ISSN: 2755-9904

Journal of Clinical Images & Reports

SCIENTIFIC Research and Community

Research Article

Open Access

The Production of Drugs Must Correspond to the Intended Purpose

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ABSTRACT

The pharmaceutical industry maintains a high standard of quality assurance in the development, production and control of drugs. The procedure for issuing a manufacturing authorization for a medicinal product ensures the compliance of medicinal products with the applicable requirements in terms of safety, quality and efficacy, which are assessed by the competent institutions. The procedure for issuing a manufacturing authorization ensures that all medicinal products that have a manufacturing authorization are manufactured/imported by manufacturers who have a manufacturing authorization and who are regularly inspected by the competent institution, applying the principle of Quality Risk Management. A manufacturing license is required for all drug manufacturers.

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Received: March 14, 2022; **Accepted:** March 17, 2022; **Published:** March 25, 2022

Keywords: Drug, Drug Use, Manufacturing. Pharmacovigilance, Patent

Introduction

Pharmachemical manufacturing is that branch of fine chemical manufacturing that is directed to the manufacture of chemicals whose ultimate use will be in a final pharmaceutical dosage form, referred to as the active pharmaceutical ingredient (‘‘API’’) [1]. This industry segment has undergone very significant changes in much the same manner, but trailing, the pharmaceutical industry itself, from the time it emerged early in the 20th century.

The changes are themselves a result of major changes that have occurred both directly and indirectly, in and on, the industry. These changes include company consolidations, both backward and forward integration, the increased and changed role of quality, the significant intensification of regulatory bodies worldwide, the impact of the greatly increased potency of APIs, thereby reducing pharmachemical requirements and the broadening of the market worldwide.

Development

There is the promotion of deliberately overlapping the experimental development of the process with its design into a manufacturing plant [2]. Valuable as it is, however, this overlap is often not used as a powerful method in seeking the better process and a manufacturing plant to match, but is practiced ineffectively, strictly as a necessity of the time to-market imperative. Sometimes the jurisdictional divide at the development=design boundary is too deep; or there is an interdisciplinary gap, with chemists on one side and engineers on the other; or the process design becomes earnest too late to influence the development. Indeed, many scaleup difficulties cannot be identified or quantified soon enough without a sufficient process design effort that runs parallel and close to the development.

Then, there is the lessened character that the process design subdiscipline has developed as the result of many bulk drug projects being handled by design and construction firms, where the practice of process design can be unduly conservative, or too pliant to the client’s wishes, or so lacking in the bulk drug processing skills so as to offer nothing beyond what the client brings to the project, with the client’s errors or limitations dutifully incorporated into the design. In other projects, such as those that outsource manufacturing, the emphasis on process retrofit into existing plant is heavy and the process design, if any, is often beyond the grasp of the client. This harsh assessment is warranted by the penalties often paid, unknowingly at the time, because of the lack of the appropriate process design skills and practices in scaling up bulk drug processes, or simply by the absence of a mechanism to exploit the opportunities in deliberately overlapping process development and design.

Alas, chemical process design skills are hardly ever taught formally; the first and last academic exposure most engineering students have to the subject is a rather superficial and highly structured ‘‘process design’’ project at the undergraduate level. To make matters worse, computer software tools that can aid process design have usurped that undergraduate task, often reducing the student’s effort to little more than filling blanks in fairly rigid templates, some times with proposed operational designs that can be hilarious (e.g., a stirred tank for a Kolbe reaction loaded with 4000 kg of 2-in steel balls!) and usually missing the learning experience of manipulating design options at the conceptual level. Yet, sound process design is a requisite of good process performance in the manufacturing plant, and creative process design is practically indispensable in achieving superior processes and plants, as well as in exploiting advantageous chemistry that might be difficult to implement in the plant. Thus the wisdom of fostering the formal development of those skills and the development=design overlap in industrial practice; placing emphasis on the conceptual and unstructured aspects, as these are not addressed well by the current

computational aids that are widely used, and are less likely to be pursued aggressively by engineering design contractors.

Drug Use

A drug can be any sort of food (e.g. chocolate) that affects the way your body functions [3]. The concept of a drug is heavily influenced by the sociocultural context and the purpose of its use. The therapeutic use of a drug means a pharmacological preparation used in the prevention, diagnosis and treatment of an abnormal or pathological condition, whereas the non - therapeutic use of drugs commonly refers to the use of illegal or socially disapproved of substances. A drug, in the broadest sense, is a chemical substance that has an effect on bodily systems and behaviour. This includes a wide range of prescribed drugs, illegal drugs and socially accepted substances, and they can be either therapeutic or non - therapeutic, or both.

The terms problem drug user and problem drinker have been used to refer to those who are dependent on psychoactive substances. The definition of problem drug user focuses on the needs and problems of the individual in acknowledging that the problem drug user has social, psychological, physical and legal needs. The definition could be expanded to incorporate the spiritual needs of the problem drug user or problem drinker. In relation to problem drinkers, the same definition for problem drug use is applicable. However, a broader category of those at risk of harmful consequences includes: hazardous drinkers, harmful drinkers, moderately dependent drinkers and severely dependent drinkers.

Hazardous drinkers are drinking at levels over the sensible drinking limits, either in terms of regular excessive consumption or less frequent sessions of heavy drinking. In the UK, the Department of Health advises that men should not drink more than 3 – 4 units of alcohol per day, and women should drink no more than 2 – 3 units of alcohol per day. Harmful drinkers are usually drinking at levels above those recommended for sensible drinking, typically at higher levels than most hazardous drinkers and show clear evidence of some alcohol - related harm. Moderately dependent drinkers or 'chronic alcoholics' may recognise that they have a problem with drinking. Individuals who are severely dependent drinkers may have been heavy users over prolonged periods and have serious and long - standing problems – 'chronic alcoholism'. This group of drinkers may have complex needs such as coexisting psychiatric problems, learning disabilities, polydrug use or complicated assisted alcohol withdrawal.

Adhesion

Adhesion is an important attribute of material behavior in the pharmaceutical, biomedical, and dental fields that influences the interactions among different substances in the human body, and it is also important as it plays an important role in various processes, including, but not limited to, the manufacture of drugs, medical devices and dental care [4]. Adhesive bonding is an important area focusing on the creation of joined substrates and composite materials. Based on the wide variety of adhesive bonding situations, the concept of adhesion can be broadly applied across different material types and interactions. Mechanisms of adhesion fall into two broad areas: those that rely on mechanical interlocking or entanglement and those that rely on charge interactions. There are seven accepted theories of adhesion. These are: mechanical interlocking; electrostatic theory; adsorption (thermodynamic) or wetting theory; diffusion theory; chemical bonding theory; acid-base theory; and theory of weak boundary layers. In addition, elastomericbased adhesives exhibit a characteristic adhesion behavior described as tackiness or stickiness that aids in the creation of an almost instantaneous adhesive bond.

The biggest challenge is that the adhesion mechanisms will typically occur in or will be influenced by the environment of the human body. The primary challenges facing adhesion in the environment of the human body include: creation of an adhesive bond in contact with various bodily fluids, blood, saliva, etc.; durability of an adhesive bond when exposed to various bodily fluids; the biochemical onslaught related to the body's immune response and cellular regeneration; and exposure to inherent bodily microorganisms such as bacteria and fungi. Common examples of adhesion in the pharmaceutical, biomedical, and dental fields include the manufacture of respiratory inhalants such as albuterol; the application of medical bandages such as Band-aids used to cover wounds; and the use of denture adhesives to secure false teeth.

Oncology

Even as our understanding of the heterogeneity in cancer makes it ever more a part of the need for personalised treatment strategies, and as our computational tools begin to make this possible, a significant barrier to adoption is becoming apparent: the cost of personalised medicine in oncology is increasing [5]. There exists a profound conflict at the heart of precision oncology between the varied and contrasting priorities of the pharmaceutical industry, local and national governments, international medical community, and patients, which needs to be reviewed and balanced. Even as the stated aims of each stakeholder align, individual incentive sets around target patient populations, the need to increase revenues and offset inefficiencies and the need to personalise treatment plans must be aligned if precision oncology is to become truly widespread.

A potential avenue for improving the efficiency of drug development comes from considering manufacturing practices. The past two decades have seen a shift from small molecules to larger and more complicated biotherapies such as monoclonal antibodies. The manufacturing methods of biotherapies are considerably more complicated and expensive than traditional small molecule therapies, which could in part account for the increasing cost of the end product. However, the efficiency of manufacture of biopharmaceuticals has increased dramatically over the same period: with typical yields increasing from 1 to 2.5 g/l during the period 2001–2014. The complexity of manufacture also creates an additional barrier to entry for new drug manufacturers. There is a real concern that identical production process will not equate to identical products, this could protect against generic manufacturers entering the market as soon as the initial patient protection has lapsed. Indeed, regulators have introduced regulatory processes for so-called biosimilars much costlier and more involved than for generics for small molecules.

Bariatric Surgery Patients

Patients undergoing bariatric surgery are highly complex and require pharmacist input to ensure safety of medicines administration [6]. Pharmacy has an important role to play in the care and management of bariatric patients both pre- and postoperatively in view of anatomical changes that occur as a result of this type of surgery, which can affect the absorption and metabolism of medication.

A member of the pharmacy team should complete medicines reconciliation at preoperative assessment; regular medication should be reviewed, taking into consideration any modified anatomy that may result in altered absorption and bioavailability of medication. To aid the healing process and encourage drug absorption, the formulation of medication will require amendment

to sugar-free liquid preparations where possible, or crushing tablets/opening capsules for 6 –8 weeks postsurgery.

Postsurgery, the patient's stomach pouch capacity is reduced to approximately 50 –70 mL, which can cause problems when administering medication in a liquid form, as the patient will feel full. The altered anatomy also results in a change in pharmacokinetic and pharmacodynamic profiles of some medications; the patient will need close monitoring for symptoms of under- and overdosing. The patient should be clinically reviewed postoperatively and counselled prior to discharge, ensuring that the GP (general practitioner) is aware of all pharmaceutical issues, both long- and short-term.

Bariatric surgery is a costly intervention; however, weight loss may improve comorbidities such as diabetes or hypertension, resulting in reduced polypharmacy and medication costs. Liquid preparations may need to be sourced from 'specials' manufacturers; this can be expensive, but these are not required long-term, and should be reviewed at the 6 –8-week follow-up.

Pharmacovigilance

Pharmacovigilance consists of the continual collection, review and analysis of adverse reactions (ADRs) to a medicinal product [7]. Thls involves the spontaneous reports received by a pharmaceutical company from doctors, healthcare workers and patients and also may involve formal studies of a medlcines adverse reactions. ADRs are notoriously under reported by healthcare workers and hence pharmacovigilance studies may be necessary.

Pharmacovigilance studies are sometimes classified as phase 4 trials, but are more appropriately called post-marketing surveillance studies. These are non-interventional and essentially observational with the aim of gathering more safety data about the newly licenced medicine. Various techniques can be used to gather such data such as cohort studies, case-control studies and computerised data bases which link prescriptions to ADRs. On average when a new medicine is licenced about 1500-3000 humans will have been exposed to it. If a particular adverse reaction to ths new medicine only occurs in 1 in 5000 patients, then it is obvious that the pre-licencing data has little chance of detecting this. Hence pharmacovigilance is only beginning when a medicine reaches the market.

There are well known examples of medicines whch were withdrawn from the market place when previously unknown adverse reactions became apparent. It is in the best interests of any company that they should learn of any safety issues as soon as possible so they may react accordingly. For example it may be discovered that the product interacts with another medicine or that the dose needs to be carefully monitored in a certain group of patients (the elderly, those with liver failure etc.). The company will want to protect patients from any harm, will want to further investigate the problem and will want to issue any warnings that are appropriate.

Pharmaceutical Companies

Pharmaceutical companies face daunting stock market expectations, short-term operating pressures on earnings, and increased regulatory requirements [8]. As a result, pharmaceutical firms need to adjust their strategy in various ways. E.g., they turn to mergers and acquisitions in order to plug strategic holes and accelerate operational improvements, they enter into strategic alliances, and they focus their activities on specific core areas. Hence, the future success will require pharmaceutical firms to develop new capabilities on many fronts. First, they have to dedicate resources in order to stay informed of technology developments and integrate the most promising technologies and (gene) therapies in-house. Second, the efficient storage and effective retrieval of the vast quantities of data provided by the new technologies have to be assured. Third, pharma companies will have to hire the right talent for each specific task and pay attention that they effectively work together. Fourth, development and marketing must continuously be informed over the advances in research and discovery, because they have to create targeted products for smaller subpopulations of diseases. Fifth, pharmaceutical companies will have to create more effective tools for portfolio selection and management.

Looking at the firm level, one needs to consider some additional trends and developments. From a competitive perspective, biotechnology challenges the historical bases of competition (blockbuster drugs, vertical integration, role as supplier) in the pharmaceutical industry. Knowledge and technology are not only transforming drug discovery, they are also redefining the business structure of the pharmaceutical industry. Many new players focus on narrow elements of the pharmaceutical business, from clinical trials to specialty manufacturing to genomic databases and screening capability. This trend is called deconstruction of the value chain leading to increased outsourcing activities. Consumers are gaining more and more access to information and establishing greater control over decisions about their care. Accelerating progress in genetic understanding creates the possibility for pharmaceutical firms to segment patients on the basis of genomic descriptors and tailor therapy according to their specific needs. As a result pharmaceutical firms need to become more consumer-centric.

Industry

The pharmaceutical industry has traditionally been a conservative sector, researching and developing preferentially small-molecule drugs intrinsically featuring (1) stability, (2) adequate potency for therapeutic purposes, and (3) acceptable toxicity for the vast majority of the consumers [9]. Among the most powerful approaches in pharmaceutical R&D (research and development) is the systematic chemical screening of molecular variants in combinatorial libraries, with the aim to provide novel molecules with positive features to be exploited in healthcare. However, this approach alone is becoming insufficient in providing novel pharmaceutics to the increasingly demanding healthcare industry.

A number of causes can be identified for the limited success of this approach in the R&D of new pharmaceuticals. First, small-molecule drugs, for example, simple molecules easily obtained by chemical synthesis such as penicillin-derived beta-lactam antibiotics, have been largely investigated already for synthetic alternatives, leaving only a few and often problematic new candidates for future development. Further, very stable and potent molecules are already on the market for many therapeutic areas, producing a hard-to-surpass benchmark for new molecules. Next, the ever-harder path through clinical studies and aggressive competition from generic companies make the development of novel molecules less profitable in the absence of defensible product protection strategies, with the exception of a few specific applications or rare-disease niches.

Costs

One of the great ethical problems of the twenty-first century is the challenge presented by new drug control and distribution systems [10]. Pharmaceuticals are becoming increasingly expensive. As the cost of health care rises society will develop ever more sophisticated

strategies for containing costs. These will certainly involve efforts to eliminate or control the use of pharmaceuticals that are not cost-effective. Some drugs currently in use can be eliminated if they can be shown to be ineffective for the patient's condition. That should raise few ethical problems. The controversies will arise when health system planners discover that sometimes a very expensive drug is only slightly better than a much cheaper drug. A newly approved agent intended to reduce repeat heart attacks and costing a thousand dollars per patient might, for example, show a success rate that is only a tiny bit better than an older agent costing hundreds of dollars. Even claiming that a new drug is "a tiny bit better" is hard to say with certainty, as there are few head-to-head trials. Most clinical trials of new drugs are versus a placebo. A trade name pharmaceutical preferred by a clinician only because she is more confi dent in the manufacturer costs, on average, four times the generic equivalent that meets all current standards. A continuous-release hypnotic that is chemically identical to the shorter-acting agent that has been on the market much longer may cost many times more. Systems managers will realize that the savings obtained by limiting clinicians to the cheaper options can do much more good for patients than permitting indiscriminate use of the more costly alternatives. Pharmacists increasingly find themselves on the committees that will set the standards for formularies used by health system pharmacies and insurers responsible for paying for the cost of pharmaceuticals.

Patent

A patent is a private property right granted by the government that gives exclusivity of limited scope and for a limited period of time to inventors for their disclosure of an invention that has met the government's patentability requirements [11]. If an inventor wishes to obtain exclusivity in several countries, then he or she must obtain a patent in each country and satisfy each country's patentability requirements. Our discussion will be focused on US patents. A patent may be granted to anyone who invents any new, useful and non-obvious process or method, machine, article of manufacture or composition of matter. Compositions of matter include chemical compounds, pharmaceutical formulations and purified natural products such as proteins or genes. The patent must conclude with claims that define, in technico-legal words, the scope of the protection conferred by the patent, or the protection sought in a patent application. Similar to the language in a deed for land, the claims set out the 'metes and bounds' of the intellectual property protected by the patent. For example, a patent could be issued with claims on a method of diagnosing disease X, or a composition of matter for use in such a method.

Patents have been and continue to be granted on isolated and purified products of nature, including isolated human genes or portions of genes that encode proteins or peptides. Patents are also granted on methods of using such genes or their information for diagnosing, preventing or treating diseases.

The goal behind granting exclusionary patent rights to an inventor of a test is to protect the time and money that an individual or company may have to put into its commercial development. This guarantees that only the applicant of the patent has the opportunity to produce and market the test for the limited term of the patent. Exclusivity is seen as essential to encourage investment in and development of new services and products, especially of risky inventions in the health sciences.

Conflict of Interest

Several factors in the development and marketing of drugs result in conflicts of interest [12]. Use of pharmaceutical industry funding to support FDA approval processes raises the possibility of conflicts of interest within the FDA. Supporters of this policy point out that chronic FDA underfunding by the government allows for few alternatives. Another important source of conflicts of interest is the dependence of the FDA on outside panels of experts who are recruited from the scientific and clinical community to advise the government agency on questions regarding drug approval or withdrawal. Such experts are often recipients of grants from the companies producing the drugs in question. The need for favorable data in the new drug application leads to phase 2 and 3 trials in which the new agent is compared only to placebo, not to older, effective drugs. As a result, data regarding the efficacy and toxicity of the new drug relative to a known effective agent may not be available when the new drug is first marketed.

Manufacturers promoting a new agent may pay physicians to use it in preference to older drugs with which they are more familiar. Manufacturers sponsor small and often poorly designed clinical studies after marketing approval and aid in the publication of favorable results but may retard publication of unfavorable results. The need for physicians to meet continuing medical education (CME) requirements in order to maintain their licenses encourages manufacturers to sponsor conferences and courses, often in highly attractive vacation sites, and new drugs are often featured in such courses. Finally, the common practice of distributing free samples of new drugs to practicing physicians has both positive and negative effects. The samples allow physicians to try out new drugs without incurring any cost to the patient. On the other hand, new drugs are usually much more expensive than older agents, and when the free samples run out, the patient (or insurance carrier) may be forced to pay much more for treatment than if the older, cheaper, and possibly equally effective drug were used. Finally, when the patent for a drug is nearing expiration, the patent-holding manufacturer may try to extend its exclusive marketing status by paying generic manufacturers to not introduce a generic version ("pay to delay").

Conclusion

The holder of a medicinal product manufacturing authorization must perform the production in such a way as to ensure that the medicinal products meet the intended purpose, the requirements of the manufacturing authorization or the clinical trial authorization and do not pose a risk to patient health in terms of safety, quality and efficacy. The top management of the company is responsible for meeting all quality requirements, and staff from different organizational units and different levels of responsibility, as well as all suppliers and distributors who cooperate with the drug manufacturer, actively participate in their implementation. In order for quality requirements to be met, there must be a comprehensively planned and implemented Pharmaceutical Quality System that includes Good Manufacturing Practice and Quality Risk Management. The pharmaceutical quality system should be fully documented and its effectiveness monitored regularly. All segments of the Pharmaceutical Quality System should have appropriate, competent staff, appropriate and sufficient space and equipment.

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