WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Identification of the Competency Requirements of the People who are Involved in Development and Manufacturing of the Products Similar to Pharmaceutical or Chemical Products for Utilisation in the Medical Devices

Sandip N Kulkarni, Prasad Dongarkar, Nitin Kumar S. More

Global Technology Center & Technical Director and Astute Labs Pvt Ltd , Pune, Maharashtra, India

A B S T R A C T

The pharmaceutical industry is distinguished by its structure and design, all unusually well known, but which have an effect on the method of introducing new pharmaceuticals to the patient. The creation of a new medication is very time-consuming, very complex and high risk, with no chance of success. The research and development process and all its challenges, including environmental challenges, are identified. The market realities and limitations, along with its existing challenges are addressed and some potential trade and technological advances in the business, including the development of a greener pharmacy, are discussed.

Keywords: Pharmacy, Industry, Health, Human, Research

1. Introduction

A variety of peculiar aspects in the pharmaceutical industry are somewhat different from those that people usually think of as businesses. It's also an industry full of inconsistencies, for instance, in view of the unquestionable reality that for over a hundred years the industry has contributed greatly to human well being and the elimination of ill health and misery, public perception polls are always routinely listed as one of the lowest-confidence sectors, frequently unfavorably contrasted with nuclear industry. It is definitely one of the riskiest companies to spend money, however the market perceives it to be overly profitable. The main pharmaceutical firms rightly advertise themselves as science-based organizations, but most people agree that they invest more on marketing than research 1.2 In terms of the known dangers and costs involved with pharmaceutical growth, many people still feel that pharmaceuticals need to be created in order to satisfy all human needs.

The purpose of this opening chapter is to understand how the industry operates and to clarify some of its inconsistencies. The goal is to provide the company with a context to better appreciate the complexities of the problem of pharmaceuticals in the environment.

* *Corresponding author.*
E-mail address: mail2sandipk@gmail.com

Notice that the terms "medicine," "pharmaceutical" and "drug" often use interchangeably and, depending on the meaning, the term "drugs" can often mean the medicine as well as the controlled substance. This section randomly applies the label "pharmaceutical" to end products used by consumers in the pharmaceutical industry. The term 'drug' is primarily used for future prescription products as the market is developing

2. Methods

The following directories have been searched: WHO, FDA, ICH, and EU to import their corresponding instructions. The Google search engine has downloaded a variety of papers and posts. The terms used were: medicinal quality, pharmaceutical quality and business. Articles not of an academic type have been dismissed (for example, those that did not provide reference citations).

The final sample consisted of 102 papers, 56 directly related to the safety of pharmaceuticals and 46 to general quality practices.

In the papers reviewed in this literature review two research subjects may be listed.

Including:

- Prescription consistency standards.
- Recently applied general practices in the pharmacy industry.

The authors synthesize the key conclusions and recommend further analysis on any of these research topics.

2.1. Research theme 1: guidelines of the pharmaceutical quality

The most important guidelines that are widely applied in the pharmaceutical industry are**:**

2.1.1. WHO guidelines

WHO has published a handbook on the GMP in particular, entitled: Quality assurance of pharmaceuticals, a compendium of guidelines and related materials, Volume 2: good manufacturing practices and inspection (Quality Assurance of Pharmaceuticals, 2004).

It consists of 4 chapters:

Chapter 1: WHO GMP: main principles for pharmaceutical products.

Chapter 2: Good manufacturing practices: starting materials.

Chapter 3: Good manufacturing practices: specific pharmaceutical products.

Chapter 4: Inspection.

2.1.2. FDA guidelines

Pharmaceutical companies have just begun to grasp and apply the 21st-century FDA cGMPs: a risk-based approach; the initiative identifies immediate, near and long-term phases which FDA expects will take two years to enforce (Larson 2004).

On the scientific side, the FDA outlines three principles that will drive the reevaluation process: innovations in the area of risk control, advancement in quality management, and progress in pharmaceutical and industrial research (Larson, 2004).

The most important guidelines are 21 CFR Part 210, 2005, 21CFR Part 211, 2005.

21CFR Part 210: The Legislation provides for the minimum existing good practices of the manufacturing, packaging, packing or storing of a drug for use of the facilities or controls to ensure that such products satisfy the safety standards of the law and have the identification and strength, as well as the purity and purety characteristics reported to have.

21CFR Part 211: The rules in this section include the minimum existing good production practice for the preparation of pharmaceutical products for human or animal administration.

The FDA has concluded that current quality mechanisms and product expertise can accommodate different forms of modifications of structures, facilities and processes without needing any regulatory submission. (Fraser, 2005).

2.1.3. EU guidelines

The central EU medicinal law is compiled in Volume 1 and Volume 5 of the publication: 'Rules on medicines in the European Union.'

- Volume 1 – EU drug regulation on human pharmaceutical products.
- Volume 5 – EU pharmacy regulations on veterinary medical products.
- A set of recommendations also published in the following volumes of "Rules governing medicinal products in the European Union" follows the basic legislation:
- Volume 2 – Alert to claimants and pharmaceutical goods for human use regulatory guidance.

- Volume 3 – Clinical recommendations for human medical products.
- Volume 4 – Recommendations for safe medical product production standards for human and veterinary uses.
- Volume 6 – Applicants' warning and administrative requirements for veterinary pharmaceutical products.
- Volume 7 – Clinical Recommendations for veterinary medical products.
- Volume 8 – Full residue limitations.
- Volume 9 – Recommendations for pharmacovigilance of human and veterinary medical products.
- Volume 10 – Clinical Trial Recommendations.

2.1.4. ICH guidelines

A special project is being coordinated by regulatory authorities in Europe, Japan and the United States and experts from the pharmaceutical industry in three separate regions to address scientific and technological aspects of product registration. The International Conference on Harmonization of Technical Requirement for Registration of Phardactics for Human Use (ICH)

It seeks to allow more effective use of human, animal and material resources and to eliminate any delays not vital to the global production and availability of new drugs while safeguarding efficiency, protection and effectiveness, as well as regulatory public health obligations.

2.2. Research theme 2: general practices recently applied in the pharmaceutical industry

2.2.1. Quality risk management

All products and processes have an inherent risk element (Griffith, 2004).

A clear definition of the considered "risk" should be agreed in an organization that intends to apply an effective approach to quality risk management, because of too many players and their respective diverse interests in the pharmaceutical industry (ICH Q9, 2003).

The FDA has realized that its procedures and processes must be reorganized to combine risk management (RMP) programs within and within the industries it regulates. The FDA has therefore begun to publish position papers and guidelines on what it expects to see in an RMP (Griffith, 2004).

Risk management plans to identify risks should be used (Griffith 2004).

Quality Risk Management is defined as a method for evaluating, controling, communicating and examining the risks to drug quality via the product lifecycle, when decisions can be taken at all points in the procedure (ICH Q9, 2003).

The Medical Device Use-Safety Guideline clarifies how hazards related to medical devices should be targeted during device development as part of risk management processes. Human factors are included in the risk management guideline (CDRH, 2000).

2.2.2. Quality by design

The design space of ICH Q8 is characterized by the principle that consistency is not tested by product but must be constructed to integrate it (ICH Q8, 2005–2008).

Centered on ICH Q8, which deals with pharmaceutical creation with quality design in materials, formulations and production processes in order to achieve the expected product output. Applicants present their construction spaces and are subject to regulatory review and approval (ICH Q8, 2005–2008).

In these cases, more versatile regulatory approaches can be established.

The nature and execution of studies on pharmaceutical production should be consistent with their scientific goal (ICH Q8, 2005–2008).

2.2.3. Corrective action and preventive actions

In order to identify patterns or trends, QMS non-conformities and other machine faults like legal non-compliance should be examined. Trends should be identified to help the producer predict and avoid potential issues (EPA, 2009).

The organisation should concentrate on problem correction and avoidance. Preventing issues is normally easier than repairing them. The company should still consider issues as ways to change (EPA, 2009).

"Root cause analysis" is a mechanism by which the producer may determine the triggers and preventive steps (EPA, 2009).

CAPA researchers typically propose that root cause research take a four-step procedure (Bartholomew, 2006):

Define problem. Identify problem.

- •Evaluate its magnitude, including risk management.
- •Study and delegate responsibility.
- •Analyze the root cause of the issue and record it.

For example, Alcon Laboratories Inc. had been helped by a new corrective action tracking system to unite its many corrective and preventive action systems worldwide, which leads to quicker closures on corrective actions, much greater access and speed of information, and ultimate focus on quality professionals is being given (Davis, 2003).

2.2.4. Process capability analysis

Method capacity is a contrast of the "Customer's Voice" (VOC) with the "Process Voice" (VOP). VOC is based on customer expectations and is specified by set process parameters, while VOP is defined by control limits based on output data and which are changing over time (Tarpley, 2004).Metrics such as Cp and Cpk power index were established several years ago to measure this comparison between control and specification limits (Tarpley, 2004).

The power index compares the distribution to tolerance spread of the mechanism and results in a single number. It is a management framework for comparing process output (Ruth II, 2005).

2.2.5. Six Sigma

Harry and Schroeder (2000) describe Six Sigma as "...a business process which allows companies to radically improve profits by streamlining transactions, improving quality and eliminating defects and mistakes in all that a company does..." (Harry and Schroeder, 2000; Johnson and Swisher, 2003; Pande et al., 2000; Williams 2003; Goeke and Offodile, 2005) Six Sigma ventures are based on the model DMAIC (Stamatis, 2002).

The DMAIC model is the generic six-sigma model. It is an acronym for describing, evaluating, assessing, enhancing and regulating. Often this model is recognised as an aspect of understanding of the model. Each part tackles another element of the overall strategy for change and breakthrough (Stamatis, 2002). The sigma range in the pharmaceutical industry is from 2 to 3; this results in 25 to 35% defects (Hussain, 2005).

AstraZeneca is an example of pharmaceutical organizations that have implemented the Six Sigma approach, with processes and quality workers trained to incorporate DMAIC concepts every day in order to assess and enhance efficiency through cross-functional "continuous improvements" (CI) teams (Shanley, 2005). Two years ago, cross-functional CI teams in Westborough, Massachusetts, adopted DMAIC concepts to overcome a significant capability issue for a core commodity. The teams noticed inefficient systems and installed 20 million additional units of capacity annually. As capital spending under 100,000 dollars resulted in 60 million dollars to 70 million dollars in sales gains, without adding new people as Ron Matthews, the company's vice president of development and supply chain, reported (Shanley, 2005).

2.2.6. Process analytical technologies

Process analytical technology (PAT); is essential to facilitating the "quality by design" and technical element of development. The main goal of PAT is to consider and to monitor the development process by applying integrated methods of chemical, physical, microbiological, statistical and risk assessments. PAT has long been used in non-pharmaceutical sectors, which helps in cost savings and production efficiency (Fraser, 2005).

Process analysis technology (PAT) deployment offers a number of advantages and enhancements to certain pharmaceutical systems. The advantages include shorter manufacturing cycle times, higher production performance, decreased rejections and improved production running time (Rockwell Automation, 2004).

A number of effective PAT-based comparability protocol submissions have been submitted in the pharmaceutical industry, range from single unit operation implementations at GlaxoSmithKline to a further application at Sanofi-Aventis involving all drug substances and drug products (Shanley, 2005).

2.2.7. Lean manufacturing

After the Second World War, Japanese factories rebuilt faced dwindling human, material and financial capital. This lead to the emergence of new, cheaper production processes. The early Japanese founders, such as Eiji Toyoda Toyote Motor Company, Taiichi Ohno and Shingeo Shingo, created a structured, process-focused method of development, which is now known as the 'Toyota Production System,' or lean production system (Womack et al., 1990).

Lean output is about eliminating duplication in a whole organization and reflecting on the larger picture by learning how to do something for fewer (Nystuen, 2002).

Lean involves first placing the best items in the right place while eliminating waste and being able to adapt. This results in less expense, less design time, less company levels and less vendors with more staff resources, more flexibility and capacity, better competitiveness, greater consumer loyalty and, without a doubt, more economic performance in the long run. Lean values today in the workplace will decide future company survival (Nave, 2002).

In 2002 the organization initiated a limited initiative at its global plants, Pull Manufacturing in AstraZeneca; this initiative mandated the manufacturing teams of AstraZeneca shift their emphasis from production to customer alignment and operation. The initiative further lowered the cycle time. In one example, lead times for a main 1,5-million dollar medication per year were shortened by 25% over an era where demand for the drug was raised by 30% (Shanley, 2005)

2.2.8. Total quality management

Total quality management (TQM) is not a methodology but a philosophy. It is a theory that emphasizes a systemic, integrated and clear perspective, including everyone in the organisation (Isaac et al., 2004).

TqM is a management philosophy which establishes a customer-driven learning institution committed to customer satisfaction by continually improving the organization's performance and efficiency and the processes associated with it (Corrigan, 1995).

TQM is widely recognised for improving the efficiency and other results of organizations of different kinds, such as production, benefit, market share and competitive edge (Sun, 2000; Isaac et al., 2004).

2.2.9. ISO series

Series ISO 9000: ISO 9000 is for quality control. This ensures that the corporation enhances customer loyalty and consistently improves efficiency by compliance with customer and regulatory requirements (ISO 9000 and 14001 in brief, 2009).

ISO 14000: ISO 14000 is an environmental management system which defines the specifications of an environmental management system and can be used to certify/register and/or to self-declarate an environmental management system of an entity (ISO 14001, 2004).

This is what the company is doing (ISO 9000 and 14001 briefly, 2009):

- •Minimize adverse impacts of the actions on the climate.
- •Make the environmental efficiency continually improved.

ISO 17025: It contains the general research and calibration laboratory expertise criteria (ISO/IEC 17025 2005).

A particular version of this standard was developed for medical laboratories; ISO 15189:2003 and then ISO 15189, 2007 were issued on 19 April 2007 (ISO 15189, 2007).

The research laboratory reaches the status of an autonomous entity through the accreditation process (Mettler-Toledo GmbH, 2003).

2.2.10. HACCP

The hazard analysis and critical control point approach (HACCP) is recognized as a food industry safety management scheme. Their main objective is to prevent and reduce known dangers in certain areas of the food chain (Annex 7; WHO TRS No. 908, 2003).

Procedures, like GMP, discuss and provide the basis for HACCP operating requirements. HACCP is a systematic method for identifying, evaluating and controlling hazards in safety. The dangers are classified as biological, chemical, or physical agents or operations that may, unless controlled, cause disease or injury. This includes the production of certain antibiotics, hormones, cytotoxic substances or other highly active drugs in the manufacture of pharmaceuticals. Granulation is an example of hazardous unit operations, together with operations such as fluid bed drying. The use of flammable solvents (solutions) and some laboratory operations can also lead to dangers (Annex 7; WHO TRS No. 908, 2003).

Seven principles form the basis of the HACCP system (Annex 7; WHO TRS No. 908, 2003):

- •Drive a risk study.
- • Evaluate the points of vital control (CCPs).
- •Set critical cap and goal levels (s).
- •Establish a CCP tracking scheme.
- •Establish the corrective measures to be taken when the surveillance shows that a specific CCP is not under control.
- •Set up procedures to verify the effectiveness of the HACCP system.
- •Establish history of all processes and preserve documents suitable for and execution of those standards.

3. Environmental Impact

The environmental effect of the pharmaceutical industry was widely viewed as negligible until the late 1990s. Any environmental impacts were known to occur only from processing plants and, since they were comparatively minor with well regulated pollution, environmental impacts were not seen as a concern. The pharmaceutical drugs themselves were appreciated as biologically active, but due to the limited volume produced and high processing costs, escapes of the active substance from manufacture to the atmosphere were assumed to be very small.

However, the discovery in the surface waters of pharmaceutical residues after 1994 led to a revision of this opinion. While Richardson and Bowron had expected pharmaceutical residues in surface waters in the mid-80s,29 this time was not for another decade until the residues began to be systematically assessed following the 1994 discovery by Stan and his colleagues of clofibric acid in German rivers. 30 Residues have now been identified in land, estuarine and coastal waters and rivers. Low pharmaceutical concentrations of surface water are now considered omnipresent, but seldom find >0.1 μg l−1 and frequently <0.01 μg l−1.31 waste water concentrations are normally in the range of μg l-1 although in certain situations substantially higher values.

We now know that pharmaceutics will reach the atmosphere in three ways: by effluents emitted from plants, the recycling of discarded and obsolete medicinal goods and by excretion from patients under care. Detailed quantification is difficult for specific pharmaceutical uses, but there is general agreement that the second source dominates over the global environmental inputs, with comparatively limited contribution to effluent discharges and the disposal of non-utilized drugs36,37.

Many researchers, states, governing authorities and the industry who have analyzed reported research have come to the conclusion that there seems to be no significant impact on acute marine activity as a result of medicinal compounds in the atmosphere 38. However, the evaluation of future chronic

consequences in order to improve these tests continues. This does not suggest that all pharmaceuticals are benevolent in their environmental effects. The damaging effect of diclofenac on Asian vulture39 and the role of EE2 in fish feminisation40 demonstrate that this is not the case. However, pharmaceuticals should not be regarded as a consistent category of substances on a case-by-case basis according to their individual properties.

One field of interest is those hormones since they are theoretically a class of compounds which have detectable effects at concentrations of environmental significance. When evidence accumulates, however, it becomes apparent that not all hormonally active drugs have identical characteristics and this reinforces the opinion that such medications must be investigated on a case by case basis rather than as a single class. Scientific understanding of the possible long-term environmental impact of pharmaceuticals on plants and animals is only in its early stages and is an area of intensive study.

The other area of great concern is antibiotic resistance41. The serious and rising problem of antibiotic resistance in contemporary medicine has arisen as one of the major issues of public health in the 21st century. An growing number of pathogenic bacteria, including widely used antibiotics, have gained resistance. MRSA (methicillin-resistant staphylococcus aureus) which has now produced an epidemic of community-acquired MRSA.42 There continues to be concern that the release of antibiotics into the environment might be contributing to the growth of antibiotic resistance. There is actually, however, relatively little scientific evidence to support this theory, 43,44, although this is still a very important area of study.

4. Trials

"They are indeed essentially an empirical discipline of medicinal chemistry. (How little math every one of us wants to know should have been evident). We have large ideas, patterns, thumb laws – but none is adequate to support us a lot, and our data constantly shocks us. That may be fun if you have the right sort of personality, but it definitely doesn't rest, and it isn't really lucrative at times."

This section offers a simplified description of the mechanism in which a new medication is created. With the poor performance rate, the R&D divisions of the pharmaceutical research firms will not only study one drug but will also analyze at various stages in the production cycle at a time several different compounds. A big corporation will have 100-200 substances at any point in the production pipeline.

Pre-clinical Trials

The identification of a new treatment continues with studies into the actual illness or disease. This can be carried out in the pharmaceutical company's research labs, but also in academia, government research departments, independent "shop" pharmaceutical firms or some combination of these. Patient science is now so dynamic that the bulk of research is actually done by big pharmaceutical firms along with their collaborators.

In cases where the study recognizes a particular recipient or objective within the organism that may have beneficial results, a possible substance could be sought. A broad range of items may be the goal: a specific cell type, enzyme, gene, pathway or process. More than 500 targets of research pharmaceutical industries are reportedly under investigation.

Once a target has been selected, the next move is to find any substances that could control it. Advances in automated chemical synthesis techniques such as combinatorial chemistry have permitted the rapid expansion of chemical libraries. For starters, Aurora Fine Chemicals53 has a compound library of more than 18 million substances, and for a pharmaceutical firm, the compound library would now usually contain samples of 1 to 2 million different substances.

The quest for a likely candidate medication inside these broad chemical repositories has been streamlined in the 20th century with the advent of high-distance screening techniques (HdS), which use advancement in the field of robotics, automation, miniaturization and data manipulation54. Ultra-high-performance screening innovations (UHTS) since 2010 now permit testing speeds of 1 000 000 samples a day. Typically, screening takes place in many stages. At first a basic test is used to pre-screen a great deal of samples, perhaps the whole library, but a more explicitly specified subset is also used. A more complicated test is then used to refine the initial group that may contain several hundred compounds to a reasonable amount, usually <10. Original pharmacokinetic evidence on ingestion, delivery, metabolism and excretion can now also be used for HTS/UHTS techniques (ADME). Guiguemde and colleagues have carried out a valuable analysis of their application in the quest for candidate medicines to treat or mitigate the impact of malaria55. The consequence of this activity is the discovery of a limited number of substances which may contribute to a candidate and, ultimately, a functional medicinal product.

This "lead identification" is the second main step after "target selection" of the R&D process, and marks the transition from research to production. While a further 10 years of research work would potentially required before a medication can be applied for a marketing permit, the drug is likely to be patented at this stage. For now, the R&D costs would be relatively small at a few million US$, but after that, the expense is increasing quickly and the firm must protect its assets.

The next step in the process, "Lead Optimisation," is to reduce the amount of possible outcomes from roughly. 10-15 substances down to 3-4 substances. At the same time, efforts would be made to change the molecular structure in different ways with the goal of increasing the performance and at the same time eliminating possible side effects. It sounds easy, but normally takes 2-3 years of comprehensive, in-vitro and in-vivo pre-clinical experiments. During the time, the design of process chemistry will also be started, which will first be used to produce the batches of tests of the material (active ingredients) for use in the subsequent clinical studies and finally for full-scale development.

Around the same time, work is being initiated on the possible "druggability" 56 of these drugs, i.e. the active agent can be transformed into a shape in which a patient can use it to communicate with the goal. This is by no means a simple mission. The perfect medicine from the patient's point of view is a

pill administered once a day. Any divergence from this ideal would impair conformity, i.e. the probability of the patent adhering to the treatment regime. But if, for example, the pharmaceutical needs to be absorbed into the gut, you must make sure that it passes in the highly acidic stomach conditions without being degraded.

At the end of all this operation a candidate drug and probably a candidate for the reserve could have appeared. The reserve applicant would typically be the second best candidate to come up at this stage and will be quickly substituted if any unforeseen complications occur during the clinical trials.

Clinical Trials

Therefore, it is important to consider whether to send the applicant into clinical development, where the costs will again rise exponentially. Although advised by the scientific team, this is largely a business judgment. Alongside scientific activities, a considerable amount of additional work would have been carried out to determine the candidate's economic potential. During the pre-clinical production have there been any harmful indications? How successful is the treatment as it meets the prescription criteria? Are there still serious problems in formulation or production? What is intellectual property safe? What is the competitive situation today? What's the potential rivalry known? How high is the goal market? And most critically, what is the probable purchase price, etc.? If those questions are satisfactorily resolved, the applicant then progresses through the first step of clinical trials.

Clinical tests are carried out in four separate stages, the first three before the prescription is sold, and the fourth step starts as the pharmaceuticals are first administered and continue throughout the product's life.

The aim of clinical trials is to offer answers to two main questions in creating a new drug: (a) does it work? And (b) is the patent legal to take if it does? In certain cases, though, particularly at the broad scale of these experiments, the solution to these questions can not be obvious. Often think that a clinical trial would improve all (or at least the majority) of patients, but this is an unusual phenomenon. We know that not every patient responds in the same manner to a prescription, even though we seldom know exactly why. An example of the cause is the breast cancer medication trastuzumab (marketed as herceptin)58, which only has good outcomes for patients with a certain mutation. Fortunately, this fact is established and a screening procedure is required to classify the patients who would benefit. Otherwise, we will be in a condition that extends only to certain patients with certain pharmaceuticals. For this cause, the outcomes of a clinical trial typically require sophisticated mathematical methods to be understood, among many others.

Clinical trials also include a host of practical59 and ethical60 problems. An ethics committee must authorize any trial and all patients must give prior informed consent. To remove spectator bias, many experiments will be blinded in patients, supervisors and physicians (i.e., patients taking drugs will not know if they belong in the study group or to the control group), and all trials are double blind today (i.e. neither patient, nurse nor physician will be aware of this information). All clinical trials performed for the purpose of approval of drugs shall be subject to the criteria for good clinical practice (GCP).

A candidate medication is taken to complete the first three stages of clinical trials for six to ten years. The amount of time taken is measured by the period of the illness being treated and the length of time it may take to obtain enough patients.

The findings of the in silico, in vitro and in vivo tests in laboratory animals shall be repeated in human subjects by Step 1 tests. For brief periods of time under closely controlled and supervised environments, small numbers (10-15) of healthy human volunteers are exposed to extremely low levels of candidate medications. Test results are matched with data from preclinical trials to ensure that the drug performs as planned. This tests are the "first experiments in man," and the unexpected will occur in spite of the caution and planning taken. One of the most prominent examples is the awareness that sildenafil, a medication under development by Pfizer for the treatment of high blood pressure which is later sold as viagra, has a significant effect on male erectile dysfunction.

If in Phase 1, Phase 2 trials things have gone according to schedule, the primary goal is to assess if the treatment is successful, i.e. is it successful against the target disease? More information is often gathered on pharmacodynamics and protection. These trials are larger (100-300) and now include people with the disorder in question.

In Phase 3 tests, care is then delivered to large patient populations (1000–3000) to validate their efficacy, track any side effects, compare them with standard interventions and obtain knowledge that would allow for safe use. Despite the massive amount of knowledge provided on the candidate medication before the Phase 3 trial, many medicines fail now, with some researchers predicting the failure rate to be as high as 30%.

It is the first time a significant number of people have administered the medication and only now can low level side effects begin to arise. Also a severe, potentially life-threatening side effect that occurs in less than 1 person out of 100 individuals may not have previously been identified.64 However, the higher statistical power level in the Phase 3 trial can also indicate that the medication is actually quite little, if any, efficate.65 The drug does not work or work much less often than was initially expected or where only. This information itself is of tremendous importance in improving our understanding and pharmacology will resort to simple anecdotal findings without this thorough empiric data, which would mean that further advances in pharmacology were postponed.

The lack of drug candidates at this late stage is, of course, bad news for the organization. By now a tremendous sum of capital, time and research has been spent, much of which will have been in vain. The effect of the research team on morals should also be remembered; for instance, it is not rare for a surgeon to have spent his entire career in the field and never working on a good product. In the last few decades the industry has therefore put significant pressures in solving this late-stage crisis.66 As a result, more and more innovative drug candidates are being ended early, in the first indication of some possible problem, which experience has taught us might have contributed to the unnecessary removal of many otherwise effective pharmaceutical products. For example, under new medication production systems, neither aspirin nor penicillin would have been on the market.

People are also shocked that the production of medications takes too long. Around 10 years will potentially elapse between news media stories "Scientists have found a cure for X" and patients who receive the drug, if the progress is successful. The reason is that it actually takes this amount of time and the extensive clinical trial procedures involved to discover if the treatment will actually work. However, this poses ethical concerns, in particular for life-

threatening conditions in which patients and their physicians choose to explore a new medication as soon as possible. This becomes a concern as early data indicate that the medication can have substantial positive effects, but that many future patients may die as soon as a marketing authorisation is authorised. As a result, a variety of regulatory programs67 have been created to offer 'expanded' or 'compassionate access' to critical or life-threatening patients who don't meet the registration requirements for a clinical trial, where it is clear that patients can be treated in a healthy manner, where the medication should be performed beyond the framework of clinical trials, with no such alternative treatment. However, all systems are closely monitored so that the clinical trial results themselves are not affected. However, demand for broader and quicker access to unproven treatments is growing where the need is serious. The successful completion of the Phase 3 trials would enable the innovating business to compile to the respective regulatory body, e.g. the Federal Drug Administration (FDA) in the USA and the European Medicines Agency (EMA) in the European Union all the details related to the applicant's application for a marketing authorisation. If the application is satisfactory, the medication with its trade name will be launched and patients will be administered. Step 4 of the clinical trial process starts at this stage.

Step 4 concerns continuing safety monitoring and pharmacy technological assistance. The safety screening, generally referred to as pharmacovigilance, helps to track unusual or long-term adverse effects over a significantly broader patient pool and longer than possible during phase 1-3 clinical trials. In some cases, the control authorisation will include pharmacovigilance regimes; in some cases the creative organization will conduct more investigation into novel uses of pharmaceuticals. In these step 4 studies, it is generally rare to see significant adverse results, although in certain situations the evidence may contribute to the pharmaceutical being no longer marketed, or limited to some applications.

The commodity will then be sold at a high premium before the patent of the innovator expires, typically between 5 and 10 years after its initial launch. Subsequently, the generic product will arrive on the market and the price will fall considerably.

Environmental Issues

The overwhelming majority of the R&D effort expended in the design of a new drug is concerned with its effects in humans. The environmental effects of the general pharmaceutical industry and its products in particular, as we saw in Section 1.3, were not deemed important until the end of the last siècle. Study is now being carried out in the R&D process in two separate environmental sectors. The first is to move towards more sustainable development and the second is to strengthen awareness of possible environmental risks resulting from the use of a new medicine. Many pharmaceuticals are processed at comparatively limited quantities, i.e. 0,1-10 tons annually –1 compared with chemical goods such as terephthalic acid, which can be generated in plants that generate >500 000 tons annually –1. Unlike the majority of "bulk" chemicals, most pharmaceutical products are very complex organic molecules, often involving the isolation of intermediate products, and must be constructed using multiple synthetic steps. As a result, process productivity has traditionally been very low71 and the waste-to-product ratio has been very high considering the limited quantities generated in the pharmaceutical industry.The pharmaceutical firms have been market leaders in recent years, motivated both by cost and environmental concerns when incorporating green chemistry and technology techniques into their process design. Anastas and Warner proposed the 12 principles of green chemical manufacturing in 1998.72 Since then, the pharmaceutical industry has been deeply involved in the field of process design and are now pushing upstream and affecting medical chemists in research and development laboratories.

The study on process design will commence in phase 1 trials at some point. By this stage medicinal chemists have been able to satisfy the demand for laboratory-scale experimental material; however, Phase 2 trials and particularly Phase 3 trials involve considerable quantities of material, mostly at pilot-plant level. Although pace remains a key criterion in process improvement science, greater attention is now being paid to ensuring an effective process in electricity, water, solvents and raw materials. Any residual waste generated must therefore be minimized to a minimum and can be satisfactorily and efficiently recycled.

In spite of increasing concern about the presence of pharmaceutical residues in the environment, few legal standards still remain, aside from within the European Union, to determine the possible environmental impacts of a medicinal product.73 There have been regulations for many years in other countries such as Canada and Japan, but the only applicable legislation to date is the EU. Nonetheless, the pharmaceutical research industry is conscious of its manufacturing duties and for many years, most companies have voluntarily undertaken environmental risk assessments of their new products. Moreover, some businesses, e.g. AstraZeneca has made its data public74 and introduced ecopharmaco vigilance systems to some degree to represent the human population's pharmaco vigilance activities.

Discussions

There are emerging techniques that are currently found in the pharmaceutical industry but are commonly applicable in non-pharmaceutical markets, such as: lean manufacturing; Six Sigma; the overall quality control. It's also proposed that the literature spends more in the implementation and relevance of standards and practices. Both pharmacy managers and the literary field should concentrate on the implementation of these activities in the pharmaceutical industry, using the previous studies in the non-pharmaceutical industry. New case studies should be carried out to show that these methods are feasible.

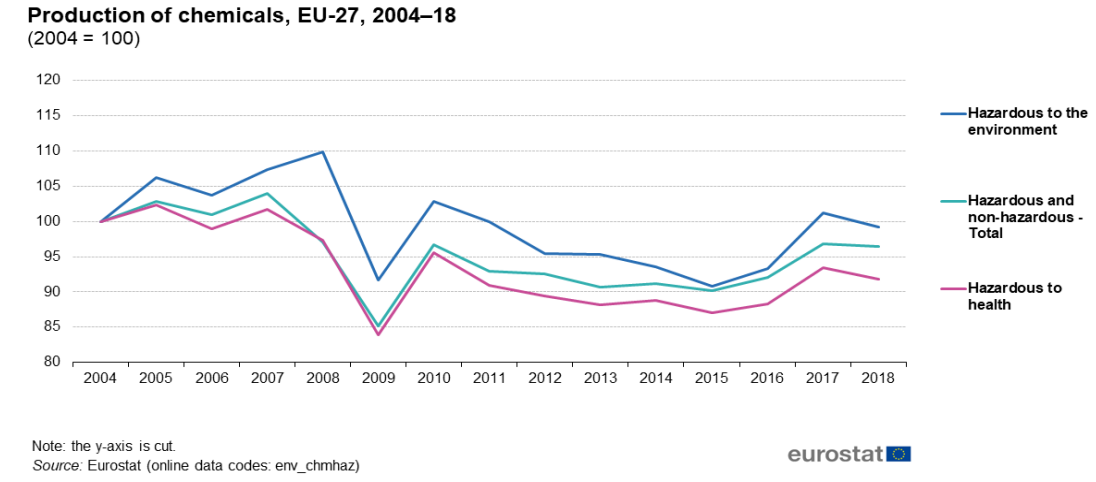
The pharmaceutical testing industry is already facing challenges, most of which seem to have no apparent solutions. While it has the exclusive rights to market new medication in its patent life, increasing enforcement leads, with ultimately shortened periods, to additional costs and longer production times; increasing risk aversion by management teams contributes to a decline in the appearance of new pharmaceuticals; lowering risk perception in patient groups and restricting them

However, with the growing dominance of biopharmaceutical drug production pipelines, we should be confident that the next wave of human pharmaceutical drugs would have considerably lower environmental contaminants than those arising from the use of existing medicinal products.

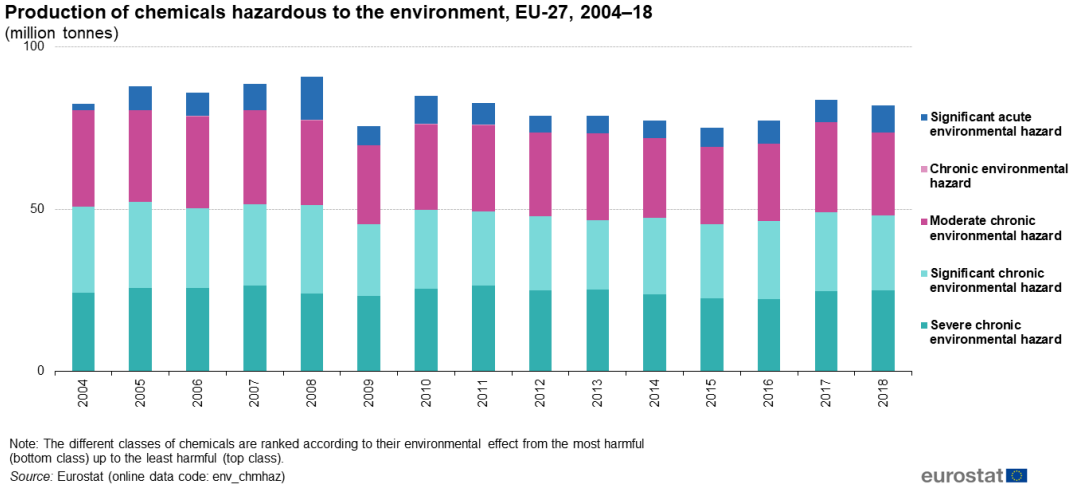
Process failure mode and effects analysis of the chemical process

Link to the EU Hit Directive: (Abbreviation for Chemical Registration, Assessment, Authorisation and Restriction)
REACH (EC 1907/2006) attempts to enhance human health and conservation of the environment through clearer and earlier recognition of the substances' inherent properties. This takes place through four REACH procedures, including the registration, inspection, licensing and restriction of chemicals. REACH also seeks to boost EU chemicals industry's creativity and productivity.'No details no market': the Scope Legislation puts on industry responsibility for handling chemical risks and supplying safety records for chemicals. Manufacturers and importers are expected to collect and record the information in a central database in the European Chemicals Agency (ECHa) in Helsinki on the characteristics of their chemical substances, which will allow their safe handling. The Department is the focal point of the REACH scheme: it maintains the necessary databases to run the system, coordinates the comprehensive review of suspicious chemicals and establishes a public archive on which users and experts are able to locate information on hazards.
The Law also calls for the phasing-in of the most toxic chemicals (the so-called 'extremely necessary substances') where sufficient substitutes have been found.
One of the big factors for establishing and implementing the REACH Rule are that for years a vast amount of drugs, often in very high numbers, have been imported and put on the market in Europe, although inadequate evidence is available about the risks to human health and the environment. These knowledge holes must be filled to ensure that the industry can determine the threats and hazards of the chemicals and to define and enforce risk control strategies for the safety of humans and the environment.
The Scope provisions, which came into effect in 2007, was gradually in force over 11 years. Companies may find REACH details on the DG Development websites or on ECHA's websites and can contact the national assistance offices.

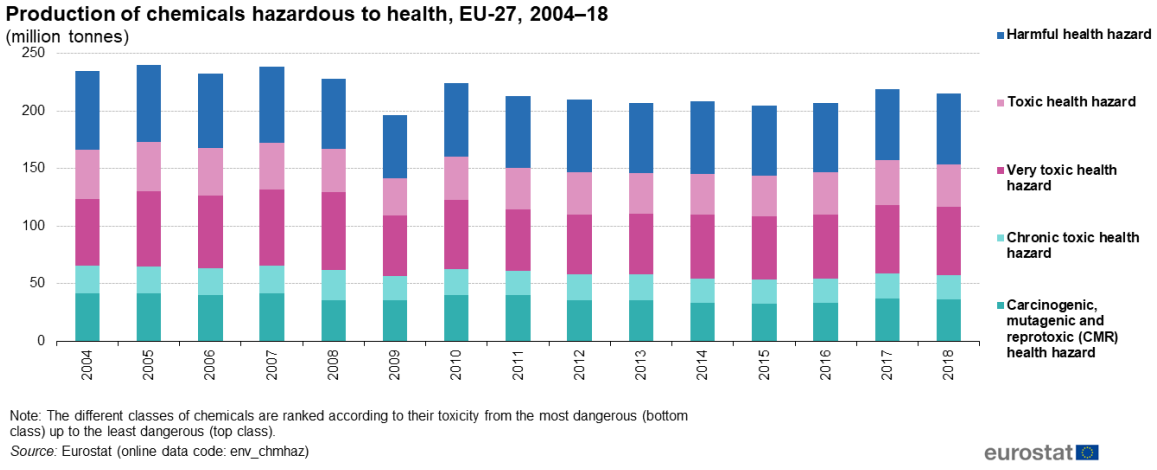
Chemicals production and consumption statistics:



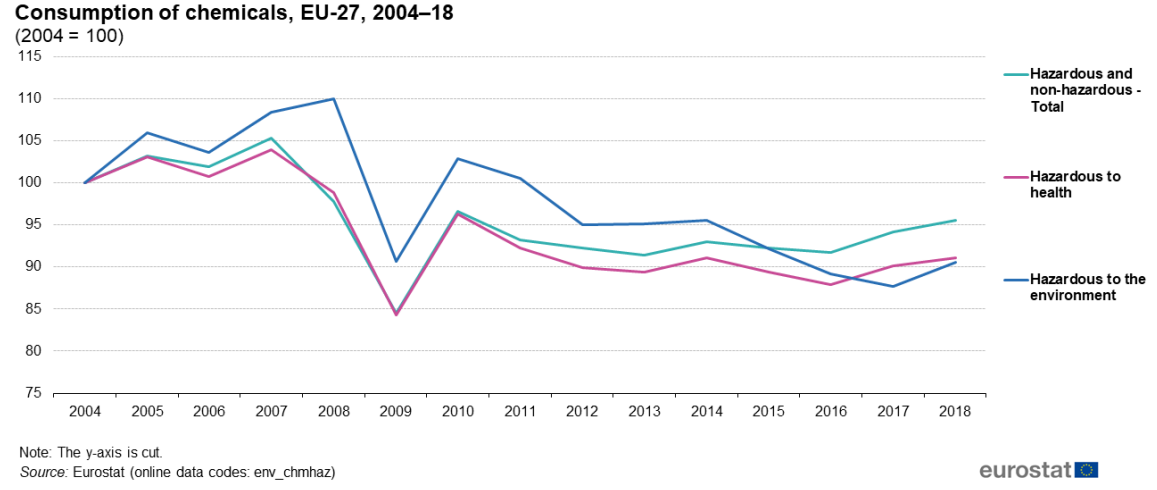
Source: https://ec.europa.eu/



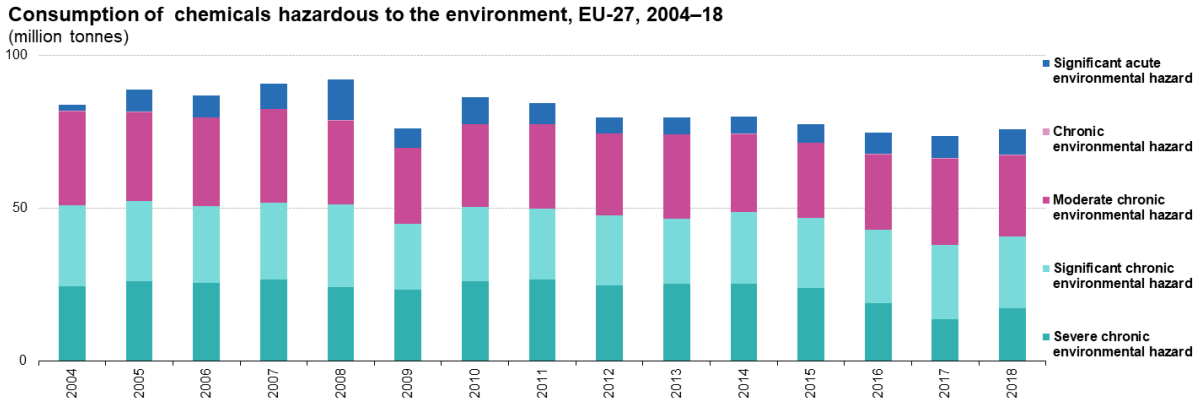
Source: https://ec.europa.eu/



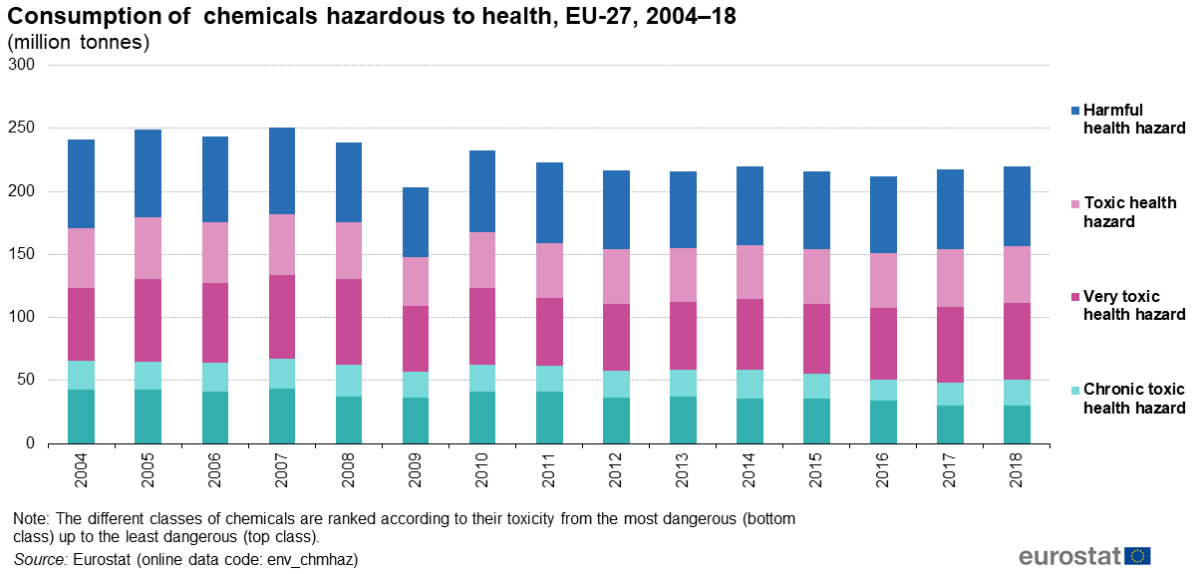
Source: https://ec.europa.eu/



Source: https://ec.europa.eu/



Source: https://ec.europa.eu/



Source: https://ec.europa.eu/

References of the Applicable Standards:

Following are the chemicals used in the medical device industry which are harmonised by European Council:

EN ISO 10993-18:2009 Biological evaluation of medical devices - Part 18: Chemical characterization of materials (ISO 10993-18:2005)

EN ISO 11140-1:2009 Sterilization of health care products - Chemical indicators - Part 1: General requirements (ISO 11140-1:2005)

EN ISO 11140-3:2009 Sterilization of health care products - Chemical indicators - Part 3: Class 2 indicator systems for use in the Bowie and Dick-type steam penetration test (ISO 11140-3:2007, including Cor 1:2007)

EN 13624:2003 Chemical disinfectants and antiseptics - Quantitative suspension test for the evaluation of fungicidal activity of chemical disinfectants for instruments used in the medical area - Test method and requirements (phase 2, step 1)

EN 13727:2012 Chemical disinfectants and antiseptics - Quantitative suspension test for the evaluation of bactericidal activity in the medical area - Test method and requirements (phase 2, step 1)

EN 14348:2005 Chemical disinfectants and antiseptics - Quantitative suspension test for the evaluation of mycobactericidal activity of chemical disinfectants in the medical area including instrument disinfectants - Test methods and requirements (phase 2, step 1)

EN 14561:2006 Chemical disinfectants and antiseptics - Quantitative carrier test for the evaluation of bactericidal activity for instruments used in the medical area - Test method and requirements (phase 2, step 2)

EN 14562:2006 Chemical disinfectants and antiseptics - Quantitative carrier test for the evaluation of fungicidal or yeasticidal activity for instruments used in the medical area - Test method and requirements (phase 2, step 2)

EN 14563:2008 Chemical disinfectants and antiseptics - Quantitative carrier test for the evaluation of mycobactericidal or tuberculocidal activity of chemical disinfectants used for instruments in the medical area - Test method and requirements (phase 2, step 2)

EN ISO 15883-4:2018 Washer-disinfectors - Part 4: Requirements and tests for washer-disinfectors employing chemical disinfection for thermolabile endoscopes (ISO 15883-4:2018)

EN ISO 15883-4:2009 Washer-disinfectors - Part 4: Requirements and tests for washer-disinfectors employing chemical disinfection for thermolabile endoscopes (ISO 15883-4:2008)

Link with country specific regulations:

Various national laws usually show the risk-based methodology to be taken into account during assessment, using this guide

Link with clinical evaluation:

In conjunction with the recent EU MDR Legislation on Medical Instruments and the relevant policy criteria on health, biological and technical protection and compliance parameters, this paper will assist the clinical assessment process by presenting some additional details on procedures that may lead to an unreasonable danger to the medical equipment in question.

Link with first party audit:

The internal auditor cannot arrange its own method from the point of view of the effect of certain systems on end product compliance, during the internal audit of the relevant business. This would allow companies to recognize vulnerabilities and possibilities for detecting future substance non-conformities around controls in the system.

Link with second party audit:

Since second-party audits usually concentrate on the provider's capacity to threaten the compliance of the product requirement with the regulatory requirements, the second-party auditor may use the paper to question the processes undertaken by the provider.

Link with third party audit:

The licensing agency, the informed body, auditing organisations' auditors ought to question procedures in relation to apparent non-conformities during a third-party audit. This paper will be used to assess the holes (even if they are minor in nature)

5. Conclusion

This paper is dealing with chemicals and medication compounds, the other processing systems often include mechanical assemblies, electronics, and so on. Essentially, the compatibility of the other technology should be taken into account when achieving the difficulties of chemical processes such as compounding and buffering.This paper will be found in other fields that are not in the medical device but use chemicals as part of the commodity or for its manufacturing.

REFERENCES

1. U.S. Food and Drug Administration [Internet]. Silver spring, MD; 2014 Jun
2. Incra Med, Medical Device Solutions [Internet]. Ireland; 2010
3. Feldman MD, Petersen AJ, Karliner LS, Tice JA. Who is responsible for evaluating the safety and effectiveness of medical devices? The role of independent technology assessment. J Gen Intern Med 2007;23(Suppl 1):57–63.
4. Guezuraga RM, Steinbring DY. View from industry. Eur J Cardiothorac Surg 2004;26:19–24.
5. Keselman A, Tang X, Patel V, et al. Institutional decision-making for medical device purchasing: Evaluating patient safety. MedInfo 2004;11(Part 2):1357–1361.
6. Master Control, Compliance Accelerated [Internet]. Utah; 2014