THE OPTIMIZATION OF GMP/GLP LABORATORIES:

The laboratory utilization and work safety improvement project

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ABSTRACT

Tampereen ammattikorkeakoulu
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The pharmaceutical industry is regulated by the Good Manufacturing Practices (GMP) and Good Laboratory Practices (GLP) in order to minimize the risks that might have an impact on the safety of the patients. The purpose of the regulations is to assure, that the pharmaceutical products meet the safety requirements and have the intended product identity, quality and purity characteristics. Regulations are regulating and covering the whole manufacturing process from the used premises and starting materials to the manufacturing process and final product and disposal of the product.

This study aim was to optimize the pharmaceutical biotechnology company FIT Biotech's Finn-Medi 3 building laboratory premises to meet the assessed quality requirements. The study objectives was to evaluate how to implement the appropriate quality requirements of different laboratory activities in accordance with GLP/GMP regulations. Additionally laboratory system efficiency, working practices and work safety was evaluated before and after the optimization of the laboratories was performed. The impact of the laboratory optimization process was studied through internal audits and the questionnaire was used as a self-evaluation tool for evaluating personnel perspectives of the optimization project.

The experimental work consisted of the laboratory optimization project, where selected laboratory rooms were optimized to a higher quality level as deemed necessary by their intended use. As a result of the optimization project, all optimized laboratory rooms were meeting the set quality level at the time of the second audit. Only few quality related documents were still under updating at the time of the performance of the second audit. The quality level of the Finn-Medi 3 laboratory premises were noticed to be improved and conducting the audit. Audit as a method of evaluation, was noticed to be sufficient for detecting even small deficiencies in the laboratories. Questionnaire results partly supported the audit results, but due to the limited participants wich completed the queries it was difficult to draw any conclusions from the feedback obtained. However, from the evaluation of the completed questionnaires it was indicative that the optimization project influenced to the improved quality level of premises and work practices and result verified also by the audit conducted.

Key words: Good manufacturing practice, laboratory optimization project, audit

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Lääketeollisuudessa lääkkeiden valmistus on tarkoin säädeltyä GMP (Good Manufacturing Practice) ja GLP (Good Laboratory Practice) säädöksissä. Sääntelyn tarkoituksena on vähentää lääkkeiden käytöstä johtuvaa turvallisuusriskiä ja varmistaa, että lääkinnällinen tuote vastaa asetettuja turvallisuusmääräyksiä ja tuotteella on sille tarkoitetut ominaisuudet sekä että se täyttää sille asetetut laatu- ja puhtausvaatimukset. Säädökset kattavat koko tuotantoprosessin tuotantotiloista ja raaka-aineista aina valmiiseen tuotteeseen ja tuotteen hävitykseen saakka.

Tässä työssä bioteknologia lääkeyrityksen FIT Biotech:n Finn-Medi 3 rakennuksessa sijaitsevat laboratoriotilat optimoitiin vastaamaan niille asetettuja tiukentuneita laatuvaatimuksia. Työn tarkoituksena oli kartoittaa kuinka päivitetyissä laboratoriotiloissa GLP/GMP laatuvaatimukset voitaisiin parhaiten toteuttaa. Laboratorioiden toiminta, työkäytännöt ja työsuojeluun liittyvät asiat kartoitettiin ennen ja jälkeen laboratorioiden optimoinnin. Henkilökunnan kokemuksia laboratorioiden optimointiprojektista kartoitettiin laboratoriotilojen päivityksen jälkeen tehtävällä kyselyllä.

Työn käytännön osuuden muodosti laboratorioiden optimointi projekti, jossa tietyt laboratoriohuoneet optimoitiin vastaamaan nykyistä tarkoitustaan. Optimoinnin jälkeisessä auditoinnissa todettiin, että kaikki muutetut laboratoriohuoneet täyttivät niille asetetut laatuvaatimukset. Kokonaisuudessaan Finn-Medi 3:n laboratoriotilojen laadun todettiin parantuneen ja auditoinnin todettiin olevan sovelias menetelmä GLP/GMP sääntöjen noudattamisen kartoittamiseksi. Auditoinnissa ilmeni vain muutamia laadunvalvontaan liittyvien dokumenttien puuttumista. Kyselyn tulokset tukivat osittain auditoinnista saatuja tuloksia, mutta kyselyn perusteella ei voitu tehdä lopullisia johtopäätöksiä optimoinnin vaikutuksesta kyselyyn vastanneiden vähäisen henkilömäärän vuoksi. Kyselyn tulokset kuitenkin viittasivat siihen, että laboratorioiden optimoinnilla on ollut positiivisia vaikutuksia laadun parantumisen ja työkäytäntöjen kehittymisen suhteen.

Asiasanat: Good manufacturing practice, laboratoriotilojen optimointi projekti, auditointi

CONTENT

1. INTRODUCTION

The pharmaceutical industry is regulated by the Good Manufacturing Practices (GMP) and Good Laboratory Practices (GLP) in order to minimize the risks that might have an impact on the safety of the patients. The purpose of the regulations is to assure, that the pharmaceutical products meet the safety requirements and have the intended product identity, quality and purity characteristics. This requires continuous quality monitoring in laboratory premises and work practices to assure that there are intended for the purpose and are meeting the applied requirements. Since workload in the pharmaceutical companies and tendency to have continuous change in laboratory activities have significantly increased, in order to maintain a high quality level of the manufacturing process and its productivity, laboratory facilities and workflow have to be critically reviewed frequently taking into account the quality requirements and work safety of the specific laboratory type.

In laboratory evaluation and optimization process laboratory personnel are challenged to work jointly for achieving compliant results as well as increasing the knowledge of implementing regulations in practice. Pharmaceutical companies should evaluate their laboratories from the operations and maintenance perspective jointly with the laboratory personnel for ensuring personnel awareness of quality requirements and safe laboratory practices (Modica 2007, 25). It seems, that quality auditing alone may not be sufficient method for performing laboratory utilization projects, but combining it to the staff education and supported by the administration and its feedback system, it increases the success of the laboratory utilization projects (Calderon-Margalit, Mor-Yosef, Mayer, Adler & Shapira. 2005. 243). Repeat cycles of the clinical audits combined with the personnel active role and the administrative support in improvement projects and empowerment of the personnel, increases the personnel competence and quality of the work unit (Ved & Coupe 2007, 294).

In this study the pharmaceutical biotechnology company FIT Biotech's Finn-Medi 3 building laboratory premises were updated to support the current laboratory activities and meet the quality requirements according to FIT Biotech's internal audit recommendations.

Audit was used to evaluate how to apply appropriate quality requirements per specific laboratory type and for evaluation of the quality level of the laboratories. Laboratory premises were updated according first audit recommendations in laboratory optimization project. Nine months after the optimization project of the laboratories, laboratory premises were audited for evaluation of quality, laboratory work practices and laboratory safety. - To evaluate how to improve the laboratory system efficiency, working practices and work safety.

Questionnaire result was used as a self-evaluation tool as well assessment tool to evaluate the feedback regarding the impact of the optimization project. Questionnaire resulted feedback how optimization project was affected to the quality of the premises, work practices and work safety.

2. THEORETICAL FRAMEWORK

Pharmaceutical companies are regulated by the law for ensuring the safety of the medical products. For ensuring the safety and quality of the manufacturing process, pharmaceutical companies have to follow specific quality requirements wich have an impact of the whole management and manufacturing process of the company. The current Good Manufacturing Practices (GMP) regulations were originally generated by the Federal Food and Drug Administration (FDA) in the United States of America (USA). Governmental surveys revealed in the 1970's, that pharmaceutical company's clinical research documentation had serious reliability problems. As a survey result, and with the other criteria, modern GLP regulations were then established in 1976. (Anderson 2000, 5.) The regulations were later adopted into Europe, where European Medicinal Agency (EMA) started to control the pharmaceutical industry in the same manner. Both agency's tasks are to ensure, that the regulated industries comply with a total quality control concept through it's manufacturing process. The responsibility to comply with the requirements is determined by the law. (Willig, Tuckerman & Hitchings 1982, 2.)

Adherence to the regulations is a minimum requirement, but it does not ensure, that the manufacturer is in compliance. In addition, manufacturer is bound to continuous practices and processes improvements. Thus, if a new practice is introduced anywhere in the industry which is better than the current one, manufacturers may seem obligated to adopt the better practice or improve own practices into same level. (Willig, et.al. 1982, 4.) New practices must be evaluated frequently for ensuring the compliance of the changed item. For example product, premises or manufacturing process can be audited with different type of audits. Audit is defined as "A planned, independent, and documented assessment to determine whether agreed requirements are being met and it is essential tool for pharmaceutical company for evaluation of quality, work practices and safety of the laboratory premises. (Russel 2000, xxvi.)

2.1. Quality Assurance (QA)

GLP as well as GMP states, that the pharmaceutical company should have a Quality Assurance Unit (QAU), that is responsible for monitoring each study to assure that the management of facilities, equipments, personnel, methods, practices, records and controls conform within the regulations (ref. EMA/FDA Guidelines). QAU is not specifically designated to address the technical items of the study, but rather to assure conformity with the procedural and administrative requirements.

QAU develop strategy, policy and standards on how to implement quality regulations and standards on operational level. QAU monitors by auditing implementation of processes and proper applications, ensures that the specification, production master formula, or other procedures impacting the product are approved and deviations from the procedures are documented. Quality assurance approves contract manufacturers, review and approves validation protocols and reports, makes sure that quality related complaints are investigated and resolved, effective systems for maintaining and calibrations of the equipments are used. Quality assurance also makes sure that there is stability data to support retest or expiration dates and storing conditions. (Anderson, M. 2000, 7-8; Guide to good manufacturing practice for medicinal products part I. 2009, 3; Skubch & Zimmer 2009, 27.)

Implementing quality assurance in to the organization have generally long lasting positive impact on organization culture, if quality system have quantifying measurement tools to detect it's significance and usability (Silimperi, Franco, Veldhuyzen van Zanten & Macaulay 2002, 72). Quality assurance should also ensure that regular internal audits are performed, and that possible changes are approved before they are implemented in practice. Quality assurance task fields are typically accounting for 70% of total vaccine development and production time (Pora 2007, 33). In the light of this information, it can be said, that QA activities are very essential and requires resources to ensure that all quality assurance functions are appropriately implemented.

2.2 GLP and GMP

Good Laboratory Practice (GLP) embodies a set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived. Pre-clinical development is a stage of research that begins before clinical trials (testing in humans) can begin, and during which important data with regard to the safety and efficacy of a product is generated. (http://www.labcompliance.com, 2010.)

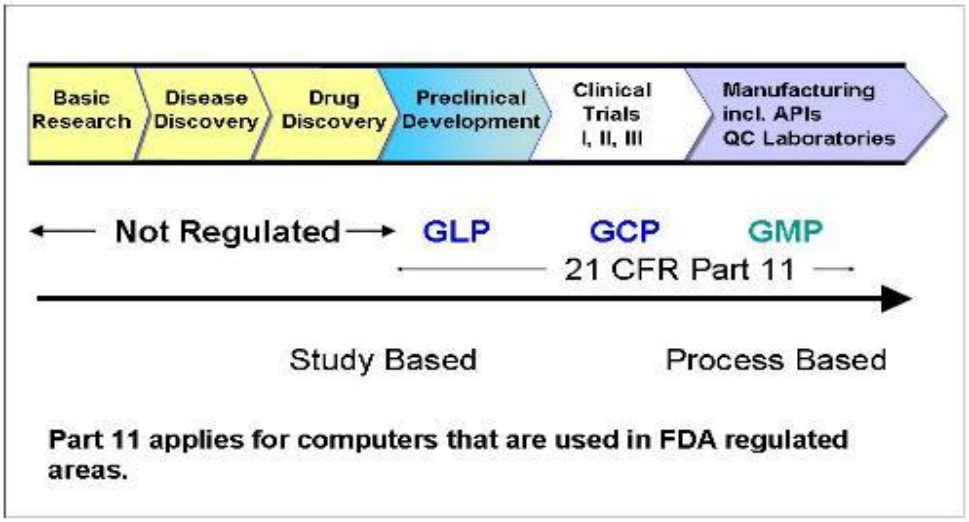
GLP requirements are requested to be followed for all non-clinical safety studies that support clinical trial applications with investigational use only products or in support of marketing authorization applications submitted to Food and Drug Administration (FDA), or to European Medicines Agency (EMEA), or by similar other national agencies. (http://www.labcompliance.com, 2010.) Good manufacturing practice (GMP) is applied when production for clinical trials is initiated.

GMP regulates both production and quality control of a product. GMP is for ensuring that the drug manufacturing process is capable to consistently produce a product of required quality requirements in accordance to pre-determined specifications. Laboratory personnel should be aware of the principles of GMP that affect them and receive initial and continuous training concerning these specific GMP work practices. Laboratory facilities should be well designed with suitable premises and preferably be designed in such a way that it will allow a logical production and material flow in accordance to the specific cleanliness levels requirements. Their layout and design should minimize the risk of errors, contamination and cross-contamination of the product. (Guide to good manufacturing practice for medicinal products part I. 2009, 11.) Biggest difference between GLP and non-GLP work is the type and amount of documentation needed. Characteristic for GLP requirements is that they are study based while the GMP requirements are process based (Stanescu, I. 2010. Personal consultation).

Different development phases require different quality requirements. Picture 1 in the next page illustrates the drug development phases in a pharmaceutical company. As seen from the picture, quality requirements evolve from the least regulated drug discovery to GLP regulated preclinical development phase.

When a company intends to conduct clinical trials and enters the product manufacturing phases, these stages are regulated by the Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP). (http://www.labcompliance.com, 2010.)

Picture 1. Drug development phases (http://www.labcompliance.com, 2010).



2.3 GLP/GMP laboratory characteristics

It is very typical that new projects frequently start in the pharmaceutical company wich is focused to research and development activities. New projects might change the need of laboratory configurations, case-work, equipment, utilities, associated capacities and personnel resources. Some pharmaceutical research laboratories might change layout even several times a year. It is clear, that due to the special requirements of the projects, companies have to customize their laboratories for their new purposes and according to the new quality requirements. (Traknyak 2006, 42, 48.)

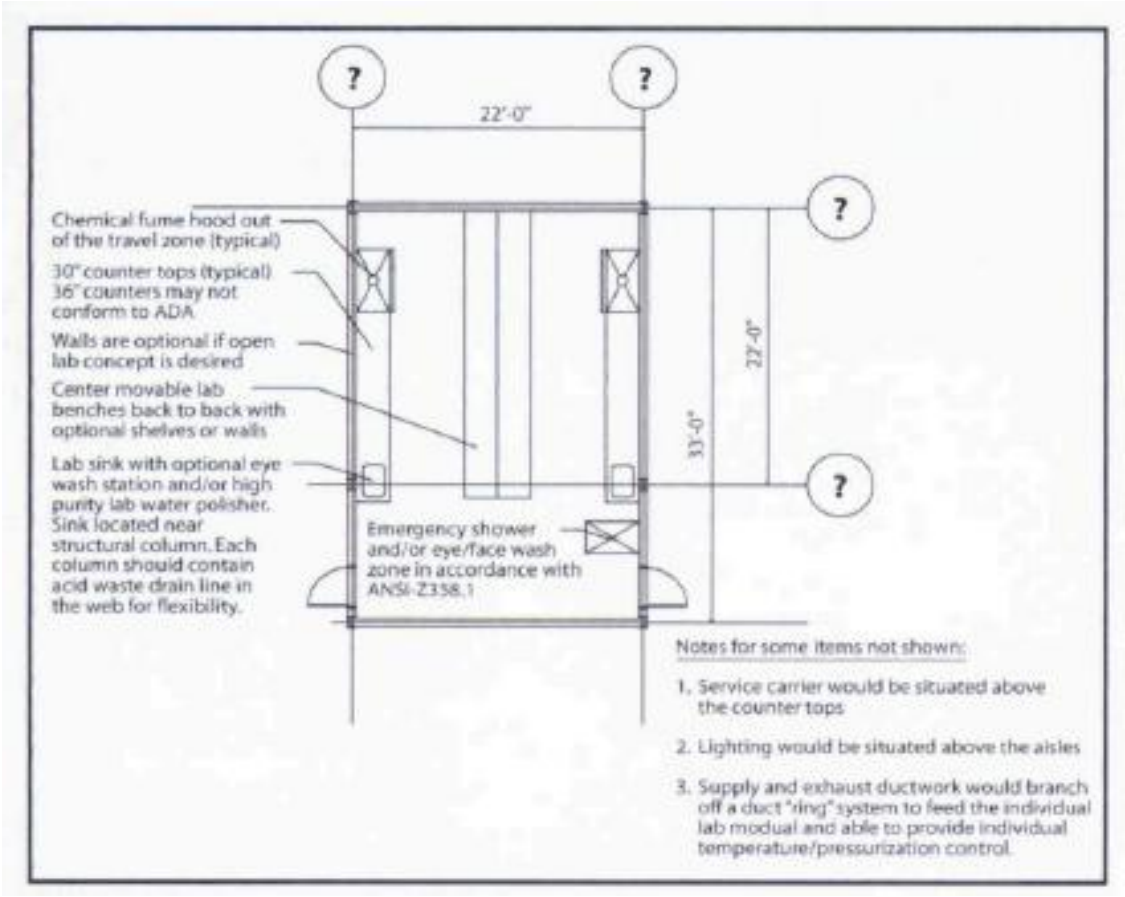
There are four general laboratory function categories; basic laboratories, laboratory support facilities, offices and personnel support facilities. Laboratories can be categorized in numerous types according to their functions. Typical examples of pharmaceutical biotechnology laboratories are microbiological laboratory, molecular biology- and cell culture laboratory, and chemical laboratory. Laboratory support facility includes for example equipment and storage rooms, glassware wash rooms, chemical storage rooms and waste rooms. (Diberardins, Gatwood, Baum, Groden, First & Seth 1987, 13.)

A significant number of procedures in pharmaceutical laboratories are less complex, but delicate, requiring extremely careful sample handling. Quality control laboratory process includes different samples, reagents and different levels of investigations involving various automated and manual methods. Analyses are performed in specialized working cells using sophisticated equipments and computers (eg. separative methods such as chromatography, electrophoresis or image analysis) or activities requiring a controlled environment such as cell culture or DNA characterization based assays. All though some experiments and equipments may be similar with the cell biology, molecular biology and biomedical research laboratories, they may differ from the experiments and equipments point of view. Analytical activities should also have specific proper support system for logistical and engineering activities. (Truchaud, Le Neel, Brochard, Malvaux, Moyon & Cazaubiel 1997, 1710.)

Different laboratory models are more flexible than another. Single corridor laboratory model is a typical laboratory type in small units, and in this type of laboratory, the areas on both sides are same width and rooms are located on both sides of the central corridor. Under 20 year old laboratory facilities have also usually central corridor enough wide to accommodate for example cabins or refrigerators. Laboratories are usually fixed models, and modification of the laboratories is therefore rather difficult without constructive change. (Griffin 1998, 32-33.)

Many special laboratory research and analysis functions are performed manually on a laboratory bench. Typically workbenches are arranged so called “peninsula benches” at the right angles to the window walls. This arrangement creates working cells free from through-traffic. Work aisle is the floor space between the laboratory benches. Equipments and computers occupy significant laboratory bench space and shelves above peninsula benches are usually occupied by reagents and materials. Picture 2 on next page illustrates, a typical fixed laboratory model. (Griffin 1998, 21.)

Picture 2. Laboratory module (Griffin 1998, 21).



Storage of laboratory supplies are usually accommodated under the workbench, on the shelves at the back of the workbench, or in the glass fronted wall cabins. Recently due to the safety awareness, laboratory designers have favored full height wall storage cabinets with the doors and shelves in the operation height. Reaching over and across the instruments on benches for reagents is considered hazardous for personnel and instruments. Also reaching and bending down under or above the laboratory table is considered to be not only un-ergonomic, but also be hazardous for equipments and to the personnel passing by. (Griffin 1998, 48.) Under laboratory tables, there should be sufficient amount of free space for the legs and laboratory chairs should be capable to be modified for different users. In general, laboratory systems, equipments, materials and reagents should be placed into same room, if possible and extra traffic between laboratory rooms should be avoided.

Good reliability in laboratory analysis is greatly influenced by a control and traceability of environmental factors such as temperature and humidity. In clinical chemistry, or molecular biology, where methods are able to reach a very low detection limit for the analyte determination, environmental control is essential for the success of the laboratory analyses. Another issue is biosafety, which has two aspects in the laboratory; prevention of sample contamination and prevention of personnel exposure to hazardous materials. Laboratory should be organized taking into account the needed biosafety requirements in a manner, that implementation of microbiological work and waste management operation is safe, easy and fast. (Biosafety in Microbiological and Biomedical Laboratories 2009, 27; Truchaud, et.al 1997, 1712.)

2.4 Laboratory safety

Pharmaceutical companies are imposed to follow many standards, good laboratory practices and work safety related laws for ensuring the safety of the personnel. Laboratory safety have also wider aspects; which contains product safety for the patient, laboratory personnel safety risks, environment control factors, organization chemical management and waste system and laboratory safety culture.

2.4.1 Safety regulations in the pharmaceutical laboratory

In the pharmaceutical industry, the laboratory safety has played an important role in the good manufacturing practices since regulations were established in 1978. A guide to a good manufacturing practice from year 1982 states, that pharmaceutical companies should have a safety program, which is including detection of hazardous materials, training of the personnel and safety inspection teams to audit work areas periodically. It also recommends organizations to encourage laboratory personnel to be in the discussions with managers to improve the quality control and safety. It was also recognized, that personnel's active role had a positive correlation between work satisfaction, productivity, and the desire of the worker to perform assigned tasks. (Willig, et.al. 1982, 18, 20.)

Over the last two decades, significant changes in the pharmaceutical regulations have occurred and resulted in the adjustment of the original regulations to the current situations. The Food and Drug Administration's (FDA) concept paper "Pharmaceutical cGMP's of the 21st Century": A Risk-Based Approach" forced companies to evaluate and focus more on risk assessments and laboratory safety of their critical operations. (Ahmed, Baseman, Ferreira, Genova, Harclerode, Hartman, Kim, Londeree, Long, Miele, Ramjit, Raschiatore & Tomonto 2008, 1.) Despite of the increased regulation, we have to admit that the manufacturing and use of a drug entails always some degree of risks for the patients. Risks should be evaluated throughout the risks of the product lifecycle from the beginning of the manufacturing process to the end user and disposal of the product. (ICH Guideline Q9, 1.) Product contamination and prevention of the personnel exposure to the hazardous substances could be together evaluated through the laboratory risk assessments. Quality Control implementation and follow up is essential for ensuring that the product risk for the patient is not increased. Pharmaceutical companies risk assessment strategies may vary, but their purpose is always to detect risk factors in a best possible way.

Due to the unique laboratory practices, safety requirements and research applications per laboratory, safety and health considerations must be evaluated on a case-by-case basis (Modica 2007, 24). Although laboratory accidents seldom reach the public media, statistics shows that serious laboratory accidents do happen and small laboratory accidents are quite common, despite of the basic laboratory safety training of the personnel (Diberardins et.al. 1987, 2). It is recommended, that pharmaceutical laboratories should evaluate their laboratories from the operations and maintenance perspective for ensuring personnel awareness of safe laboratory practices. A comprehensive safety program and chemical management that includes medical surveillance, hazardous material control and hazardous work detection as well as proper waste management is essential in pharmaceutical company for a good laboratory safety. (Modica 2007, 25-27.)

Chemical management is also detected to be cost-efficient in improving organization of chemical usage and therefore waste management is often supported by the company's managers (Tischer & Scholaen 2003, 573).

Detailed safety instructions are given in a separate guidelines, standards and safety laws. Each country has own national regulations and it should be noted, that in the case a pharmaceutical company is planning to operate internationally, it is wise to predict regulations and fulfill international or target country requirements already from at the beginning. This requires knowledge of different national requirements and continuous follow-up of international and country specific regulations development. (Karinen 2002, 10.)

2.4.2 Laboratory work safety culture

Another important laboratory safety issue is the laboratory work safety culture. Following questions should be evaluated: How easy laboratory mistakes endanger another laboratory worker or product safety are reported to the manager? Is there a risk not to report or correct the item due to avoiding criticism or disciplinary action by the managers? Does the laboratory personnel share a common language to communicate with? For example along with the language barriers, acceptable safe practices in another country may not be compatible with safe practices in the host country. (Modica 2007, 30.) Laboratory personnel might also have difficulties for understanding the significance of adverse events, or risk factors if they do not understand the matter, where item is related (Reed, Kim, Farquharson & Astion 2008, 959, 961-962). Therefore, support and fluent collaboration and discussions between the personnel and management is needed for the explanation of the risks and how to reduce it.

Organization culture may have a negative or positive impact on how new practices are adopted in the organization. It is said, that the organization culture has its own history and it has been formed on the personnel relationships and management practices. When performing changes, one should also know organization specific culture environment and perform changes by respecting it. (Vartola 2004, 126.) It is always better if there is sufficient time and resources to plan and do the changes jointly with the personnel. Authoritarian style should be avoided whenever possible, since by this way personnel's motivation for work is significantly lower. (Peltonen 2007, 136.)

Open discussions and common agreements between personnel and management, as well as innovative, self-aware and self-learning working communities are seen as the most efficient way to perform changes and lead in the work society (Graber 2006, S47; Harisalo 2008, 286-287).

Laboratory personnel in the pharmaceutical industry have continuous training of the regulations affecting their work. However, knowing the regulations is not the same as applying them into practice. Like Dr. Edward Deming said, profound knowledge is a perception of the truth, which comes from a deep understanding. He has claimed: "Without theory, experience has no meaning. Without theory, one has no questions to ask". (Fasser & Brettner 2002, 39.) Experience of the personnel can not bypass, but competence of the personnel is considered to be profound only if it is based on a theoretical knowledge. This enables personnel to make right decisions in their work and to understand why work has to be done according to GMP requirements.

2.5 Audits

Auditing is a widely used and popular quality improvement tool. In 2006, Pricewaterhouse Coopers survey detected that 50% of the U.S. companies (of all financial sectors) are using continuous auditing techniques and 31% of the rest intend to implement continuous auditing (Alles, Kogan & Vasarhelyi 2008, 196). The purpose of internal control activity is to ensure that the company is on course toward profitability goals and achievement (Gountaras 2009, 932-933). Audits should be conducted in order to monitor the implementation and compliance of the GLP/GMP principles and to propose necessary corrective actions. Furthermore, auditing is used for evaluating the effectiveness of the system in meeting the stated goals, and to identify opportunities for continuous improvement in the system.

One measurement of effectiveness is the degree to which objectives are achieved in an efficient and economical manner. Inspections usually covers personnel matters, premises, equipment, documentation, production, quality control, distribution of the medicinal products, arrangements for dealing with complaints and recalls.

It should be examined at intervals following a pre-arranged program in order to verify their conformity with the principles of Quality Assurance. (Russell 2000, 37, 113; www.who.int 2010.)

Internal audits should be conducted in an independent and detailed way by designated competent person(s) from the company which evaluate the compliance of the quality from different angles (Stanescu, I. 2010. Personal consultation). Auditors should be preferably familiar with the profession to be audited, but like Bowie et.al. (2008) study showed, clinical audit specialists with the sufficient audit training could be as competent auditors, as specific professionals of the area (Bowie, McKay, Murray & Lough 2008, 1041). The ethical issues associated for all parties of the audit should be also evaluated before conducting audits (Patel 2010, 33). The benefits of the audit include the ability of a service to identify deficiencies, areas of excellence and to develop appropriate recommendations that will promote change (Patel 2010, 29). However, despite many good results of auditing, Berk, Callaly & Hyland (2003) show, that if the monitoring of the implementation of audit recommendations is absent, the quality improvement activity might be left incomplete and all goals of quality improvement process is not achieved. (Berk, Callaly & Hyland 2003, 256).

It seems, that quality auditing alone may not be sufficient method for laboratory utilization projects, but combining it to the staff education and supported by the administration and its feedback system, it increases the success of the laboratory utilization (Calderon-Margalit et.al. 2005. 243). Repeat cycles of the clinical audits combined with the personnel active role and the administrative support in improvement projects and empowerment of the personnel, increases the personnel competence and quality of the work unit (Ved & Coupe 2007, 294).

Evaluation of work practices and quality do not always require auditing. Self-evaluation is a useful tool for experienced personnel to evaluate their own work. It is a useful method for soliciting information on that kind of questions, where the participants have the first-hand knowledge. It seems, that self-evaluation tool, especially combined to the survey, is a useful tool for evaluating work practices. It also gives first hand information for the personnel about the level of knowledge and easy the work society to focus on the future improvement targets. (Asadoorian & Locker, 2006. 965-968; Blok, Sleegers & Karsten 2008, 379; Tzavaras-Catzambas, et.al. 2002, 78.)

3. AIM OF THE STUDY

The aim of this study was:

- To evaluate how to implement the appropriate quality requirements of different laboratory activities in accordance with GLP/GMP regulations.

- To evaluate how to improve the laboratory system efficiency, working practices and work safety.

- To study the impact of the laboratory optimization project for the laboratory utilization, work safety, work practices and quality requirements.

4. METHODS, MATERIALS AND STUDY PROCESS

The research laboratory activities in FIT Biotech's Finn-Medi 3 building was changed many times in the past years in a need to adapt new research projects. According to the principle of continuous improvement in pharmaceutical companies, Finn-Medi 3 building laboratory premises were audited in June 2010. The purpose of the first audit made on 9th of June 2010 was to follow-up the cGMP compliance status of the QC laboratories and evaluate also the good laboratory practices in FIT gamma, specifically related to research and development activities.

Totally 11 laboratory rooms were audited in the first audit in June 2010 according FIT Biotech's internal audit procedure by the FIT Biotech's Quality board. Average rate of the evaluated laboratories by four independent auditors was varying from 1 to 3, the average result being 2. None of the rooms were rated as 0 (unsatisfactory). Four rooms of eleven were rated as 1 (not up to acceptable standards), six rooms were rated as 2 (adequate) and one room was rated as 3 (very good). Audit was covering all type of laboratories, eg. protein work laboratory, microbiological laboratory, chemical laboratory, molecular biology work laboratory, cell culture laboratories and bacterial work laboratory. Audit was also including storage areas and facility maintenance area.

As a consequence of the audit, totally 7 out of 20 laboratory rooms were decided to be optimized for upgrading the quality level of the laboratories and to utilize the current usage of the premises. Selected rooms were decided to be optimized and rest of the rooms rated as 2 were evaluated and maintained according to the corrective action plan recommendations and rooms rated as 3 were maintained based on general maintenance procedure applied for the specific laboratory. For rating the laboratories, following rates were used in audit June 2010:

0 = Unsatisfactory	Item/area/system is missing or implies serious quality/compliance errors
1= Poor	Item/area/system is weak and not complying with acceptable standards
2= Adequate	Item/area/system meets basic standards

3= Very good Item/area/system is superior

Practical work for making required changes was agreed to be conducted as part of the laboratory optimization project and required changes were made between August 2010 and January 2011. For implementing the recommendations, the head of the quality control department supported and coordinated the laboratory optimization project. Optimization of the laboratories was decided to be performed from the beginning jointly with all the personnel working in the respective laboratories. The laboratory personnel had the chance first to evaluate the critical working steps, material flow and current work practices, as well as to assess the safety aspects per laboratory room for detecting any deficiencies and possible optimization targets.

After this, the laboratory personnel made needed changes and modifications for the specific laboratory room during August 2010 and laboratory safety officer inspected changes at the end of September. After rearrangement, laboratory rooms risk assessments were updated for detecting any compliance or safety risks of changed room layouts.

Personnel was informed before rearrangement, that made changes will be inspected as part of a periodic internal audit during spring 2011 and the self-evaluation of the impact of laboratory optimization on the quality, work efficiency and work safety will be done by introducing a volunteer based questionnaire.

For evaluation of the impact of laboratory optimization work done during Autumn 2010, a follow-up audit was performed on 23rd of March 2011. Following topics were evaluated by the FIT Biotech's Quality board, representing the inspection team. Audited rooms were selected by the QA with the following inspection topics:

1. Risk assessment reports
2. Procedures applied as described in approved SOPs
3. Sample flow and analyses related reports
4. Equipment qualification and maintenance documents
5. Out of specifications (OOS) results during 2010-2011.

First audited laboratory was functioning before optimization as a storage area for research purposes and was containing not used equipments and materials. Since some laboratories were detected to be overcrowded in previous audit, this room was taken into use and ordered to upgrade to GMP status.

Second laboratory was shared between research and GMP activities prior to the optimization project. Laboratory status was shared also after the follow-up audit, but all equipment and materials in the room were now maintained according to the highest standards. The last two audited laboratories were not under optimization process and their quality status was stated to be the same as at the time of the first audit.

Both audits were based on FIT's own standard operating procedures (SOP) complying with the GMP/GLP audit guidelines. In both audits, results were collected and reported by the head of FIT Biotech's Quality Assurance (QA). Results were presented as a report where observations were listed and proposal of corrective actions and question of compliance were stated.

For evaluating the work safety, improvement of work practices and quality compliance quality, the survey was sent to the personnel participating in the laboratory optimization project on July 2011. The questionnaire layout and persons selected to participate in the survey were agreed jointly FIT Biotech. As part of the optimization of the survey, the questionnaire was pre-tested with one worker, who had taken part in the laboratory optimization work. Pre-testing of the questionnaire was done by the one project worker and final version of the questionnaire was elaborated after pre-testing and discussions with FIT Biotech.

The questionnaire was sent to 13 persons, who had taken part in the optimization work at least to some level, including persons from FIT Biotech's administration, Quality Board and Fit Gamma laboratory personnel, as well as laboratory activities maintenance personnel. Answering to the questionnaire was decided to be voluntarily and without identification. Purpose of the questionnaire as well as instructions how to complete the queries were informed through e-mail. Questionnaire sheets were translated both in English and Finnish and they were sent to the personnel through the in-house post system. The duration for completing the forms was assigned not to exceed one month. Collection of the questionnaires and results were analyzed on August 2011

5. RESULTS

5.1 Laboratory audits

As a consequence of the optimization process, totally 7 laboratory rooms were optimized. The optimization of the selected rooms consisted in upgrading the quality level, evaluation of work practices and safety of the laboratory. In the table below is presented in the laboratory room status before and after the laboratory optimization project. Research grade laboratory requirement is a laboratory where common good laboratory practice is followed, while GLP and GMP level laboratories have specific activities and need to meet the specific regulatory requirements.

Table 1. FIT Biotech's Gamma laboratory status before and after optimization.

RG= research grade, GLP=good laboratory practice grade, GMP= good manufacturing practice grade

Laboratory number	**Status before optimization**	**Rationale for change**	**Status after optimi-zation**
1	Shared RG/ GMP laboratory	RG/GMP grade laboratory should be updated to GMP level, since work has to be done according highest standards.	GMP
2	RG	Nature of work has been changed to GLP	GLP
3	RG	Area containing GMP and GLP material should be minimum GLP grade	GLP
4	GMP/RG	Nature of work has been changed to RG	RG
5	RG	Nature of work has been changed to GMP	GMP
6	RG	Nature of work has been changed to GLP	GLP

7	RG	Area containing GMP and GLP material should be minimum GLP grade	GLP

As a result in the follow-up audit, it was noted, that the quality level of the laboratories was improved to desired quality level. Only some quality related documentation work was still pending at the time of the second audit and one new functionality test was proposed for the extract hood located in one laboratory.

As a result of the optimization project, premises were cleaned and available materials was mapped and introduced for further use. Not used, but available materials were categorized and stored accordingly or materials were found to be useful in another purpose. New storage follow-up system was established for the laboratory materials and awareness of consuming materials was improved. Storage area was re-organized for increasing the storage capacity. Not-in-use equipment was listed and some of them were located more efficiently. All equipment in the laboratory rooms was reviewed and not used equipments were located and recorded to storage. Used equipments were all maintained and documentation was upgraded to have at least GLP grade documentation. Also, equipment database was updated and maintained. All Finn-Medi 3 related risk assessments was updated taking into account all the safety aspects of the quality control laboratories as well as of the maintenance service area.

After optimization project, research grade laboratory work was more clearly separated from the GMP level work and because of the re-organization of the work, the amount of the shared research grade and GMP grade laboratories was reduced. As a result, company was capable to use Finn-Medi 3 laboratory premises in their fully, optimized capacity.

5.2 Questionnaire results

The questionnaire was containing a total of 20 questions related to laboratory quality, laboratory activities and safety. Suggested questions were designed and selected jointly with FIT Biotech's team as described in chapter 4. Questionnaire was used as a self-evaluation tool for the personnel taking to a part of the optimization work and as a feedback from the laboratory optimization process. Totally 7 persons out of 13 answered the questionnaire and from 7 only four answered to all required questions.

Since only four persons answered the survey, questionnaire results can be thought only indicative. However, from the questionnaire can be seen, that the need to have GMP compliant laboratories was understood well among people and introduced changes also stated well (question 1, 2 and 5). Also, changes were stated well, and most answered, that laboratory rearrangement supported the GMP compliance in Gamma very well or well. People provided more "very well" or "well" answers also when they evaluated if they had the possibility to influence laboratory optimization work (questions 3 and 16), but when they were asked about the impact of the laboratory optimization project on their own work (question 6), most answered that it had only some influence. However, most answered, that work practices were improved rather well (20). According survey, different opinions and experience was appreciated during optimization process, and work practice was felt to be improved in Gamma. However, personnel evaluated, that optimization did not have major influence in their own work. The reason of this might be the lack of working with the optimization process, or general facility improvements was perhaps not be seen the way to improve the personal work practices.

When asked about improvements of the laboratory safety and ergonomic topics, personnel evaluated it rather well improved (questions 9-13). According to the personnel, the storage area was mostly improved from facility area, but also the common system utilization was evaluated to be improved rather well. According to the results, the information flow in the laboratory was working rather well, but limited between different departments (question 14).

In the questionnaire (table 2) in the next page is gathered the personnel feedback obtained. Number of specific box illustrates the number of the persons agreed with the claim.

Table 2. Questionnaire form and evaluation.

Questions	Very well	Well	Some	Not at all
1.How well laboratory rearrangement supported the GMP compliance in Gamma?	3	2	1	
2. How well did you find that rearrangement project was supporting company's quality goals?	2	3	1	
3. How did you find that all opinions were taken into account in optimization project planning?	2	2	2	
4. How well information flow worked in Gamma during rearrangement process?	2	4	1	
5. Were chances in the work practices well stated?	2	3	1	
6. How well you felt that because of this project, you had opportunity to influence for your own work?	1	1	4	
7. How much you participate for the optimization of the laboratory work?		2	5	
8. How much you feel that you expanded your knowledge about for applying the GLP/GMP regulations to the laboratory work?	2		1	2
9. How waste handling is improved in FIT Gamma?		4	1	
10. How work safety is improved in Gamma?		4	2	
11.How ergonomic aspects are taken into count in Gamma?		3	3	
12. How system utilization (space, equipments, reagents) are now organized than prior to the re-organization project?	1	5	1	
13. How is the laboratory storage area improved?	3	3	1	
14. Did the project generate information for the other laboratories (outside of the QC) about available materials and equipments in Gamma?	1	3	1	1
15. How you feel, that your work efficiency is improved when working in Gamma?		2	3	1
16. How well you think that your suggestions were taken into account in the optimization work?	2	3	2	
17. How do you think that this optimization project increased the co-operation between different departments?	1	1	4	
18. How well changes made were evaluated with you before and after the project?	1	2	3	1
19. How well you get support during the rearrangement project in Gamma (extra hands or advices)?		3	2	1
20. How well you think that work practices have improved in FIT Gamma?		4	2	

6. CONCLUSIONS

The objective of this study was to evaluate how to implement the appropriate quality requirements of different laboratory activities in accordance with GLP/GMP regulations. Additionally laboratory system efficiency, working practices and work safety was evaluated before and after the optimization of selected laboratories. At last the impact of the laboratory optimization process was studied through internal audits and feedback evaluation of the completed questionnaires.

Totally 7 out of 20 laboratory rooms were optimized in the laboratory optimization project. Project was made with the collaboration of the personnel and was concerning many people from the different level of the organization. Rooms were critical from the quality control work as well as sample and material flow point of view. As seen from table 1, as a result of the optimization, the quality level of the Finn-Medi 3 premises was improved. All seven optimized rooms were having the designed quality level and function as planned at the time of the second audit. Some of the quality documentations were still pending, but under the progress. Safety of the laboratories was inspected after the rearrangement and noted to be sufficient. Audit method was noticed to be capable to detect even small deficiencies in the laboratory and was a sufficient method for detecting the quality level of the laboratories.

The questionnaire was sent to the personnel five months after the second audit. All though the questionnaire was pretested, it was noticed that some personnel did not answer all the questions and many did not answer for the questionnaire at all. Questionnaire was instructed by e-mail and evidently there was further need of having additional instructions provided to increase the rate and interest of completing the queries. Also, survey was made during the holiday season and all though the assigned answering time was over one month, the questionnaire perhaps did not reach all parties. Answering five months after the optimization process could be also too long. Because the lack of numbers of answerers, results are rather indicative and not conclusive.

Personnel were very aware of the set quality requirement and they were interested to give own suggestions for improving work practices and also ready to implement changes in practice. According survey, different opinions and experience was appreciated during optimization process, and work practice was felt to be improved in Finn-Medi 3. However, personnel evaluated, that optimization did not have major influence in their own work. The reason of this might be the lack of working with the optimization project, or maybe general facility improvements not seen be seen the improvement of *own* practice. Also according survey, there might was a sign, of the lack of information flow between different departments.

Project shows, that it is possible to develop further laboratory practices, quality level of the laboratories and safety of the laboratories, if all parties from the different organization level support and take part of the process. As seen from the previous studies, quality auditing alone may not be sufficient method for performing laboratory utilization projects, but combining it to the staff education and supported by the administration and its feedback system, it increases the success of the laboratory utilization projects (Calderon-Margalit, Mor-Yosef, Mayer, Adler & Shapira. 2005. 243). Project indicates, that it is essential to agree the common rules of the project management practices; like responsibilities, sharing information practices and distribution of work tasks in between the project workers before launching the project. Also the feedback system from both the audits and project work was found to be important, since by this way made changes and improvements can be documented and organization is learning from the previous experiences. Project show, that quality level of the laboratories can be improved without making constructive and often expensive changes in the laboratories. However, laboratory optimization is then limited due to the building and premises layout and in some cases work practices and safety can not be improved any further. Results of the questionnaire were leaving still open questions, wich could be studied further. For example, questions such; what are the items in the laboratory work what are changing most efficiently personnel own working practices or what are the best supportive items for achieving improvements for personnel work efficiency? The challenge of this project was to keep continuous, and from both sides reflective information flow between the project workers. According to this experience, the laboratory quality level, and work practices can be improved through audits and shared improvement project, if all parties are work jointly for it.

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APPENDIX 1.

The questionnaire.

Tämä kyselylomake koskee FIT Gamman laboratoriotilojen uudelleenjärjestämistä, joka tapahtui syksyllä 2010. Kysely on lähetetty kaikille järjestelyyn osallistuneille. Kyselyn tarkoituksena on selvittää, millainen vaikutus laboratorioiden uudelleenjärjestelyllä on ollut työnteon ja työturvallisuuden kehittymiseen kannalta FIT Gammassa. Kyselyn tuloksia käytetään Heli Suurosen YAMK opinnäytetyössä. Kysymykset koskevat vain FIT Gammaa ja kyselyyn osallistuminen on täysin vapaaehtoista. Palauta kysely nimettömänä postilokeron vieressä sijaitsevaan palautuslaatikkoon. Kiitos osallistumisesta!

Anna arviosi laittamalla rasti ruutuun:

Kysymykset	**Erittäin hyvin**	**Hyvin**	**Hieman**	**Ei ollenkaan**
1.Kuinka hyvin laboratorioiden uudelleenjärjestely täytti GMP vaatimukset Gammassa?				
2. Tukiko uudelleenjärjestely mielestäsi yrityksen laatu tavoitteiden toteuttamista?				
3. Kuunneltiinko mielestäsi kaikkia osapuolia uudelleenjärjestelyn suunnittelussa?				
4. Tukiko tiedonkulku riittävän hyvin toimintaa uudelleenjärjestelyn aikana?				
5. Oliko toimintamuutokset mielestäsi riittävän hyvin perusteltuja?				
6. Koitko, että pystyit kehittämään omaa työtäsi projektin avulla?				
7. Kuinka aktiivisesti otit osaa laboratorioiden uudelleenjärjestely työhön?				
8. Koitko omaksuneesi jotain uutta tietoa GLP/GMP sääntöjen vaikutuksesta laboratoriotyöhön?				
9. Kuinka jätteiden käsittely on mielestäsi parantunut Gammassa?				
10. Kuinka työturvallisuus parantunut mielestäsi Gammassa?				
11. Kuinka ergonomia on mielestäsi huomioitu Gammassa?				
12. Kuinka tilat on organisoitu (laitteet, reagenssit) alkutilanteeseen nähden?				
13. Kuinka varastointitilat ovat parantuneet?				
14. Tuottiko projekti mielestäsi tietoa muille laboratorioille (QC:n ulkopuolelle) Gammassa saatavilla olevista materiaaleista ja laitteista?				
15. Edistikö järjestely työskentelysi tehokkuutta Gammassa?				
16. Onko ehdotuksesi mielestäsi otettu huomioon lopputuloksessa?				
17. Kuinka projekti mielestäsi lisännyt yhteistyötä eri osastojen välillä?				
18. Onko muutoksia käyty kanssasi läpi ennen ja jälkeen projektin?				
19. Saitko resurssitukea uudelleen- järjestelyn aikana (työtukea tai neuvoja)?				
20. Kuinka toimintatavat ovat parantuneet Gammassa?				

This questionnaire is for the feedback of the laboratory optimization project, made during autumn 2010. This questionnaire is send to all personnel involved with the rearrangement project. Purpose of this questionnaire is to evaluate the impact of the laboratory rearrangement for work practices and work safety in FIT Gamma. Results are evaluated briefly in Heli Suuronen's master's degree thesis. Answering for this question is totally volunteering, and questions are concerning only FIT Gamma. Return this questionnaire unidentified to the box beside the mailboxes. Thank You for your effort!

Please, estimate by marking X to the box.

Questions	Very well	Well	Some	Not at all
1.How well laboratory rearrangement supported the GMP compliance in Gamma?				
2. How well did you find that rearrangement project was supporting company's quality goals?				
3. How did you find that all opinions were taken into account in optimization project planning?				
4. How well information flow worked in Gamma during rearrangement process?				
5. Were chances in the work practices well stated?				
6. How well you felt that because of this project, you had opportunity to influence for your own work?				
7. How much you participate for the optimization of the laboratory work?				
8. How much you feel that you expanded your knowledge about for applying the GLP/GMP regulations to the laboratory work?				
9. How waste handling is improved in FIT Gamma?				
10. How work safety is improved in Gamma?				
11.How ergonomic aspects are taken into count in Gamma?				
12. How system utilization (space, equipments, reagents) are now organized than prior to the re-organization project?				
13. How is the laboratory storage area improved?				
14. Did the project generate information for the other laboratories (outside of the QC) about available materials and equipments in Gamma?				
15. How you feel, that your work efficiency is improved when working in Gamma?				
16. How well you think that your suggestions were taken into account in the optimization work?				
17. How do you think that this optimization project increased the co-operation between different departments?				
18. How well changes made were evaluated with you before and after the project?				
19. How well you get support during the rearrangement project in Gamma (extra hands or advices)?				
20. How well you think that work practices have improved in FIT Gamma?				