different job titles that exist in these few distinct areas can be overwhelming. Each role plays a part in delivering one or many components of a number of clinical research deliverables or assets.

Figure 8 shows a table produced by Duke⁹ and represents one view of where certain functions get involved in the clinical research process. The table lists various job roles on the left axis. From clinical development through to study monitoring then on to data management, statistics and medical writing and then finally regulatory, these functions are shown. Throughout many of these functions the role of a programmer is essential. Programmer in some ways is a misnomer. The efficient collection, storage, manipulation and analysis and reporting of data is carried out in increasingly sophisticated software tools. This suite of tools is often referred to as the clinical reporting environment CRE. The CRE is a technologically advanced system that needs maintenance and development in its own right. The professionals that ordinarily assume this role are often referred to as programmers. The role can range from technical expertise where the programmer will support a specific software product to analytical expertise where the programmer will operate a particular software product to produce a desired output. This could be Oracle Clinical to validate or clean then store the clinical trial data or SAS to process the data and analyse the results of the trial amongst myriad other possible tasks.

Figure 8 – Clinical Research Assets by Role

Functional Roles	Protocol	CRF	Analysis Plan	Study Report	ISS, ISE, etc	Label	Re-Use
Clinical Dev	x	x	x	x	x	x	?
Monitoring	x	x		?			
Data Mgmt	x	x	?				
Statistics	x	x	x	x	x	x	x
Medical Writing	?			x	x	?	?
Regulatory	x	?	?	x	x	x	

The assets listed in figure 8 by Duke⁹ are some of the key deliverables in the clinical development process. Perhaps added to this list could be the database or more correctly the CRE. Each of these assets historically has had its own structure, say a list of visits for a trial, and that structure has had to be mapped or copied or transferred between systems. As the systems have developed they have all started including machine-readable mechanisms for sharing this sort of data. This data about data is called metadata. If one system is told that there are 5 visits and given a name for each, this data should be shared with all subsequent parts of the process, without the need for human intervention. In the utopian future, a protocol will be prepared with some key elements of it machine readable and selected from a defined subset of options and this standardized, machine-readable information will propagate throughout the entire CRE. To make this utopian idea a reality the industry will need to develop standards. Standard data structures, standard trial designs and standard reports. There has been considerable progress made with data standards, CDISC (<http://www.cdisc.org/>) have published a vision to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare. PhUSE (<http://www.phuse.eu/wiki.aspx>) have promoted a wiki for sharing and collaborating with the regulatory agencies with a view to establishing standard data transformations and reports amongst many other objectives. This is still a work-in-progress and will be a huge challenge for the brightest joining the profession today.

CONCLUSION

An established and disciplined industry with substantial investment in research and development and an urgent need to develop sophisticated and comprehensive global standards and practices, the industry is and will continue to be a worthwhile and rewarding place for a career. As an information scientist with an aptitude for software development or technical operations there will be many opportunities to develop new career skills. In fact with the increasing pace of change it is vital that all staff, newcomers and established professionals, must engage in continuous professional development. The requirement to attend conferences, training courses and scientific meetings is paramount to maintaining a professional credibility and we must encourage all societies and professional bodies to embrace their role in maintaining the competency of their members. The future for the industry will inevitably demand quicker access to data and information, the sooner that a safety signal can be detected and a programme halted or on a positive note, a successful product can be more quickly tested, submitted to the authorities and marketed, the better. This imperative will continue to drive innovation within the industry. The growing importance of India and China as markets in the own right will see a subtle change in our perspective. For too long many have perceived the East as simply a low-cost job market, as time passes and remuneration packages converge, we will increasingly see these regions as partners in the same development process. Partners that will need help to establish systems and standards that integrate with the extant systems and standards globally.

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