

PLANNING PROCESS OF PILOT BATCH PRODUCTION OF AN INNOVATIVE DRUG FOR CLINICAL TRIAL IN A PHARMACEUTICAL INDUSTRY

Lila M. Harada^a; Adriano Maniçoba da Silva^a

^a Federal Institute of Education, Science and Technology of Sao Paulo (IFSP) - Suzano, SP, Brazil

ABSTRACT

Purpose – Clinical trials are the most critical step in the process of drug development and evaluation to bring a new drug to market. The purpose of this article was to show an approach of the planning and production of a new innovative drug for a clinical study, based on the presentation of decision-making process in a national pharmaceutical industry.

Design / methodology / approach – Through a case-study methodology, it was described the pilot batch production planning of a new drug for clinical trial, focusing on how the company evaluates the adequacy of the available systems at the manufacturing plant and how they use them in drug production planning process.

Findings – A previous planning for clinical trial supplies production is determinant to decide the order, amount and timing of the products to be produced when the manufacturing plant is shared with the production of commercial products. Also, even in a small pilot batch production, there is a substantial waste of supplies during the process.

Research Limitations/Implications – This study showed the production planning process of one investigational product with the recruitment of few patients for the clinical trial. However, the number of patients enrolled can reach thousands in many clinical trials, and it does need a more complex production planning to avoid wastes and try to reduce the process costs.

Practical Implications – This article provides a picture of the production planning of clinical trial supplies chain under uncertainty and the decisions that affect the large-scale production of commercial drugs and the pilot batch production of experimental drugs.

Originality/Value – Although the results of clinical trials are the most significant source of uncertainty in the development process of any new drug, a good clinical supply planning and processes management can avoid or attenuate the imminent risk of process failure.

Keywords: Drug development; Pilot batch; Production planning; Clinical trial supply.

1. INTRODUCTION

The recent economic reports have shown a great growth of the global pharmaceutical market, pointing a sales volume of trillions of dollars in the coming years (IFPMA, 2014). In this scenario, Brazil has emerged as the sixth largest pharmaceutical market of the world, showing a growth and profitability of pharmaceutical companies marketing thousands of drugs, all they approved and regulated by the official regulatory agency of the country (INTERFARMA, 2015).

On the other hand, the new drug development follows an extended sequence of steps, since its discovery, animal trials, regulatory agency application, development of products and process, clinical trials tests in humans, approval and launching to market. It is known that for each new drug that reaches a pharmacy rack, approximately 5,000-10,000 other potential drugs have been tested and failed to achieve commercialization (IFPMA, 2014). Clinical studies are extremely expensive but are also a very important part of development process of new drugs, and comprehend the production, distribution and administration of the experimental drug in voluntary patients in different geographical locations (Lee *et al.*, 2006).

When we refer to pharmaceutical industries and the commercial drug production from their varied portfolio of products, the literature usually discusses the questions about the supply chain management of these drugs. However, data about the progress of a clinical trial are hardly published due to the confidential state and because the investigational products are not yet commercially available. The most scientific literature about clinical research and clinical trial supplies usually direct to bottlenecks problems from regulatory agencies that delay the onset of the study or to the problems generated by the globalization of these studies as a result of slow patient recruitment and high clinical research costs (Thiers *et Sinskey*, 2008). Because of the expansion of international studies, it is becoming increasingly difficult to have the right inventory in the right place at the right time and for the right patient (Abdelkafi *et al.*, 2009; Chen *et al.*, 2010).

While the production of commercial drugs requires a very complex and strategic planning since its manufacture, transport and distribution in suitable conditions to reach the final consumer, the clinical supplies are produced in a small scale, limited pilot batch and then they are distributed to clinical sites for its safety and efficacy evaluation. Even with small and limited amounts, the clinical trial supplies production requires a very detailed planning at the same conditions for the production of commercial drugs. One of the stages of this planning is to match this production within the commercial drug production plan. This implies the temporary interruption in the production

of some commercial drug batch to allow the production of the experimental drug. However, there is always a great difficulty in production planning of clinical trial supplies, due to the uncertainty of a clinical study (Chen *et al.*, 2012). A substantial amount of works have been reported the optimization process in industry supply chain (Abdelkafi *et al.*, 2009; Chen *et al.*, 2010), but only a limited literature has addressed to the problems faced by the pharmaceutical industries.

In an attempt to resolve this problem of capacity and production planning under clinical trial uncertainty in the pharmaceutical industry, some authors have proposed stochastic mathematical programming formulations (Colvin *et Maravelias*, 2008; Gatica *et al.*, 2003; Gupta *et al.*, 2003). These programs are based on the optimization to select the end products portfolio, the production planning and the strategic investments under the uncertainties of the clinical trials results for each potential drug. However, the methods seem to be very limited to single or two-stage problems and are computationally expensive. In a review article, Shah (2004) presented an analysis of the key issues to optimize the strategic decisions in the pharmaceutical supply chain, demonstrating the research activities for development of new products, process and plant design, but the issue of planning and management of drug production schedule for clinical trials has not yet been well studied.

In view of this, the aim of this study was to analyze the production planning practices of an investigational product for a clinical trial, focusing on how the company evaluates the adequacy of available systems and how to use them in drug production process. For this approach, this study was conducted in a national pharmaceutical industry, where it was taken as an example the development of an innovative investigational product for the treatment of acute low back pain.

2. LITERATURE REVIEW

2.1. Clinical trial and evaluation of new drugs

A clinical research or clinical trial can be defined as any research conducted in humans in order to discover or confirm clinical and pharmacological effects, identify any adverse reaction related to the experimental drug and verify its safety and/or efficacy under controlled conditions (ANVISA, 2015).

Clinical trials present different phases and can be classified as pre-clinical phase (in animals) and clinical (in human) phase. These studies are performed to ensure the safety and effectiveness of the new drug to a proposed treatment. In the pre-clinical phase, the new molecule with some therapeutic potential is evaluated for toxicological and pharmacological effects through in vitro tests and in

laboratory animals. In this phase, only those molecules with some pharmacological activity and a low toxicity profile will be further tested in humans, and it corresponds to only 10% of substances initially developed. (Lee *et al.*, 2006; Lopes *et al.* Harrington, 2015)

In Phase I trial the safety and dosage ranges of the new active ingredient are tested in a small group of health volunteers and the pharmacokinetic and pharmacodynamic profiles are evaluated. In Phase II trial, further tests of safety and efficacy are carried out in a larger group with a particular disease. At this stage is established the dose-response relationship, the types of patients, the frequency of administration, or other safety features and therapeutic efficacy. In Phase III trial the results of safety and efficacy are confirmed in hundreds or thousands patients in various national and / or international centers. At this stage, in addition to determining the efficacy and safety of the new drug, the most common adverse reactions, as well as the therapeutic profile and the demonstration of the potential advantages of the new therapy compared to other already on the market are identified. Assuming success in Phase III, the new drug is submitted to the official regulatory agency to obtain marketing approval. Phase IV trial is the observational phase of post-marketing surveillance, when additional details about their efficacy or safety profile are collected (Lee *et al.*, 2006; Lopes *et al.* Harrington, 2015).

According to information from the International Federation of Pharmaceutical Manufacturers & Associations (PhRMA, 2015) about research and development of medicines, the pharmaceutical industries invested in 2014 approximately US\$ 51.2 billion in research and development of approximately 7,000 drugs around the world. It is estimated that is required between 10 to 15 years to develop a new drug or a vaccine, and only one in 10,000 compounds reaches the patients as a drug to be evaluated in efficacy and safety (INTERFARMA, 2015). This is because although it is possible to know how many patients are needed at each stage of the clinical trial, it is important remember the existence of the inherent uncertainty associated with each clinical trial: the risk of study failure.

2.3. Planning and production of new drugs for clinical trial

In the pharmaceutical industry, the development activities that are necessary to bring a new drug to market may take more than 10 years and involve considerable expense (over

US\$ 1 billion) (Hovde, 2006). At the end of the screening of the investigational product, the team of Research and Development should design the production process of this new drug. The primary manufacturing process involves the production of small quantities of the drug or active ingredient. The active ingredient is then transferred to a secondary output for its conversion into usable dosage form for the patient.

Clinical trials are an extremely important part of this and costly development process as the chain supplies associated that includes the production, distribution and the new drug candidate's administration to volunteer patients located in different geographical regions.

A clinical trial supply chain begins with the manufacturing process of the active ingredient (investigational product), which is then converted into a new product by the addition of various excipients in the course of performing a series of pharmaceutical production steps. Subsequently the new drugs are packaged and labeled in the final product form to be distributed to various clinical sites performing the clinical trials by the companies providing clinical research services (Contract research Organization, CRO), as shown in Figure 1. In addition to the final drug product, placebos (a product without active ingredient) and comparator drugs (a dosage form containing a commercial drug intending to treat the same disease) are also produced and used in clinical trials. These products suffer the same production, packaging and labeling stages as target drugs to make the appearance of these three types are the same, thus helping to preserve the integrity of double-blind clinical trials

The manufacturing process of drugs is characterized by a task with a long processing time often rounded to multiples of turns, which are operated for multistage processes, and often considerable stocks are produced between the stages (Shah, 2004). In the case of clinical trial supplies production, the processes are faster although they use the same design for the production of commercial products, due to the smaller amount and batch size required for the clinical study. This procedure occurs in many pharmaceutical companies that allocate own commercial production plant for clinical research purposes, which ends up generating a timely reformulation of the general planning of the company for clinical trial supplies production due to the lack of specific facilities and the high cost of implementation and maintenance of a pilot plant.

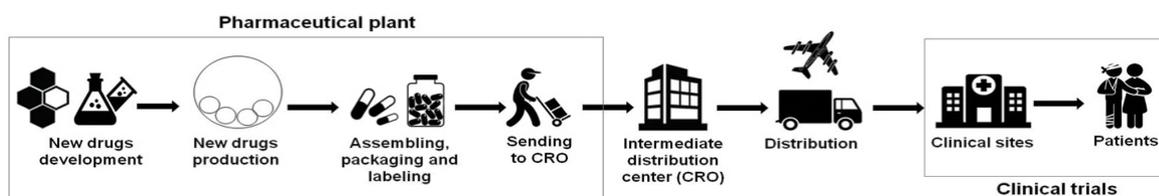


Figure 1: Flowchart of a general clinical trial supply chain.
Source: Adapted from Chen *et al.*, 2012

A pilot plant is a part of the pharmaceutical industry where a laboratory scale formulas is transformed into viable product by the development of practical procedure for scale manufacture simulating the entire industrial production, allowing for numerous short run production lines of various batches that are essential to ensure the success of clinical trial. In these facilities, the orderly transitions of laboratory manufacturing routine processing occurs in a production unit on a larger scale, but well below the commercial scale, and include a careful examination of the formula to determine their ability to withstand changes in a batch or process. In addition, constant revisions must be done in all equipments of material processing and the availability of raw materials with the product specification, since this process consists of a simulated production of a probable and future commercial batch (Chaudhary *et al.*, 2012).

In any pharmaceutical industry the batch production processes are dominant and have many advantages, including the versatility of use of equipment, production planning and flexible scheduling, quality control fidelity and the ability to quickly retrieve specific batches of products; however they have drawbacks such as mixing the scalability and low efficiency operational assets (Plumb, 2005). Thus, the clinical supply production decisions range from the start time, number and size of each product batch, processing time of each batch, type of products (new drug, placebo or comparator) and total production. In all stages of production, several other production lines working in parallel, so each production line can be used for different products, demonstrating that production scheduling tools play an important role in the production (Chen *et al.*, 2010). Production planning models aimed at determining the supply and optimal allocation of limited resources of a company to manufacture, in order to meet the requirements of the product with reasonable value for money (Gupta *et Maranas*, 2003). The decision by a manufacturer to expand or reduce a process is ultimately rooted in the production process economy, i.e., the cost of material, equipment personnel and availability related to the process and its control (Chaudhary *et al.*, 2012 ; Papavasileiou *et al.*, 2007).

It should be noted that besides the final product, the material produced in one intermediate stage is also often submitted to the quality control assays before the approval for downstream use in the process. The quality standards must be very strict with the application of Good Manufacturing Practices, as defined by the World Health Organization (WHO, 2014).

3. METHODOLOGY

3.1. Case Study

This case study was conducted in a pharmaceutical industry considered one of the biggest generic medication

companies of Brazil and is constantly investing in research and development by increasing its portfolio and product offer. Some years ago, this company entered to new markets by investing in clinical research, biotechnology and acquisitions within the national market, aiming to become one of the three biggest pharmaceutical companies in the country.

For this study, it was selected as an example the investigational product called XYZ to illustrate how was done the planning and production of experimental drugs for a clinical research study (phase III), to evaluate its safety and efficacy in humans. The experimental drug XYZ was a new innovative drug, an association of two drugs with analgesic and anti-inflammatory action for the treatment of acute to moderate pain.

The pharmaceutical industry was the sponsor and the manufacturer of novel drug used in this clinical trial. It was also one of the shareholders of a joint venture company of RD&I (Research, Development and Innovation) who developed the innovative drug.

3.2. Production of the investigational product

The planning horizon of this clinical study was 36 months and three batches were produced new drugs whose production intervals varied from 10 months between the first and second batch, and 22 months between the second and third batch. Each batch of investigational product was produced in the form of coated tablets, and they were compared with reference drugs also at the same dosage according to the Good Practices of Drug Manufacturing recommendations from the Brazilian National Health Surveillance Agency (ANVISA, 2010) and the World Health Organization (WHO, 2014). According to the ANVISA regulation, the pharmaceutical company must produce at least three batches of the medicine, each with a minimum equivalent amount to 10% of industrial batch planned for future marketing, or in equivalent amount to the minimum capacity of industrial equipment used in the commercial drug production (ANVISA, 2009). So, the innovative drug production was made as pilot batch and sought to play the maximum the technical, operational and manufacturing processes of the proposed industrial batch, and ensure a high level safety and quality for the product and the process can be reproduced on an industrial scale in the future. In Brazil, minimum pilot batch of solid oral dosage forms must be at least 50,000 units, although internationally, it is 100,000 units.

For each pilot batch of new drug were also produced batches of placebo pills for blinding purpose undergo the same manufacturing to avoid psychological biases. These ones were the placebos of the new drug, the comparator of drug 1 and the comparator of drug 2, following the exact

composition of medicinal products, except without active ingredient, to make sure the appearance of these three types of placebo were the same to insure effectiveness in double blinded clinical trials.

All pilot batches production was notified to the ANVISA. After the clinical protocol has been approved by the regulatory agency, they were available for use according to the manufacturer's criteria for the clinical trial. Special attention was done to the expiry date of the products, counted from the date of effective manufacturing (ANVISA, 2009).

3.3. Assembling of clinical trial supplies

According to the clinical protocol, the total of patients that should be included to evaluate the efficacy and safety of the new drug in this study was defined statistically. The protocol required the inclusion of 171 patients (57 patients in each arm study) and a specific oral administration schedule of three capsules per day for 7 days. The experimental drugs (XYZ), comparator drugs (C1 and C2) and the placebos of the drug XYZ (PL-XYZ) and the comparator drugs (PL-C1 and PL-C2) were placed on opaque gelatin capsules for blinding according to arm study design, as shown in the Figure 2. This was the way to insure effectiveness in double blinded clinical trial.

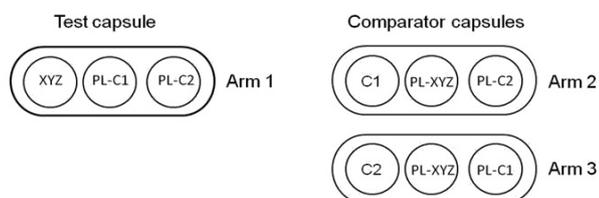


Figure 2: Assembling the clinical trial supplies and blinding the new drug and comparators.

Source: The authors own.

The capsules of each arm were then packed in appropriate flasks containing 25 capsules each, and along with their bottles of rescue medications were sent to CRO (Contract Research Organization) for labeling, storage and randomization. Then, the clinical supplies kits were distributed according to demand to the clinical sites. A total of 69 kits with 25 capsules were done for each arm. It corresponded to an additional of 20% in clinical trial supply kits for inventory in case of replacement due to loss or damage, if necessary.

3.4. Data collection and analysis

The data relating to the pilot batch production of drugs and the assembling of clinical trials kits were collected from the manufacturer/sponsor. The results were qualitatively analyzed and presented in tables detailing the profile of production of clinical supplies used in this study.

4. RESULTS AND DISCUSSIONS

Clinical trials are the most critical steps in the process of any drug development. The production step of the new drug that should be tested in patients in the phase III study is preceded for its approval by the regulatory agency and the launch of this new product on the market. While the planning production of the approved drugs is well documented within a pharmaceutical plant, there is only a limited literature addressed the issues to discuss the development process, plant design, production planning and management of the clinical trials supply chain.

This study aimed to show an approach of the planning and production of new experimental drug for a clinical trial to evaluate its efficacy and safety, based on the presentation of decision-making process in a national pharmaceutical industry. The chosen drug, XYZ, was an innovative product, i.e., it is not yet commercially available in the formulation presented by the manufacturer, but the active components are already described and known. In this case, according to ANVISA, the new investigational product was supported by the conduction of pharmaceutical equivalence and bioequivalence tests and it could be evaluated directly as a phase III clinical trial.

The choice of XZY product for clinical trials started from the decision of the clinical research department, which defined statistically the quantity needed for conducting a clinical study to evaluate the efficacy and safety of the new drug and to compare with the reference drugs for the same pathology as well as the dosage form (coated tablet). The exact definition of all formulation components (active principle and excipients) was made by the team of pharmaceutical technology, whose application for manufacturing was shipped to the manufacturer to arrange their production of both experimental drug as the placebos in form of pilot batch (minimum quantity required for clinical trial) and further blinding (the drug and placebo tablets in opaque gelatin capsules). Although the production size requested have been small, the production planning had to consider a larger amount of drugs to meet the requirements of ANVISA regulations that determine the size of each batch as at least 10% of future commercial batch.

The Figure 3 shows the mains steps of the drug production process for this clinical study.

As the pharmaceutical company of this study did not have a pilot plant dedicated exclusively to the clinical trial supplies production due to the high costs (both fixed and variable) of equipments for low demand volume and its maintenance, it was used a commercial production plant. For each pilot batch production for clinical trial, it was required a detailed and early planning with at least 6 months in advance to do not interfere in the volume production of commercial products.

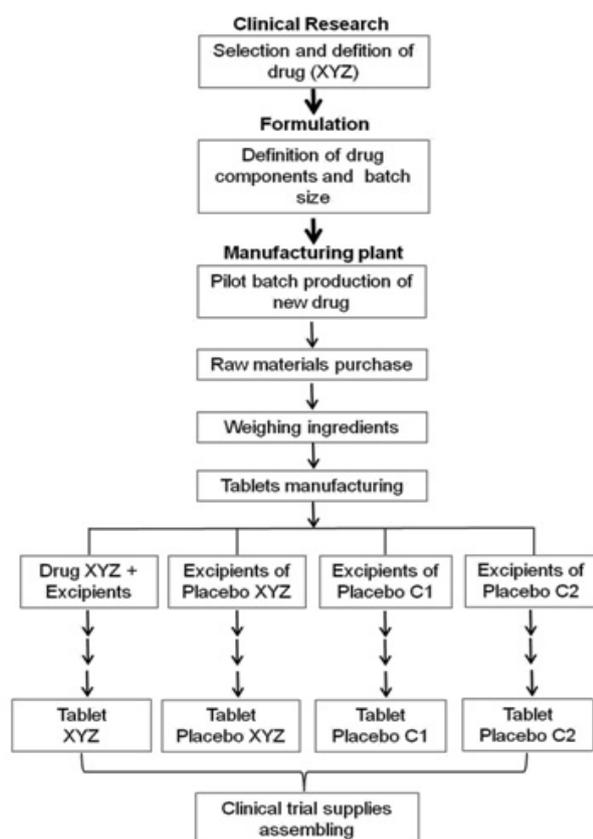


Figure 3: Main steps of drug production process for clinical study.

Source: The authors own.

At the time, the company's portfolio contained more than 150 pharmaceutical products in its production line, half of them in the form of tablets, and it caused a considerable delay to achieve the allocation of equipments at the manufacturing plant, to purchase of materials and to get staff availability for producing the first batch of tablets for clinical trial. All pilot batches of new drugs and placebos were produced by multistage process as in the manufacturing of commercial tablets batch (Tousey, 2015).

The main steps for the tablet manufacturing can be described as the following. After weighing the ingredients for both the production of medicines as placebos, they were milling to ensure the particle size of each excipient to be blended and only then were subjected to compression to acquire the shape and size desired tablet for the study. The production of each pilot batch of new drugs resulted in coated tablets and placebos for the plain tablets which were used for assembly of clinical kits. In all production steps were followed the recommendations of Good Manufacturing Practices. To avoid cross-contamination in production, special care was taken regarding to the requirements for cleaning validation and exchanges of long production processes of other pharmaceutical products.

Typically, clinical trials with different objectives (e.g., efficacy, safety, side effects) are performed at the same time

to accelerate the new drug development process. However, while the clinical trials are in progress, the development team must also continue working to improve the manufacturing processes. This is because the pharmaceutical industries often face uncertainties on a number of factors such as requirements of products, prices of raw materials and products, faster delivery of raw materials and the production and distribution of the final products, process faults and failures quality (Jung *et al.*, 2004). Although there is no absolute guarantee of success for the development phase of the clinical trials, the pharmaceutical companies continue betting in the possibility of large profits when the new drug is launched on the market.

For this reason, the pharmaceutical industry often uses batch processes for the manufacture of pharmaceuticals for both at the pilot scale and the commercial scale. Since these facilities are usually shared among several products, especially for the quantities required for the clinical trials, it is necessary to decide on the order and timing of products to be manufactured. These kinds of decision can have a major economic impact on the company at the clinical trial stage, because the lack of delivery of clinical trial supplies to patients may significantly delay the completion of the trial and therefore delay the time to launching to market, which in turn can mean significant loss of revenue (Chen *et al.*, 2010).

Another aspect that usually draws concern during the development of a clinical trial is the generation of waste produced from medication batches. If on the one hand there is a need of the drug production for the clinical trial regardless of cost, on the other hand there is the spending containment policy by pharmaceutical companies to reduce the high cost of each clinical trial stage.

In this study, although the clinical trial supplies have been produced in a very small number when compared to the commercial drug manufacturing to meet the demand of the clinical trial, this production process also resulted in waste disposal by not using or exceeded of validity. According to the progress of the clinical trial and delayed regulatory decisions, three pilot batches were made to produce experimental drug and placebos. The intervals ranging varied from 10 months from the first and second batch, and 22 months between the second and third batch. For each new pilot batch, a new application of production was sent to the manufacturing sector that provided the schedule for use of the plant as well as the purchase of all raw materials and others excipients.

The output of the pilot batch 1 was used for initial testing of the product stability for at least 6 months, and also was performed studies to demonstrate the bioequivalence of the new drug with the reference products and others of quality assurance. With the positive results, it was produced the

second pilot batch that was used for the clinical trial which purposed the inclusion of 171 patients after the approval of the protocol study by ANVISA. Because of the long time to obtain the regulatory approval (8 months after request submission), the shelf life of the pilot batch 2 has expired and it was not possible to complete clinical stage due to the difficulty of including patients. So, a new pilot batch had to be produced to replace the expired date products that were disposed for destruction.

As can be seen in Table 1, complying with the minimum production of drugs for clinical trial is regulated by ANVISA. In each pilot batch of this study were produced 50,000 units of coated tablets of the experimental drug XYZ as well as the respective placebos that were used in the assembly of clinical supplies. After the production of three pilot batches at the end of the study the amount of the tablets used in the clinical trial was only 2% of the new drug and 3% of placebo, demonstrating the enormous percentage of waste in each pilot batch production of the drugs and placebos. But it is a necessary step for planning the clinical trial supply chain. According to the norms of the regulatory agency, independent of the amount of drugs that will be used in the clinical steps, the amount of manufactured drugs must be at least 10% of industrial batch scheduled for marketing or in an amount equal to the minimum capacity of industrial equipment to be used (ANVISA, 2009).

Table 2 shows the needs of the experimental drugs XYZ and its clinical comparator for assembling the clinical trial supplies kits. The comparators 1 and 2 were reference products obtained commercially with a longer shelf life as

possible. Usually, the shelf life of tablets is around 2 years. Because of the slow patients recruitment process that is a typical bottleneck in conducting clinical trials, 32% of clinical trial supplies from pilot batch 2 was discarded due to expiration of shelf life. Although we can see that there was also again some waste of products, however the amount of clinical trial supplies that should be discarded was smaller than the initial batch production of the tablets.

In this context it can be noted that despite the difficulty to meet the patient recruitment deadlines, the highest source of waste was the elevated amount of tablets produced to clinical trial based on the minimum recommendation from the regulatory agency, considering the small number of patients that should be recruited for each arm of the study protocol. However, in larger and longer international multicenter trials, when thousands of patients are enrolled, it is necessary to produce larger batches of finished drugs (target drug, placebo, and comparator) that must be shipped to various clinical sites located around the world. It is inevitable in these cases the large amount of the waste resulting from unused clinical trials supplies that should be returned for a proper disposal site for the destruction. Furthermore, when is detected a loss of use condition of clinical supplies due to expiration of shelf life or due to inadequate transportation, handling or storage, all these affected products should also be replaced, leading to production of additional batch, which carries more costs in the development of clinical study.

Although Fleischhacker *et al.* (2015) emphasize in their work that to avoid waste of clinical trial supplies, the

Table 1: Pilot batch production of new drug XYZ and placebo tablets (units) for clinical trial.

	Pilot batch 1		Pilot batch 2		Pilot batch 3		Total		
	Stability and bioequivalence study		Clinical trial		Clinical trial				
Tablets	Produced	Used	Produced	Used	Produced	Used	Produced	Used	Wasted
Drug XYZ	50,000	650 + 45	50,000	1,725	50,000	550	150,000	2,950	147.050
Placebo XYZ	50,000	840 + 60	50,000	2,300	50,000	1110	150,000	4,310	145.690
Placebo C1	50,000	840 + 60	50,000	2,300	50,000	1110	150,000	4,310	145.690
Placebo C2	50,000	840 + 60	50,000	2,300	50,000	1110	150,000	4,310	145.690

Source: The authors own.

Table 2: Requirements of new drug XYZ and placebo tablets (units) for assembling of the clinical trial supplies.

	Pilot batch 1		Pilot batch 2			Pilot batch 3		Total		
	Stability and bioequivalence study		Clinical trial			Clinical trial				
Capsules	Total required	Total produced/purchased	Total required	Total produced/purchased	Exceeded expiry date	Total required	Total produced/purchased	Used	Produced/purchased	Wasted
Drug XYZ	675	675	1,725	1,725	550	550	550	2,400	2,950	550
Comparator drug 1®	675	680	1,725	1,730	550	550	550	2,400	2,950	550
Comparator drug 2®	675	696	1,725	1,728	550	550	552	2,400	2,976	576

Source: The authors own.

manufacturers could produce small batches, however, the high production costs of installation have led the manufacturers to choose to larger batches to prevent the inconsistencies that constitute the variables of high costs. To balance this optimized clearing waste and destruction against the inefficiency of production, Fleischhacker *et Zhao* (2011) generalized a stochastic model to incorporate the risks of failure that adjusts properly the cost parameters to reflect failure and the costs of destruction, suggesting that the increase of power failure rates would lead to reduced production size batches, and would lead consequently to substantial cost savings.

In order to minimize the high capital costs in clinical trial, some authors have proposed some tools of simulation-based optimization approach combining mathematical programming-based planning that can play an important role in the development and manufacturing of a new drug development and avoid the waste (Chen *et al.*, 2010; Colvin *et Maravelias*, 2008; Gatica *et al.*, 2003; Gupta *et al.*, 2003). According to Papavasileiou *et al.* (2007), simulation models can be used to adjust the size of the batches, to discover of certain cycling steps, to estimate cycle times revenue, and so on. A continuous simulation planning should be performed until to obtain an improvement in all supply chain. However, these models are not always adequate; none of them can face the uncertainties in the clinical trials supply chain. While market uncertainty is clearly very important, the uncertainty in the outcome of clinical trials is the most significant source of uncertainty in the development process (Colvin *et Maravelias*, 2008). Nevertheless, it is not only the patient to be recruited is a variable of a study, but also other uncertainties can arise in other stages of the supply chain, such as in manufacturing, process failures and drug production. Furthermore, the average life of a clinical trials supplies chain is about 1-2 years, which is significantly lower than that of a commercial drug supply chain which usually exceeds 10 years. Thus, the strategies used to exclude the uncertainty in commercial supply chains are ineffective when we refer to the of clinical trial supply chain, mainly because each clinical study has its own characteristics that are determined by the influence of factors that can accelerate or delay the completion of the clinical trial.

5. FINAL CONSIDERATIONS

The clinical trial supply chain is characterized by a sequence of planning and programming that are made in order to synchronize better the activities and operations involved throughout the all clinical trial process. This study was based on primary sources of information to describe an overview of the new drug environment and how is made the planning and production for a clinical trial supplies under demand uncertainty based on the decision-making presentation of the process and product portfolio in a

national pharmaceutical industry, focusing as an example an investigational product for a specific clinical trial. Because of the high costs of a pilot plant installation for the exclusive use to clinical trials supplies in a pharmaceutical industry, the commercial products batches production is always redesigned to share with the new drugs pilot batches production within the manufacturing unit, even if the clinical trials outcomes are uncertain: if the drug either passes or fails in a clinical trial. Although the market uncertainty is clearly very important, the uncertainty resulting from the clinical trials is the most significant source of uncertainty in the development process of any new drug. If a drug is successfully launched, it usually leads to great profits that exceed development costs; if it fails, all previous investment is wasted and new drugs have to enter the R&D pipeline again.

The future challenges in the clinical research are still large and complex, and provide a good field for research addressed to clinical supply planning and processes management. These actions can lead to incremental improvements in already existing production processes for new medicines; improvements in the strategic decision-making process to the development of integrated models of the product's life cycle from the drug discovery to consumption; and the creation of scenarios to facilitate the process optimization without the typical bottleneck found along the clinical trial supply chain.

REFERENCES

Abdelkafi, C., Beck, B. H., David, B., Druck, C. and Horoho, M. (2009), "Balancing risk and costs to optimize the clinical supply chain - a step beyond simulation", *Journal of Pharmaceutical Innovation*, Vol. 4 No. 3, pp.96-106.

[ABRADILAN] Associação Brasileira dos Distribuidores de Laboratórios Nacionais (2015), "Genéricos somam 23,7% do faturamento das 10 maiores indústrias farmacêuticas", available at: <<http://www.abradilan.com.br/index.php?m=noticiaFEHYPERLINK> "http://www.abradilan.com.br/index.php?m=noticiaFE&id_noticia=1326"&HYPERLINK "http://www.abradilan.com.br/index.php?m=noticiaFE&id_noticia=1326" id_noticia=1326">. Accessed on 16 november 2015.

[ANVISA] Agência Nacional de Vigilância Sanitária (2009), Instrução Normativa n.2, de 30 de março de 2009, "Determinar a publicação do Guia para Notificação de Lotes-Piloto de Medicamentos", available at: <[http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?jornal=1&pagina=41&ata=01/04/2009"&HYPERLINK "http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?jornal=1&pagina=41&ata=01/04/2009"pagina=41HYPERLINK "http://pesquisa.](http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?jornal=1HYPERLINK)

in.gov.br/imprensa/jsp/visualiza/index.jsp?jornal=1&pagina=41&data=01/04/2009">HYPERLINK "http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?jornal=1&pagina=41&data=01/04/2009">data=01/04/2009". Accessed on 16 november 2015.

[ANVISA] Agência Nacional de Vigilância Sanitária (2010), Resolução - RDC nº 17, de 16 de abril de 2010, "Dispõe sobre as Boas Práticas de Fabricação de Medicamentos", available at: <http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?data=19/04/2010>HYPERLINK "http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?data=19/04/2010&jornal=1&pagina=94&totalArquivos=148">HYPERLINK "http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?data=19/04/2010&jornal=1&pagina=94&totalArquivos=148">jornal=1HYPERLINK "http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?data=19/04/2010&jornal=1&pagina=94&totalArquivos=148">HYPERLINK "http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?data=19/04/2010&jornal=1&pagina=94&totalArquivos=148">HYPERLINK "http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?data=19/04/2010&jornal=1&pagina=94&totalArquivos=148">HYPERLINK "http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?data=19/04/2010&jornal=1&pagina=94&totalArquivos=148">totalArquivos=148". Accessed on 26 november 2015.

[ANVISA] Agência Nacional de Vigilância Sanitária (2015). Resolução - RDC nº 9, de 20 de fevereiro de 2015, "Dispõe sobre o Regulamento para a realização de ensaios clínicos com medicamentos no Brasil", available at: <http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?data=03/03/2015>HYPERLINK "http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?data=03/03/2015&jornal=1&pagina=69&totalArquivos=140">HYPERLINK "http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?data=03/03/2015&jornal=1&pagina=69&totalArquivos=140">jornal=1HYPERLINK "http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?data=03/03/2015&jornal=1&pagina=69&totalArquivos=140">HYPERLINK "http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?data=03/03/2015&jornal=1&pagina=69&totalArquivos=140">HYPERLINK "http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?data=03/03/2015&jornal=1&pagina=69&totalArquivos=140">HYPERLINK "http://pesquisa.in.gov.br/imprensa/jsp/visualiza/index.jsp?data=03/03/2015&jornal=1&pagina=69&totalArquivos=140">totalArquivos=140". Accessed on 26 november 2015.

Chaudhary, K., Rana, A.C., Bala, R. and Seth, N. (2012), "Review: scale up process of tablet production: a prospective discussion", *International Journal of Pharmacy and Biological Sciences*, Vol. 2, No. 3, pp. 223-239.

Chen, Y., Mockus, L., Orcun, S. and Reklaitis, G.V. (2010), "Simulation-based optimization approach to clinical trial supply chain management". *Computer Aided Chemical Engineering*, Vol. 28, pp. 145-150.

Chen, Y., Mockus, L., Orcun, S. and Reklaitis, G.V. (2012), "Simulation-optimization approach to clinical trial supply chain management with demand scenario forecast", *Computers & Chemical Engineering*, Vol.40, pp. 82-96.

Colvin, M. and Maravelias, C.T. (2008), "A stochastic programming approach for clinical trial planning in new drug development", *Computers & Chemical Engineering*, Vol. 32, No. 11, pp. 2626-2642.

Fleischhacker, A., Ninh, A. and Zhao, Y. (2015), "Positioning inventory in clinical trial supply chains", *Production and Operations Management*, Vol. 24, No. 6, pp. 991-1011.

Fleischhacker, A. and Zhao, Y. (2011), "Planning for demand failure: a dynamic lot size model for clinical trial supply chains", *European Journal of Operational Research*, Vol.211, No.3, pp.496-506.

Hovde, M. (2006), "Management of clinical development costs", in Lee, C.H. et al. (Ed.), *Management of Clinical Trials of Drugs and Biopharmaceuticals*, CRC Press, Boca Raton, pp. 87-102.

Gatica, G., Papageorgiou, G. and Shah, N. (2003), "Capacity planning under uncertainty for the pharmaceutical industry", *Trans IChemE*, Vol. 81, Part A, pp.666-678.

Gupta, A. and Maranas, C.D. (2003), "Managing demand uncertainty in supply chain planning", *Computers and Chemical Engineering*, Vol. 27, pp.1219-1227.

[IFPMA] International Federation of Pharmaceutical Manufacturers & Associations (2014), "The pharmaceutical industry and global health. Facts and figures 2014", available at: <http://www.ifpma.org/fileadmin/content/Publication/2014/IFPMA_-_Facts_And_Figures_2014.pdf>. Accessed on 16 november 2015.

[INTERFARMA] Associação da Indústria Farmacêutica de Pesquisa (2015), "Comparações Internacionais no Comércio de Produtos Farmacêuticos e Balança Comercial Brasileira de Medicamentos. Evolução em 10 anos", Interdoc, São Paulo.

Jung, J.J., Blau, G., Pekny, J.F., Reklaitis, G.V. and Eversdyk, D. (2004), "A simulation based optimization approach to supply chain management under demand uncertainty", *Computers and Chemical Engineering*, Vol. 28, pp.2087-2106.

Lee, L.H., Wu, C.L, Lee, B.R. and Lee, C.-J. (2006), "Clinical Trials from Phase I to Phase IV", in Lee, C.-J. et al. (Ed.), *Management of clinical trials of drugs and biopharmaceuticals*, CRC Press, Boca Raton, pp. 113-120.



Lopes, R.D. and Harrington, R.A. (2015), “Compreendendo a Pesquisa Clínica”, AMGH, Porto Alegre, RS.

Papavasileiou, V., Koulouris, A., Siletti, C. and Petride, D. (2007), “Optimize manufacturing of pharmaceutical products with process simulation and production scheduling”, *Chemical Engineering Research and Design*, Vol. 85, No. 7, pp. 1086-1097.

[PhARMA] Pharmaceutical Research and Manufacturers of America (2015), “Biopharmaceutical Research Industry Profile”. PhRMA, Washington DC, available at: <http://www.phrma.org/sites/default/files/pdf/2015_phrma_profile.pdf>. Accessed on 16 Nov 2015.

Plumb, K. (2005), “Continuous processing in the pharmaceutical industry - changing the mind set”, *Chemical Engineering Research Design*, Vol. 83, Part A6, pp.730–738.

Shah, N. (2004), “Pharmaceutical supply chains: key issues and strategies for optimization”, *Computers and Chemical Engineering*, Vol.28, pp. 929–941.

Thiers, F. A., Sinskey, A. J. and Berndt, E.R. (2008), “Trends in the globalization of clinical trials”, *Nature Reviews Drug Discovery*, Vol. 7, No. 1, pp. 13–14.

Tousey, M. (2015), “Manufacturing Process. Tablet and capsule manufacturing”, Vol. 15, pp. 1-12, available at: <http://www.techceuticals.com/The_Manufacturing_Process.pdf>. Accessed on 16 Nov 2015.

World Health Organization (2014), “WHO good manufacturing practices for pharmaceutical products: main principles”, *WHO Technical Report Series*, No. 986, Annex 2.