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A manual bioanalysis process turning computerized

How will the security, efficiency and usability of the bioanalysis activity be affected?

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Abstract

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Authorized pharmaceuticals are developed through a long and extensive period of research and clinical trials. The security issue is of highest concern and is controlled throughout the whole development process. Quintiles AB is a Contract Research Organization, which is serving pharmaceutical companies with all kinds of performances within clinical studies. Since the customers' demands of stricter security regulations grow, and efficiency has to be improved, the department of Analytical Services (AS) at Quintiles has chosen to implement a computer system called Watson LIMS. The system is specifically designed to suit the bioanalysis activity at Quintiles AS and is also used at several large pharmaceutical companies. This master thesis treats the consequences of transforming a manual bioanalysis process, into an overall-covering computerized system. Focus is set on the parts of the bioanalysis process, which will differ the most between current and the future Watson LIMS system. These stages are then analyzed according to particularly the impact on security and efficiency, but also to the effect on system usability. The project has been carried out using a Human-Computer Interaction approach. To identify the stages of current interest, a documentation of the bioanalysis workflow of today have been performed using the method of Hierarchal Task Analysis. Information was gained through documentation, observation and semi-structured interviews. Most information about Watson LIMS has been collected through written material and by manually testing the system.

Several conclusions can be drawn from this project; some of them can be used as platforms for further discussions, while others will be important to consider when implementing Watson LIMS into customer studies. The system will improve the security due to fewer manual actions, which decreases the risk of human mistakes. However, attention has to be paid to the assignment of user roles, as well as assurance that no data is transformed to or from unvalidated systems. Watson LIMS will improve efficiency, especially during report compilation and Quality Assurance control. It is, however, clear that the first year of usage will not save as much time as estimated. Concerning usability, Watson LIMS will partly change work routines for all employees at the department. Since the system is less user-friendly than expected, an extensive employee education will be needed to make the start of usage as convenient, efficient and positive as possible.

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SAMMANFATTNING

Att utveckla ett nytt läkemedel är en otroligt kostsam och komplicerad process. En flerårig period av grundforskning av en intressant läkemedelssubstanskandidat följs av ytterligare år av kliniska studier då substansen testas på olika patientgrupper för att kontrollera bland annat effektivitet, dosreglering och eventuella bieffekter. Genom hela utvecklingen läggs stor fokus på patientens säkerhet, vilket gett upphov till ett omfattande internationellt regelverk. Läkemedelsföretagen måste följa detta regelverk för att få tillstånd att sälja ett certifierat läkemedel på en internationell marknad.

Det här examensarbetet är utfört på Quintiles AB, som betecknas som en *Contract Research Organization*, vilket innebär att företaget erbjuder olika tjänster inom kliniska studier till läkemedelsföretag. Då Quintiles kunder ständigt efterfrågar ökad säkerhet och effektivitet på tjänsterna, har företagets bioanalytiska avdelning beslutat sig för att investera i ett omfattande datasystem, *Watson LIMS*. Detta system är specifikt utvecklat för att passa Quintiles typ av bioanalytisk verksamhet. Syftet med detta examensarbete är att undersöka konsekvenserna av att omvandla en idag relativt manuell bioanalytisk process till ett system styrt och kontrollerat av datasystemet Watson LIMS. För att nå syftet har inledningsvis en kartläggning av respektive process utförts, för att kunna identifiera de moment där de båda systemen skiljer sig åt mest. Därefter har de utvalda momenten analyserats och jämförts med avseende på följande tre faktorer: *säkerhet, effektivitet och användbarhet*. Teoriarbetet är grundat på *människa-dator interaktion* och metoden som används för kartläggningen av de båda processerna är *hierarkisk uppgiftsanalys*.

Flera resultat har nåtts med detta examensarbete: en detaljerad kartläggning av dagens process respektive framtidens process har skapats och analyser av hur verksamheten kommer att påverkas av det nya datoriserade systemet har utförts. Vissa av analysens slutsatser är ämnade att fungera som diskussionsunderlag inför en kommande utvärdering av det nya systemet, medan andra kan vara viktiga att ta hänsyn till redan under införandet av Watson LIMS. En slutsats är att det nya systemet kommer att medföra en ökad säkerhet av data eftersom det automatiserar flera moment som idag utförs manuellt och därför utsätts för en risk av att mänskliga fel begås. Vidare kommer Watson LIMS att öka bioanalysprocessens effektivitet, särskilt med avseende på momenten rapportskrivning och kvalitetskontroll. Beträffande användbarheten så kommer Watson LIMS att förändra arbetsrutiner för samtliga anställda på bioanalysavdelningen. Eftersom datasystemet under implementeringsarbetet visat sig vara mindre användarvänligt än man hoppats på är det väldigt viktigt att en gedigen användarkurs hålls med de anställda för att få en så smidig, effektiv och positiv start på användandet av Watson LIMS som möjligt.

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1 INTRODUCTION

The research and development in the pharmaceutical industry are governed by the national politics, as well as the by the current condition of the business cycle. During the period of 1937-1967, the Swedish pharmaceutical research reached an international high standard, which laid the basis of today's industry. Pharmaceuticals are today one of the Swedish largest export goods. In the Stockholm area, including Uppsala and Södertälje, there are approximately 70 pharmaceutical companies and Contract Research Organizations (CRO). Some of these are global, but most of them are small. CROs are serving pharmaceutical companies by selling all kind of services within the clinical development industry. (Centrum för Medicinska Innovationer, www)

1.1 Bioanalysis at Analytical Services, Quintiles AB

Quintiles AB is the Swedish subsidiary of Quintiles Transnational, and is classified as a Contract Research Organization (CRO). The company performs the complete range of services for the pharmaceutical industry, from First-In-Man through Proof of Concept (Phase IIa) to Phase IV clinical trials. It houses fully-integrated bioanalytical and clinical chemistry laboratories, where projects and studies are being planned and prepared, samples processed and data handled and summarized in reports.

Analytical Services (AS) is a bioanalysis department at Quintiles AB, which carries out service for both the in-house phase I clinic, and projects assigned by external customers as pharmaceutical companies. Projects, called studies at Quintiles AS, include a number of samples taken from human or animal subjects in a clinical trial. Most often there are several samples from the same subject, taken at different moments. The samples contain traces of study-specific biochemical substances, which the employees at Quintiles AS are contracted to analyze the concentration of. The samples of the studies are after arrival registered and stored in one of the freezers, processed at the laboratory and then analyzed at one of the instruments (HPLC, GC or LC-MS/MS). In the end of the study, data are analyzed and compiled into a report. The current bioanalysis process is in general manual, except for two instrument specific computer systems.

1.2 Problem description

The bioanalysis department at Analytical Services, Quintiles AB, has during the past time been facing higher and more specific demands from their customers regarding especially study security and study data and results. In order to meet these increasing requirements, Quintiles AS has taken the decision to invest in a computer system; *Watson Laboratory Information Management System (Watson LIMS)*, which is specifically designed for use in bioanalysis and aimed to increase study efficiency and security. The system will highly affect the whole Quintiles AS activity and especially the bioanalysis process. The routines of the department will differ in handling of data, reanalysis decision makings, report writing and internal quality control. It will also allow for larger sample handling regarding study data and results, without affecting the data security issue.

However, installing such an extensive computer system is a complex procedure, which involves an extensive qualification before it can be taken into use. It will also take a period of time for all employees to learn how to use the new computer system. Since the Watson LIMS system is a big investment and the installation process is long and complicated, awareness of changed routines, difficulties and effects on the bioanalysis workflow, is of highest concern. To achieve this information, a comparison is made between the current manual process, and the future process when using the Watson LIMS system. Through this comparison information about the parts of the bioanalysis process which will differ the most between the new and the old system, will be gained. These certain stages are then of interest to study according to the following criteria: system security, efficiency and usability.

1.3 Aim and goals

The aim of this master thesis is to generally document the existing bioanalysis process and the future bioanalysis system, after the implementation of Watson LIMS. Detailed descriptions will be carried out regarding stages where the systems differ greatly according to changed routines in work. These various parts of the process will furthermore be investigated and analyzed regarding the systems security, efficiency and usability.

1.4 Thesis delimitation

To implement a new overall-covering computer system is a complex procedure involving many complicated tasks and decisions. Today Quintiles AS has passed through many of the stages in the installation process and is for the moment carrying out a part called *Operation Qualification*. They are planning to start using the Watson LIMS in about two months from now. An interesting topic to study would be how this installation has been performed, from the beginning of the first discussions to invest in a LIMS system, until today when a big part of the work has been done. This analysis will not be made within the delimitations of this thesis, partly due to the fact that large parts of the installation process remain. Such study would most likely be of interest for other companies going through the same kind of installation.

1.5 Disposition

The thesis starts out with an introduction which lets the reader understand the bioanalysis activity performed at the department of Analytical Services, Quintiles AB. This text narrows down to a problem description and the aim and goal of the thesis. The introduction is followed by a theory chapter 2, which explains the theoretical foundation of the study carried out, including the terminology of a technical system, work domain analysis and task analysis. Chapter 3 describes the used methods for the execution of the thesis and chapter 4 contains a short work domain analysis of Analytical Services. Furthermore, chapter 5 consists of an activity description of the current system, both in general and more detailed concerning some of the process stages, as chapter 6 deals with the corresponding descriptions in the future bioanalysis activity. In the results and analysis chapter 7, the differing stages between the systems will be studied and analyzed concerning how the new process will be affected regarding the system security, efficiency and usability. This chapter is followed by the conclusion chapter 8, which summarizes the most important and interesting results and reflections of the study presented.

1.6 Glossary and abbreviation explanations

Analyte	A specific chemical substance being measured, which can be intact drug, biomolecule or its derivative, metabolite, and/or degradation product in a biological matrix such as blood, urine or plasma.
AS	The department of Analytical Services, Quintiles AB.
Batch	A complete set of analytical and study samples with appropriate number of standards and QCs for their validation. Several batches may be completed in one day, or one batch may take several days to complete.
Blank samples	A sample including no internal standard, working as a bioanalysis reference.
Calibration samples	A biological matrix to which a known amount of analyte has been added. Calibration samples are used to construct calibration curves from which the concentrations of analytes in QCs and in unknown study samples are determined.
CRO	Contract Research Organisation, a company or organization which sells services related to clinical trials.
Customer	Most often a pharmaceutical company.

DM	The department of Data Management, Quintiles AB.
FDA	U.S. Food and Drug Administration.
GLP	Good Laboratory Practice. GLP approval is given to laboratories which are shown to meet GLP regulations as when impartial assessed. The approval is given by the Swedish Medical Products Agency, which is a GLP authority within the area of clinical products.
HPLC	High Performance Liquid Chromatography, a bioanalysis method.
Internal standard	Test compound(s) (structurally similar analog, stable labeled compound) added to both calibration samples and quality control samples to facilitate quantification of the target analyte(s).
IQ	Installation Qualification. Verifies and documents an implementation process.
LC	Liquid Chromatography, a bioanalysis method.
LC-MS/MS	Liquid Chromatography Mass Spectrometry, a bioanalysis method.
LLOQ	Lower Limit Of Quantification. The lowest amount of an analyte in a sample that can be quantitatively determined with suitable precision and accuracy.
OECD	Organization for Economic Co-operation and Development. States the series on Principles of Good Laboratory Practice.
OQ	Operation Qualification. Verifies and documents the functionality in the actual operative environment.
PQ	Performance Qualification. Verifies and documents the continued suitability of the system for its intended use.
Raw Data	Raw Data is a printed and signed paper copy of data.
Sample	A generic term encompassing controls, unknowns, and processed samples.
SOP	Standard Operating Procedures, created to suit the Quintiles AS activity in accordance to the GLP guidelines.
SWEDAC	The Swedish national committee for technical ACcreditation.
Validation	A validation procedure should provide documented evidence that a system or a product is suitable for its intended purpose.
QA	Quality Assurance. An internal quality system intended to secure that the bioanalysis follows stated quality requirements.
QA audit	Comparison of raw data and to those belonging documents, to verify if raw data have been reported correctly and if bioanalysis have been performed in accordance to protocols and Quintiles AS SOPs.
QA auditor	The occupation of a person performing the final report quality controls, including data audits.
QC	Quality Control. Regards an external or internal control program aimed to follow up and correct the bioanalysis activity.
Quality control samples	Spiked samples run in parallel with the study samples to ensure the integrity and validity of the results of the unknown samples. Normally three concentrations levels are used: the lower level are 2-3 times the LLOQ-value, the middle at the expected mean concentration range and the upper at 75-90 % of the highest calibration level.

2 THEORY

The following chapter gives the reader an introduction to the theory of which this master thesis is built upon.

2.1 Complex sociotechnical systems

Using the word *system* is very common within all kind of areas. The meaning of the word is a set of components which all together form an entirety. The different parts have different properties which affect one another and gives the whole a certain characteristics.

2.1.1 System complexity

Socio-technical systems are composed of several layers which all play a significant role in affecting the whole system. This is very important to emphasize since the technical core by tradition always has been regarded as the entire system, which is today seen as fundamentally misguided. A socio-technical system is highly influenced by the users' skills. Their capabilities and individual way to interact with the technical system will strongly affect the performance of it. (Vicente, 1999, p.12) The most common reason for system errors and accidents in technical functioning systems, are the human mistakes. Such mistakes can not completely be guaranteed to never occur, even though much human tasks are controlled and made into routines. The social-organizational factors are also important to take into account, since they play a crucial role in system performance. These factors often have great impact on the security and on the users' daily routines. A socio-technical system is also affected by the surrounding environment which naturally differs depending on type of industry. Examples of environments affecting the system are international trade laws, regulatory requirements, other companies competing for a significant share of the same market or a set of rules and regulations such as the pharmaceutical GLP guidelines.

Figure 2.1 shows a schematic picture of a complex socio-technical system, in which all the layers in practice are intimately intertwined with each other. The key is to understand the interactions among them. They form together the system as a whole, illustrating the importance to always study systems in a holistic approach. (Vicente, 1999, p.13)

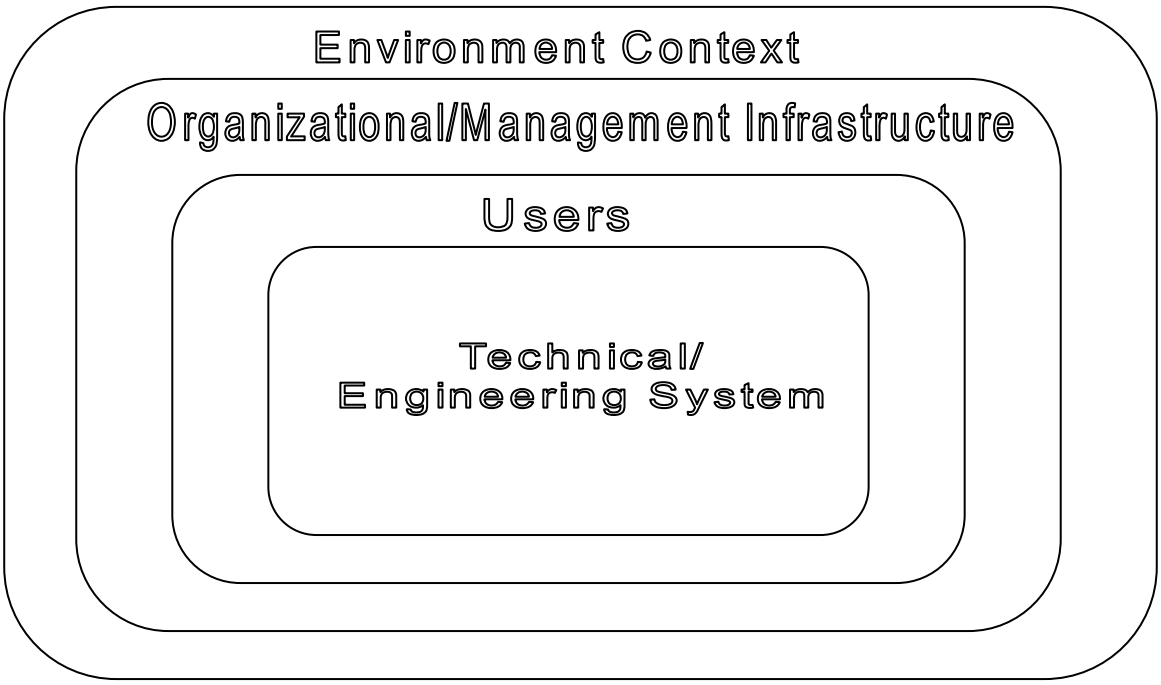


Figure 2.1 Layers of a complex socio-technical system (adopted from Moray & Huey, 1988).

2.1.2 Human Computer Interaction (HCI) – an important pattern of all modern systems

> "*In the short term, HCI can help improve interactive computer systems in two important ways: first, it can guide a systematic, careful analysis of what information, tools and capabilities people need to achieve their goals, and second, it can provide tools and techniques with which to evaluate usability in an effort to remove flaws that hinder smooth interaction between people and computers.*" (Lindgaard, 1994, p.4)

Even though this definition is made several years ago, it is still an up-to-date description of what HCI actually concerns. It has today become a scientifically accepted discipline which concentrates on an interactive computing system for human use, regarding design, evaluation and implementation. (Göransson, 2001, p.13)

HCI is a multi-disciplinary subject which has a big impact on design and development of many kinds of systems, ranging from nuclear processing where security is extremely important, to office systems where focus involves productivity and job satisfaction. The subject may be divided into four areas: Use and Context, Human characteristics, Computer and Development process. These areas need to be investigated in order to develop a successful interactive system. The users' background, skills, tasks and working environment have to be known. Also the technical limitations, possibilities and the developmental tools are important to understand, as the process or framework guiding the development of the new system. HCI has traditionally been a scientific subject built up by heavy theories of computer systems and human behaviour. This has made it difficult to use HCI methods in commercial and industry developmental projects, since it has been almost impossible to use the theories the exact way as they are described in the literature. (Göransson, 2001, p.14-17) Research results have been too specific to be able to be used more generally, or they have felt too abstract to apply on a system. Recently though, HCI has been better adapted to appliance, which has made the subject further used in practical processes and increased the interest of students. (Harrison & Thimbleby, 1990, p.2)

2.1.3 Effective systems: secure, productive and healthy

The three most essential criteria for a system to satisfy is safety, productivity and the health of the users. Current socio-technical systems in the industry often have deficiencies in the way they are dealing with these perspectives. To be able to design new improved systems or analyze existing ones, the nature and behaviour of these criteria have to be understood. (Vicente, 1999, p.20)

Security

Security is a crucial issue, not only in systems with large-scale catastrophes as potential risks, but in all kind of systems and in all kind of industries. Sometimes risks regard ecological or life-threatening consequences, but probably most often discussed are the economic ones. Whatever the threats concern, every design should be based on a work analysis framework reducing the risk of user failures. What often triggers a risky situation is an abnormal event for which there are inadequate or no procedures. This means that these situations were not encountered for during the design of the particular system. Investigations made at a nuclear industry showed that 100 percent of the unanticipated events which were not handled successfully by the users, consisted of situations for which there was no procedure or the existing procedure had to be modified. For this reason, identification of what information and support users need in case of unfamiliar events is important to include when analyzing human work. (Vicente, 1999, p.20-22)

Complex, interactive systems may have a strong or a loose connection between the interacting parts. If the interactions are "tight", the user has to make faster decisions, which sometimes make it more difficult to interpret the information correctly and to be able to view the system as a whole. A good alternative is to design the interactions more "loose", if possible, letting the user have enough time to

discuss an unanticipated situation with other users or else, find other instruments to use, if that is the problem. (Berner, 1999, p.129)

Productivity

Just as meeting the safety criteria may be problematic, also the productivity criteria might be difficult to achieve. Improving productivity is essential when analyzing human work, since the productivity is a measurement of how successful a design is. Vicente (1999, p.22-27) concentrates his discussion to a research made by Landauer (1995) about the impact of information technology on industry productivity. Landauer's research shows surprisingly that information technology has generally not led to improvements in productivity growth. He actually claims that the technology is responsible for the decline in productivity growth observed in industrialized countries since the early 1970's. One reason for the decline is that the computer systems are often not designed in a user-friendly way, including the functionality that is required to perform the work effectively and reliably. This often makes the computers complicated to use. Data also shows that office employees spend much time on unproductive computer-centred activities. Lots of time is also "wasted" on helping colleagues solve computer-based problems. This discussion states that the work analysis made when designing a computer system must focus on usability in order to overcome the productivity paradox. (Vicente, 1999, p.22-27)

By using the thinking of HCI in designing interactive computer systems, large benefits may be achieved in productivity even though these are often hidden, intangible and unquantifiable. Except HCI, there are many other issues to be taken into account when evaluating the implementation of a new system. The hardware costs are constantly decreasing, while the organizational costs of implementing new technology can be very high and often lead to changes in the organization and the structure of jobs. According to Preece *et al* (1994) many implemented systems are not leading to the planned success and the statistics presented are following:

Success	20%
Marginal gain	40%
Failure/rejection	40%

Therefore it is very important to understand the effects of new technology, in order to avoid financial loss and stress among the staff. (Preece *et al*, 1994, p.19-22)

Usability and health

According to Lindgaard (1994, p.20), "the usability of a computer is measured by how easily and how effectively it can be used by a specific set of users, given particular kinds of support, to carry out a fixed set of tasks, in a defined set of environments". How the measurements are carried out and what they are focusing on is widely different.

Some examples are:

- Percentage of tasks completed successfully at first attempt.
- Percentage of relevant functions used.
- Number of persistent errors.
- Rating scale for satisfaction.
- Frequency of reuse.

This shows that usability goals cover not only user satisfaction, but also effectiveness and efficiency of the system. Goals are essential to state, but have to be adapted to the project and the resources available.

Examples of usability goals are:

- Self-descriptiveness
  The dialog is explained to the user when requested or immediately shown from the system.
- Match between system and the real world

The system has the same language as the users instead of system-oriented terms.

- User control and freedom
  User wants for example to be able to exit a state without further dialogues. It should support undo and redo. (Göransson, 2001, p.17-26)

Göransson (2001, p.20) further states: "A product has no intrinsic usability, only a capability to be used in a particular context. Usability cannot be assessed by studying a product in isolation." The new technology does not improve or degrade people's work, what actually matter is the way it is used. Depending on how it is used it can have a big impact on the organization and the way people feel about their work.

Working practices may change in several ways:

- Work content
- Personnel policies
- Work satisfaction
- Power and influence
- Working environment

Hopefully the new system gives the workers more variation and skills, but it may also cause more routines and larger volumes of work. The best way to avoid bad consequences of new technology is to design and implement the system in parallel with design and redesign of the company's organizational structures. (Preece *et al*, 1994, p.21-23)

Vicente (1999, p.27-33) discusses the comparatively ignored perspective of work analysis; worker health. Health care of employees cost companies a large amount of money each year and by designing healthier computer-based work, great savings can be made. He further states that users with high level of psychological demands in their work and low latitude of making own decisions, suffer much from stress, which is an important factor influencing the health. Such circumstances combined with computerization leads to even more negative effects on employees' health, according to research made in the area. Therefore it is necessary to explicitly design computer systems for healthy work in order to save health care costs and create more humane jobs. (Vicente, 1999, p.27-33)

2.2 Work domain analysis

Work domain analysis is the first, and probably the most important and unique, phase of Vicente's Cognitive Work Analysis. It is often performed as a field description, which shows the controlled system independent of any particular worker, event, task, goal, or interface. The main reason to carry out the analysis is to identify the information requirements needed for workers to deal with unanticipated events. In a complex sociotechnical system, unfamiliar situations which have not been anticipated by designers are the greatest threat to security. To improve the security of a system, enough support has to be given the employees, in order for them to have a better chance of detecting, diagnosing, and compensating for unanticipated events. (Vicente, 1999, p.149 ff)

When carrying out a work domain analysis, the following questions are helpful to consider:

- What information should be measured?
- What information should be derived?
- How should information be organized? (Tang , www)

The conclusions of the questions can then be summarized in a work domain presentation.

2.3 Task analysis

Task analysis is the study of the way people perform tasks with existing systems. This includes the actions they perform, the things they act on and the information they need to know. (Dix *et al*, 2004, p.511) Task analysis at some level of detail should ideally be done early in the design process, since it

gains an understanding of what people do in the existing system. The method effectively explicit how to allocate human and machine resources to ensure the security, productivity, and satisfaction in human-machine, human-human and machine-machine interactions. (Lindgaard, 1994, p.49)

2.3.1 Different approaches to task analysis

There are many ways of ordering different kind of task analysis techniques. Dix *et al* (2004, p.511) considers three different approaches: *Task decomposition*, *Knowledge-based techniques* and *Entity-relation-based techniques*.

Task decomposition

Task decomposition studies the way a task can be divided into goals, tasks and actions. To be able to make this division, questions as "What is being done?" and "How are these tasks accomplished?" are asked (McCrohan, www). Task analysis addresses what is actually done in a system, not what should be done. The *goal* can be defined as a system state which the user wants to achieve, as for example to write a report. This goal can be accomplished using a variety of *devices* such as instruments, methods, skills, users or techniques. When a device is selected by the user, the tasks necessary to achieve the goal may be understood. A *task* can be defined as the activities that the user is needed to perform in order to accomplish the goal by the particular device. The task involves different *actions*, known as simple tasks, which are performed in a special order to perform a particular task. Actions can be defined as tasks that involve no problem solving, as for example physically moving an instrument or typing a command on a keyboard. (Preece, 1994, p.411) One type of task decomposition approach is *Hierarchical Task Analysis (HTA)* which will be further discussed in chapter 2.3.2.

Knowledge-based techniques

In contrast to task decomposition which starts with a high-level task and breaks it down into subtasks, knowledge-based analysis works from the bottom up. The analysis starts by listing all *objects* and a*ctions* relevant for the task that is being analyzed, based on collected data. These objects and actions are then organized into groups based on similar characteristics, and these groups are further arranged into larger groups. (Lindgaard, 1994, p.52) This classification results in a taxonomy – a naming hierarchy. To give a short summary; this technique basically concentrates on what the users need to know about the actions and activities involved in a task and how this knowledge may be organized. (Dix, 2004, p.519-524)

Entity-relation-based analysis

Entity-relation-based analysis is a bottom-up approach to task analysis and the most "computer-like" technique among these presented here. This analysis also concerns *objects* and *actions*, but instead of focusing on their similarities, the emphasis is on the relationships between them. There are four different kinds of objects: simple objects, actors, composite objects and events. The way these are correlated and then analyzed, is very similar to object-oriented programming. (Dix, 2004, p.519-524)

Knowledge-based techniques and Entity-relation-based analysis will not be discussed further in this thesis.

2.3.2 Hierarchical Task Analysis

How does it work?

Hierarchical Task Analysis (HTA) is the most well known form of task analysis and uses a task decomposition approach. It divides tasks into subtasks according to the *Task decomposition* theory, and also helps the analyst to establish when and in which order the subtasks should be carried out to meet the goal. The analysis can be developed to any level of detail. Therefore it may be difficult to know which level best describes a certain task. (Lindgaard, 1994, p.53)

How is it carried out?

An HTA can be divided into three stages: starting, progressing and finalizing.

1. *Starting the analysis*:
   Specify the area of work or main task and break down the main task into between four and eight subtasks, specified objectively. Order the subtasks into a logic and technically correct plan.

2. *Progressing the analysis:*
   Decide at which level of detail to stop the decomposition of subtasks, ensuring that they all are treated consistently. Continue by numbering the subtasks as shown in figure 2.2, put in a diagrammatic form.

3. *Finalizing the analysis:*
   Check the consistency of the decomposition and the numbering, and produce eventually a textual task decomposition. Ask someone else who knows the tasks well, to further check for consistency.

The tasks and subtasks are finally shown in an HTA diagram and numbered the way the analyst prefers according to the order in which the subtasks are performed. (Preece, 1994, p.414-416)

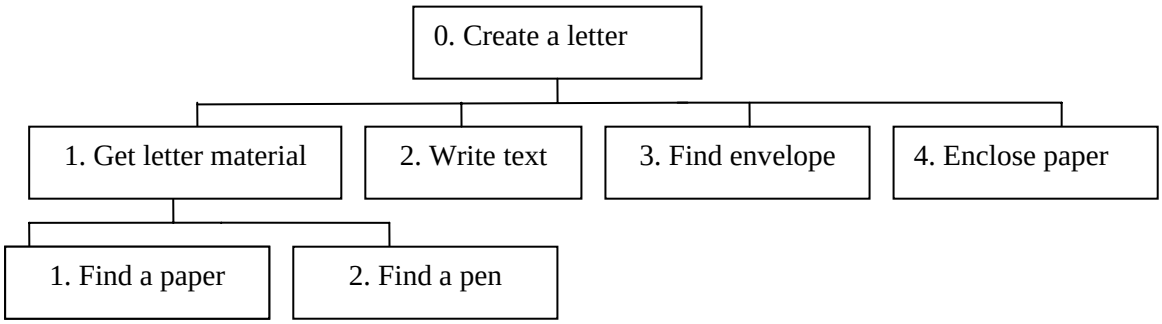


Figure 2.2 An "easy-to-understand" example of a HTA diagram (Dix, 2004, p.515).

In order to fully understand the tasks and subtasks studied, a break-down of tasks into elemental information-processing steps are a helpful process. An example of such a procedure is described in figure 2.3. These steps are typically ordered in a linear sequence. (Vicente, 1999, p.183)

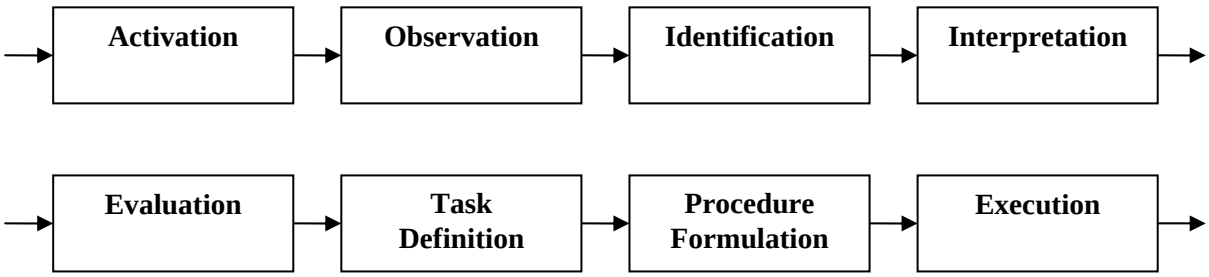


Figure 2.3 A linear sequence of information processing tasks (Vicente, 1999, p.184).

2.3.3 Practical uses of task analysis

The information utilized by task analysis depends much on chosen technique. It is therefore important to consider what the purpose and the use of the analysis will regard when finished. Task analysis may be used for several things such as manual- and tuition materials. It may also be a useful method when designing detailed interfaces in existing systems. (Dix, 2004, p.538-541)

Another application is to use task analysis in the process of designing a new computer system. The execution of task analysis of an existing system to be replaced makes a strong contribution to define the complete set of requirements for the new system. It helps considering which tasks will still exist in the new system and how these will be performed. It is also helpful to clarify which new tasks, or subtasks, that might be automated. If a task analysis is carried out on both systems, a comparison can be made which can spot important parts of the systems. A basic functionality analysis is not interesting since the relevant differences often are part of the procedures. Two systems can seem completely different regarding commandos, but have a common concept on higher levels. Task analysis makes it possible to predict how the new system will interact with existing procedures and how information will move in and out of the new system. If the new system is supposed to resemble the old one, some procedures will be the same, eventually not automated, and some procedures have to be taught from the beginning. (Dix, 2004, p.538-541)

A performed task analysis can be of great value when helping a user transfer from one system to another. Sometimes information to users about a new system focuses too much on *what* the system can do, but forget to tell *how* it will do it. (Dix, 2004, p.538-541)

2.3.4 Data collection techniques

There are mainly three different types of collection techniques that are used when performing a task analysis. These are collection of information through documentation, observation and interviews. Which of these methods to use, and to what extent, depend on both time and costs allowed for the project.

Documentation

The easiest source to data is to study the existing manuals, instruction booklets and rulebooks. One thing to remember though is that these guidelines describe how people are supposed to perform tasks, and not necessarily how they actually are performing them. Even though the structure of material in these sources might be misleading or incomplete for the purposed task analysis, it often gives a good first knowledge about basic actions and objects involved in a task. It can also provide important detail information of certain parts of the process studied, as well as it can enlighten more “hidden” parts that are difficult to detect by for example direct observation. (Dix, 2004, p.532-533)

Observation

Direct observation of users in the true process environment is essential for the analyst in order to get an understanding of the tasks. It is also the ideal form of collecting data. The observer is taking notes on how different tasks are performed and is eventually also timing sequences of actions. There are some risks involving direct observation, however. One of them is that the technique often is an obtrusive method, which can change the normal behaviours and actions of the users, and perhaps give the observer a non-correct view of the process. Another consideration is that direct observation usually will give an incomplete record of the process. (Preece, 1994, p.616-617) The observation may be passive (simply listening and watching) or active (asking questions). When an observation is passive it might be needed to perform a post-task walkthrough, which basically means that the observations made will be discussed together with the user. When having performed information gathering through both documentation and observation, comparisons between these can be carried out in order to identify which tasks are redundant or unusual. (Dix, 2004, p.533)

Interviews

The third method is to gather information via interviews. This technique may be performed in three ways; structured, flexible or semi-structured interviews. Implementing a structured form involves predetermined questions, asked in a set way to be able to compare answers of different users. In an informal flexible interview, the interviewer is allowed to ask any questions spontaneously and he/she may also follow up responses and personal attitudes. The intermediate method, semi-structured

interview, means that a set of questions are prepared, but the interviewer is free to adjust or add questions during the interview to find out as much information as possible. (Preece, 1994, p.628)

Important to remember when choosing users for interviews is that the best expert on the task area is the person who actually performs them every day. It is also valuable to interview the experienced managers, even if they might give “idealized” versions of the task. Since task experts often are not aware of all the steps taken when performing a task, careful questioning is required, especially if using the interviews as the primary source. (Dix, 2004, p.536)

Questions asked at an interview can have different approaches depending on which kind of information the interviewer is searching.
The questions may be:

- general
- reflecting over different expected or non-expected behaviors/performances
- questioning: Why do you do that? What happens if something goes wrong here? (Dix, 1998)

3 METHOD

To reach the aim of this thesis, two basic lines of actions have been adopted. Initially, theoretical methods had to be searched to recognize which approach to use when performing the actual investigation. When this was set, the different kinds of field studies at Quintiles AS could start.

3.1 Theory compilation

This part of the thesis was mainly executed during the beginning of the master thesis project and was carried out in two different periods. The first was spent on an overviewing literature retrieval, to get a picture of which authors and theoretical methods that might be of interest to use. There was a good range of literature regarding computer systems, human computer interaction and solely technical systems. Some of these books have been useful for the study. The supply of literature concerning socio-technical systems involving both human and computer based tasks, was much poorer. A few books containing relevant and interesting theory were found, which have been used in this master thesis.

To be able to specifically sort out applicable theory such as methods and models, it was needed to first learn more about the bioanalysis system studied. This was performed during a few weeks, as described below, and gave a better picture of the purpose of the thesis and work domain concerned. After this preparation, the final sorting of literature was carried out and the theory chapter was written.

3.2 Field study

Knowledge regarding the Quintiles AS activity was basically achieved through three different approaches: observation, documentation and interviews.

3.2.1 Observation

This method refers to gaining a better understanding of the activities carried out at Quintiles AS by observing how they are performed in their true environment. It has more or less been adopted throughout the whole work, though it was most central during the first two weeks. All time was then spent in the laboratory to learn as much as possible about the core activity of the Quintiles AS bioanalysis process. Observation of all tasks performed at the department during a study analysis has continuously been executed during the master thesis project, when situation has been given.

Moreover, the Watson LIMS computer system has carefully been observed by studying the different menus and by testing the many functions available within the system. Some of the functions that will be used in the future were not possible to observe, since these needed for example imported study data. This means that some usability of the functions is not observed in performance, but is studied by the Watson LIMS documentation.

3.2.2 Documentation

To get a good first knowledge about the bioanalysis activity at Quintiles AS, studying of the department specific documents have been valuable. The *Standard Operation Procedure (SOP)* documents have been read in order to gain knowledge about today's process and the basic actions and objects involved in different tasks. These SOPs have also later during the work been studied more carefully for the purpose of enlightening precise task details and actions, which have been difficult to detect by observation. Furthermore, other written material of interest for the thesis has been read. Regarding the information retrieval of the future Watson LIMS system, study of documentation has been the main method. Among others, the Watson LIMS user manual, documents regarding the Watson LIMS investment and implementation and descriptions of the computer system in general, have been reviewed.

3.2.3 Interviews

The third method of information gathering has been carried out by interviews, which can be performed in different manners (see section 2.3.4). In this master thesis, informal and semi-structured interviews have been used.

Informal flexible interviews

The best experts on the tasks involved in the current bioanalysis process are the persons performing them on a daily basis. At Quintiles AS, these are the analytical investigators and they have continuously been asked all questions regarding the tasks, actions and regulations of the system. The questions have been asked using different approaches according to the purpose of them and also to the time and opportunity given. Concerning the new Watson LIMS system, informal, flexible interviews have continuously been carried out with the four persons involved in the implementation work of the system.

Semi-structured interviews

To gain information about the work routines of the Quintiles AS Quality Assurance (QA) auditor, two semi-structured interviews have been carried out at different moments of the master thesis project.

3.3 Task analysis

As the aim of the thesis is to investigate the differences in the new and the old system according to changed tasks and actions, two separate task analyses are required to be executed.

3.3.1 Current system

When information about the existing bioanalysis system has been gathered, both theoretically and in field, the task analysis was prepared to be started. First, it was needed to define the main tasks performed during a study analysis, and specify which these are and what level they correspond to. Each of these main tasks was then broken down into a few subtasks, which were ordered in a logic plan. The decomposition of subtasks was stopped at a reasonable level of detail, attempting to be consistent throughout all divisions of tasks. As the master thesis work has been carried out, the task analysis has continuously been modified when gaining new understanding of the process. It has also been exposed to Quintiles AS task experts, for them to confirm the correctness of the workflow. The result of the task analysis of the current system is shown in two different layouts; as a Textual Task Hierarchy in Appendix A and as a HTA diagram in Appendix C.

3.3.2 Watson LIMS system

The task analysis procedure of the Watson LIMS system is in many aspects very similar to the way the analysis was performed on the current system. The main distinction though, was the differences in information gathering, in the two systems. The Watson LIMS documents consist of general descriptions of the system, and are not adapted to a specific company activity as for example the bioanalysis at Quintiles AS. Therefore, only speculations and predictions can be made regarding each specific subtask and the order they are to follow. The Watson LIMS task analysis has been created by reading documentation, studying the computer system functions by simulating a study analysis, and interviewing persons at Quintiles AS involved in the installation of Watson LIMS. How well the task analysis performed here will reflect the workflow carried out when Watson LIMS is in fully use, can only be said at that time. The Watson LIMS task analysis is included in the report in two different layouts; as a Textual Task Hierarchy in Appendix B and as a HTA diagram in Appendix D.

4 WORK DOMAIN ANALYSIS

To understand the activity and workflow carried out at Quintiles Analytical Services, it is essential to perform a work domain analysis, to identify what information the workers need to deal with in their everyday work. Except for the information flow identification, the analysis also gives a description of the employment environment.

4.1 Environment description

Quintiles AS is a department carrying out bioanalysis service for Quintiles own Phase I clinic, and extern customers. When a study is assigned Analytical Services, one of the analytical investigators is allocated the study and has the responsibility to store the samples correctly, carry out the bioanalysis at the laboratory and then generate the study report. In case the methodology of analysis obtained by the customer has never been adopted before at Quintiles AS, the analytical investigator has to be revalidate it according to Standard Operating Procedure (SOP): AS-15011/02, before applying it on a study. When developing an own method at Quintiles AS, a more extensive validation ought to be made in accordance with SOP: AS-15002/04. This validation procedure is based on FDA's *Guidance for Industry - Bioanalytical Method Validation* (2001). Furthermore, the analytical investigator keeps contact with whoever purchased the study, and sends the finished report to all relevant actors involved in the project, which the study is part of. The size and type of a study varies greatly, which means that the time needed to finish a study range from a few days to years depending on the amount of samples, the intensity of the study and the methodology required to analyze the samples. The part of a study performed during normally one day, is called a batch and includes around 50-200 samples.

4.2 Factors affecting the AS activity

The activities carried out in the bioanalysis industry are affected by many external factors. These factors are represented on Quintiles AS by for example customers' demands, well-functioning instruments and international rules and regulations.

4.2.1 Customers

Quintiles AS is assigned studies from different customers. Most often, a customer is an extern pharmaceutical company, but can also be an internal department as the Phase 1 clinic. Sometimes a study analyzed at Quintiles AS is part of a larger clinical study where several companies are engaged. All involved CRO- and pharmaceutical companies then report their results of their part of the study, to the coordinating customer. Since Quintiles AS only works by commissions from customers, the department completely have to follow their desires to carry out a satisfactory study result. This means that if a customer wants additional results according to them presented in a report template, the analyst responsible for the study has to solve the problem by doing for example extra statistical calculations. When running into difficulties, the analyst solves these together with one of the four principal investigators at the Quintiles AS department.

4.2.2 Technical facilities

The Quintiles AS activity is also characterized by the instruments used at the laboratory. There are three different kinds being used; *High Pressure Liquid Chromatography (HPLC), Gas Chromatography (GC)* and *Liquid Chromatography Mass Spectrometry (LC-MS/MS)*. Each of these instruments involves a specific computer system, which generates and compiles all the information engendered by the instrument analysis. These systems are *Chromeleon*, used by HPLC and GC, and *MassLynx*, which is used by LC-MS/MS. Even though there under normal conditions are no problems concerning the computer systems, once in a while troubles might occur which can take long time to solve. During this time the study will eventually be delayed. Another way the instruments influence the bioanalysis workflow is if they are too full-booked, which might take place when many studies are carried out simultaneously at the laboratory. This can force a study to wait for a non-occupied instrument and the

reason for this crowdedness is the finite number of each of them. Another delaying factor is an instrument breakdown, which might occur if the maintenance or handling of the instrument is not treated correctly.

4.2.3 Rules and regulations

Important factors, which also control the bioanalysis industry, are the many international, national and Quintiles AS specific rules and regulations. All worldwide CRO- and pharmaceutical companies involved in clinical studies have to follow specific guidelines. In Europe these are stated by the OECD, and in the U.S, by the Food and Drug Administration (FDA). The Quintiles AS activities are mainly clinical studies performed on humans, which formally are not studies needed to follow the international series on *Good Laboratory Practice (GLP)* or *Good Clinical Practice (GCP)*, stated by the OECD. However, the studies are following the same principals as the GLP guidelines since it is a guarantee for the customers, reassuring them that the study is analyzed according to certain criteria. The GLP guidelines cover the whole bioanalysis process and the surrounding environment; equipments, facilities, laboratory operations, study performance, organizational structure and report writing. Another authority which guidelines are to be followed is the Swedish Medical Products Agency, which is the organization inspecting Quintiles AS to follow the OECD regulations. Their regulations are much corresponding to the ones of FDA, but might eventually differ in certain moments. Finally, the concrete rules, which the analytical investigators in the end follow at Quintiles AS, are called *Standard Operation Procedures (SOPs)* and are stated in accordance to GLP and the Swedish Medical Products Agency guidelines. These documents describe all different actions and routines carried out and are specifically developed for the Quintiles AS activities and facilities. As soon as any change in routines is decided upon, the current SOP has to be up-dated.

5 ACTIVITY DESCRIPTION OF CURRENT SYSTEM

The Quintiles Analytical Services is today applying a well-developed workflow for analyzing studies assigned by customers. The way the system is carried out has been modified throughout the years with the vision to optimize the system results, user convenience and efficiency. Below is the total workflow described generally, and then the most interesting steps for this master thesis are described in detail. However, a schematic, textual task hierarchy is attached in Appendix A, as well as a HTA diagram in Appendix C, which shows the general workflow of today's bioanalysis process in a fast and easy-to-follow presentation.

5.1 How is a general Quintiles AS study carried out?

A study is assigned Quintiles Analytical Services by a customer, and then allotted a Quintiles AS analytical investigator to be the person in charge of the specific study. This responsibility includes analytical project protocol creating, sample handling, laboratory work-up, instrument analyzing, report writing and keeping contacts with the customer. All analytical investigators are assigned one of the principal investigators, which will have the overall responsibility of the study.

The customer provides the Quintiles AS analytical investigator with information regarding delivery date of study samples, non-appearing samples, method of bioanalysis and other important facts, through e-mail, phone or fax communication. When method and type of samples are set, an analytical project protocol can be written by the analytical investigator, which will be approved by the customer before the start of the bioanalysis work. This document includes study information such as study number, purpose, customer name and address, and reference to method(s) used, and also a study plan. Upon arrival of the study samples, the analytical investigator responsible for the study receives it and controls the content toward the attached sample list. Then the samples are put into a freezer and registered in the freezer logbook and a confirmation of the study samples arrival is sent to the customer.

On a set date, the laboratory work-up and following instrument analyses starts, to conclude the study specific biochemical concentration of each sample. The samples analyzed at the same moment, are called a batch. The total time spent in the laboratory on bioanalysis varies between studies, depending on the number of samples included.

When all samples are analyzed, the results from all batches are compiled together and overall-covering statistics are encountered. This statistical data, together with data sample tables, are then included in the report, which the analytical investigator generates after finished bioanalysis. The correctness of the sample data table in the report is double-checked through an internal quality control, where raw data and generated data are compared by the analytical investigator and a colleague. After finished report generation, the report is controlled by the Quality Assurance auditor (QA) of the department, who checks that all values are correct. When both the principal investigator and the QA have approved the report, a signed original report is sent back to the customer who in the end also gives their approval to the results.

The study samples are stored in the freezer until an endorsement is given from the customer, which states that the samples are to be discarded or sent back to the customer.

5.2 Delimitation of description and evaluation of current system

The future Quintiles AS study analysis procedure will in general look very much as it does today. Still, the existing system will to a large extend be replaced by the new Watson LIMS computer system. The Watson LIMS implementation will have a big impact on certain parts of current system, whereas some parts will be less affected and others will not go through any change.

In the next chapter, the stages of the study analysis procedure which will differ the most between the new and the old system will be further in detail described. Even these descriptions will not cover the complete stage, but will in particular concentrate on the areas where the Watson LIMS implementation changes the routines concretely. The systems will above all differ regarding the following activities: *Sample Receipt, Report Compilation and QA Control.* Another big difference is the elimination of the current stage *Internal Quality Control*.

5.3 Detailed stage descriptions where the systems differ widely

Following procedures will be strongly affected by the implementation of the new Watson LIMS system.

5.3.1 Sample Receipt

Upon the study arrival, the study samples are first counted and controlled by the analytical investigator to verify the samples according to the customer's order specification. The specification is sent to Quintiles AS electronically, by fax or is sometimes delivered on a floppy disk, attached to the study. The study must then be logged into a freezer where it will be stored until the laboratory work-up. The log-in starts by checking all the freezers for non-occupied storage by carefully searching through every freezer "by hand". If there is not enough room for a whole study in any freezer, the study has to be split into different freezers, which preferably is avoided. Sometimes the study is sent to Quintiles AS in different sets and it is then a good idea to try to gather the sets of the same study in the same freezer and racks, to easier keep track of them. There are today twelve freezers, of which five are situated in or nearby the laboratory, and seven are situated in the basement of the building, four floors below the laboratory.

Figure 5.2 A photo of a freezer showing the different racks and compartments.

To log in the samples in to a freezer, a logbook belonging to the specific freezer is filled out according to the scheme below.

Study No.	**AS No.**	**Study samples**	**Rack/ Compart-ment**	**In**	**Out**	**Discard**
Customer study ID.	*Quintiles study No.*	*Customer and AS study sample ID.*	*ID of the study's storage rack in current freezer.*	*Date of registration of samples in freezer.*	*Date of removal of samples in freezer.*	*Date of removal for discard of samples in freezer.*
RS-NY4-4531	Q-78258	Subj. 2301-2304	4D	23 April 2004 /CN	Back to customer 14 May 2004 /CN	
S-2-2221	Q-32795	Subj. 3210	1A-1C	12 May 2004 /CN		Discarded 21 July 2004 /CN

Figure 5.1 The figure shows the structure of the freezer log book in the present system.

The first row in the figure shows the headings of the columns that need to be filled in when logging in or out a study in a freezer. The second row is an explanation of what the heading regards and the last two rows are examples of how a logbook looks when used. The following photo shows a part of a logbook spread.

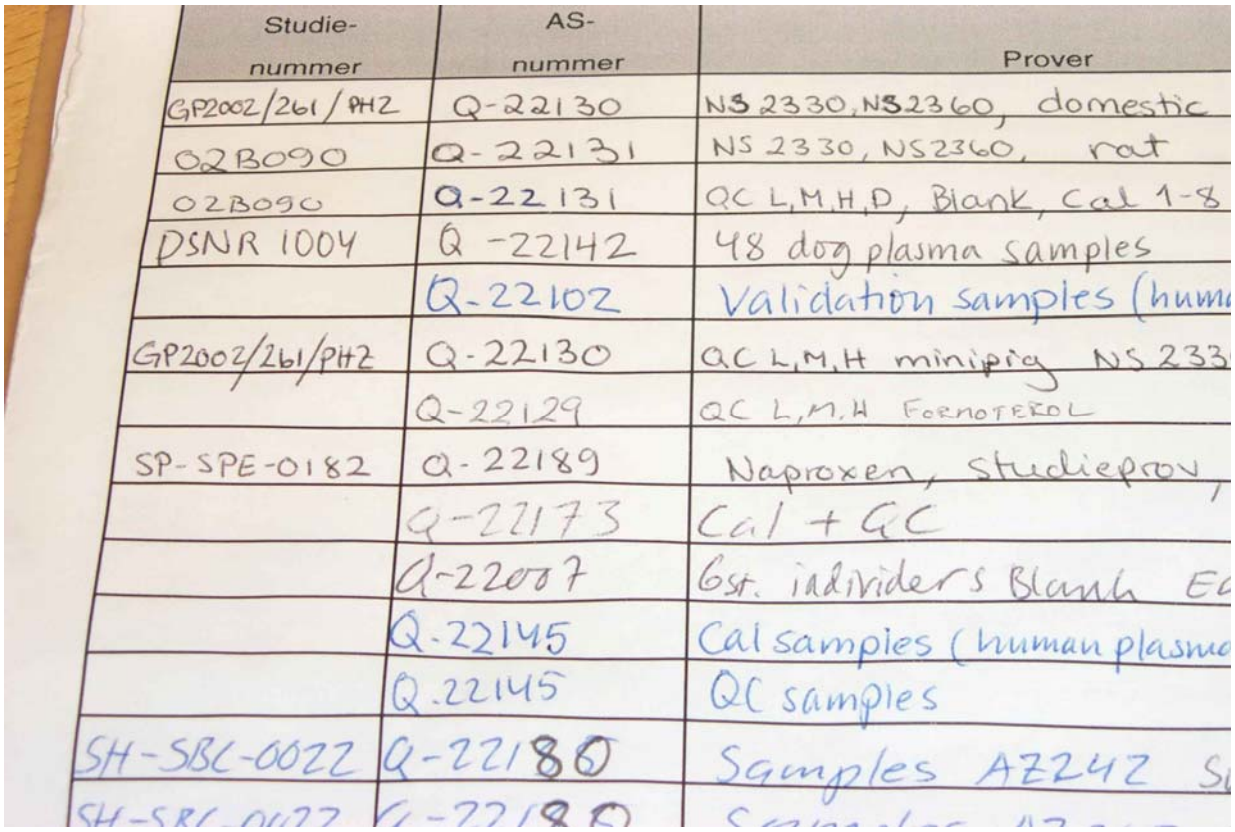


Figure 5.3 This photo shows an example of an upper part of a log book spread.

After the sample verification and the freezer log in, the Quintiles AS person in charge of the study is filling out a *Sample Receipt* document (Quintiles AS standard template), which includes short information regarding the study, the storage location, delivery date and the signature of the person. The document is filed in the study *Main binder* under section five, *Sample log*.

The customer most often requires a confirmation receipt when the study has arrived to Quintiles AS. This confirmation might need to be sent to several receivers such as for example the customer and Quintiles Phase I Clinic, in case they have performed the study trial. According to different customer desires, the confirmation is sent either by e-mail, fax or post service, often within 48 hours after delivery of the study samples.

5.3.2 Report Compilation

The analytical investigator starts the report compilation after finished laboratory bioanalysis, by exporting generated data from the instrument specific computer programs; *Chromeleon* or *MassLynx*, to the analytical investigator's personal file at the Quintiles AS server domain. This is performed on a daily basis prior to every finished batch, or in the end of the whole bioanalysis study. All summary data and tables from the batches are thus saved in: *Qtree/Freja/Biodata/Utility/personal file*. Only a few representative chromatograms, figures showing the separation of chemicals, are saved and exported to the same personal file. The analyst then opens the raw data table on his own work station, copies the document and pastes it into the chosen Excel data table template, which will be included in the report as an appendix textfile. In the local file server there are mainly two different report templates, which are being used to generate the final report. (G:\Departments\Analytical Services\Templates\Studie\Analytical report-vx.dot) The templates look a bit different from each other and are used in accordance to the customer's desires of reported information and tables. Tables of statistics, figures and study specific information are then included into the report. All statistics are compiled by pasting data into predefined formulas using Excel, as remaining information is added manually by the analytical investigator.

5.3.3 Internal Quality Control

The Internal Quality Control must be carried out before the report compilation, performance of statistical calculations and export of results to a customer. Two persons are needed; the analytical investigator of the study and an analyst that can offer the time needed. The analytical investigator reads certain values out loud from the raw data table generated from the instrument computer systems Chromeleon or MassLynx. The other person controls the correctness of the values, according to the generated Excel tables used in the report and produced by the analytical investigator. The purpose of the internal quality control is to control the correctness of the data table, as regards data transfers between computer systems and the manually written information. The whole table of QC-values is controlled against the instrument raw data report, since theses values are copied or written into the table one by one. At least 10 % (or according to the customer's requirements) of the analysis data table ought to go through an internal quality control, as also all data of reanalyzed samples, diluted samples and all results lower than *Lower Limit Of Quantification* (LLOQ). The internal quality control is recommended to do according to the GLP guidelines and it is a standard operation procedure at Quintiles AS. The exact regulations for internal quality control are described in SOP: *Kvalitetskontroller,* AS-34005.

Some examples of the reasons for internal quality control are following:

- Copying mistakes might be done when exporting data from MassLynx or Chromeleon to Excel, such as pasting lines wrongly or deleting rows.
- There is a small risk that the last significant decimal is changed during transfer from MassLynx to Excel due to further decimals. Example: 5.345 become 5.4. In most cases the transferred value is correct and does not change the result.
- Significant values might change during report compilation when copied from Excel to Word. Example: 34.50 might become 34.5.

5.3.4 QA Control

A careful and extensive quality check of the study results is performed by the *Quality Assurance* auditor (QA) of the department. The QA control is carried out when the analytical investigator has finished the report compilation and the principal investigator has revised the report. The work is performed in order

to further guarantee that no mistakes in data reporting to the customer have been carried out. It is a strictly defined work, which includes manual elements such as comparison between the instruments generated source data and the report data table, a so-called data audit. The control needs to be carried out on at least 25 % of the results data table. In some cases where the customer requires data audit before report audit, QA will check the instrument data after each completed batch, which requires a time minimum of two hours and a maximum of four hours. Furthermore, the work includes checking of Excel formulas to verify that the formulas used for calculations are correct and that accurate data are evaluated and not accidentally modified during report compilation. Also the values of calibration- and quality samples need to be checked since the analytical investigators sometimes mark these values as “out of range”, when they should have been completely excluded from the report. QA finally checks the report for compliance such as initiate date, analysis start date, general text compilation etc. Planned time per study is six hours, but depending on who wrote the report and how extensive it is, this will take QA somewhere in-between three hours and two days.

6 ACTIVITY DESCRIPTION OF THE FUTURE SYSTEM

Quintiles Analytical Services will soon be going through an extensive change in workflow routines, due to the implementation of Watson LIMS. To be able to clearly sort out the differences in efficiency, security and usability between the two systems, a detailed description of part of the future Quintiles AS system will be carried out in this chapter. A general presentation of the Watson LIMS bioanalysis process is attached in Appendix B as a schematic, textual task hierarchy. Also a HTA diagram representing the Watson LIMS bioanalysis process is attached in Appendix D.

6.1 Motives to change of systems

There are a number of strong incitements for Quintiles AS to replace the present system with a LIMS computer system. The department has reached a critical size of activity, where there are difficulties for the business to keep growing, when relying on current manual systems. The increase of studies being carried out simultaneously is restrained by for example the difficulties to utilize all the instruments effectively, such as taking full advantage of the LC-MS/MS capacity. Using a LIMS, the bioanalysis workflow will be streamlined and more efficient, which will enable analysis of more samples. This is above all due to the ease of sample handling and the less needed time on report generation.

Another incitement for installing a LIMS system is the increased demands of data security and integrity from external customers. Quintiles AS have grown to a size where a LIMS is expected to be used, which means that customers nowadays assume that Quintiles AS will deliver certain additional results and statistics, also guaranteeing full data security. One of the highest customers has stated that they, in the near future, only will work with CROs using a LIMS system, especially due to security issues and sample data transferring facilitations.

The choice of the particular LIMS system selected for Quintiles AS was considered quite natural. It is specifically designed for bioanalytical activities, it is the most common system used on the market and many of Quintiles AS customers are using it with satisfaction. It is also the system containing all requirements of Quintiles AS, and still regarded as a ready-to-use system.

6.2 Watson LIMS

The Watson™ LIMS system by *Thermo Electron Corporation*, formally *InnaPhase Corporation*, is a highly specialized protocol-driven *Laboratory Information Management System*. It is specifically designed to support and follow the process of the bioanalytical laboratory, and has also been developed to promote compliance with GLP regulations and the 21 CFR Part 11 guidance. The system is an overall covering program, which will involve every step in the study analysis performed at Quintiles AS. It supports the process of study design, sample receipt, scheduling of analytical runs, interfacing with instrument programs such as Chromeleon and MassLynx, regressing analytical results, and analyzing and summarizing the resulting concentrations. The program uses a central database and a point-and-click graphical interface.

The Watson™ LIMS system has many advantages compared to the current manual systems. One of them is the track keeping of each sample, which gives the possibility to historically find out all exact treatments and data connected to one particular sample. Furthermore, it will increase the security regarding sample data handling, since it automatically controls for example reanalysis situations. These in-built double-checking functions decrease human mistakes, which today are impossible to completely avoid. Another system advantage is the opportunity it gives to handle large amounts of studies and samples within the system, without any risk to decrease data security. Nevertheless, one big advantage is the increased workflow efficiency concerning sample tracking, data analysis and concentrations, and report compilation.

Watson™ LIMS is today used worldwide by 39 pharmaceutical companies and 28 bioanalytical CROs. This makes Watson LIMS the biggest supplier of computer systems, designed for bioanalytical activities.

6.3 Timeline of the Watson LIMS implementation

The planning and preparation of the implementation of Watson LIMS started almost a year ago. Research was carried out concerning which LIMS to use and also economical calculations was performed to work as a base for the application of Watson LIMS funds, from Quintiles AS parent company. Once the decision was forced through, the work of implementation started together with the former InnaPhase Corporation.

Project start:

Proposal Detail Description	**May, 2004.** Proposal document, including economic calculations, implementation timeline etc.
Watson Specific User Requirements Specification	**September 28, 2004.** Prepared by Quintiles AS.
Watson System Managers training course	**17-19 of August, 2004.** An introduction of the Watson LIMS and its Training Manual.

Installation procedures:

Installation Qualification Plan	**September 28, 2004** The plan was prepared by a Quintiles AS Watson LIMS super user.
Installation Qualification	**August-September 2004** Performed by Quintiles AS with the support from Thermo Electron Corporation. The Installation Qualification is a validation activity performed to verify that the system has been installed to supplier specifications.
Installation Qualification Protocol	**October 6, 2004** The protocol was prepared by a Quintiles AS Watson LIMS super user.
Operation Qualification Plan	Not yet accomplished. Prepared by Thermo Electron Corporation.
Operation Qualification	**October 2004-beginning of January 2005** Performed by the four Watson LIMS super users at Quintiles AS. Operation Qualification is a validation activity performed to verify that the system components have been properly designed and implemented to meet functional requirements.
Operation Qualification Protocol	**October 7, 2004** Prepared by Thermo Electron Corporation.
Performance Qualification Plan	Not yet accomplished. Expected since December 2004. Will be prepared by Thermo Electron Corporation.
Performance Qualification	Not yet accomplished. Performed by the four Watson LIMS super users at Quintiles AS.

	Performance Qualification is a validation activity performed to verify that the system functions meet user business requirements.
Performance Qualification Protocol	Not yet accomplished. Will be prepared by Thermo Electron Corporation.

Remaining preparation procedures:

SOP Modification / Creation	Will be prepared by Quintiles AS.
Watson LIMS staff education	Will be prepared by Quintiles AS. An introduction of the Watson LIMS and its Training Manual, adjusted to suit the Quintiles AS bioanalysis process.
Release Note	Will be prepared by Quintiles AS. States that the system is ready to be taken into use.

6.4 Detail descriptions

As Watson LIMS is not yet in use, following descriptions are based on speculations, but will describe the process as good as possible today.

6.4.1 Sample Receipt

To keep all samples in order, Watson LIMS is using a catalogue function which sorts all samples into specific studies, and all studies under specific projects. All study samples arriving at Quintiles AS need then to be checked in under a specific project and study in Watson LIMS as figure 6.1 shows.

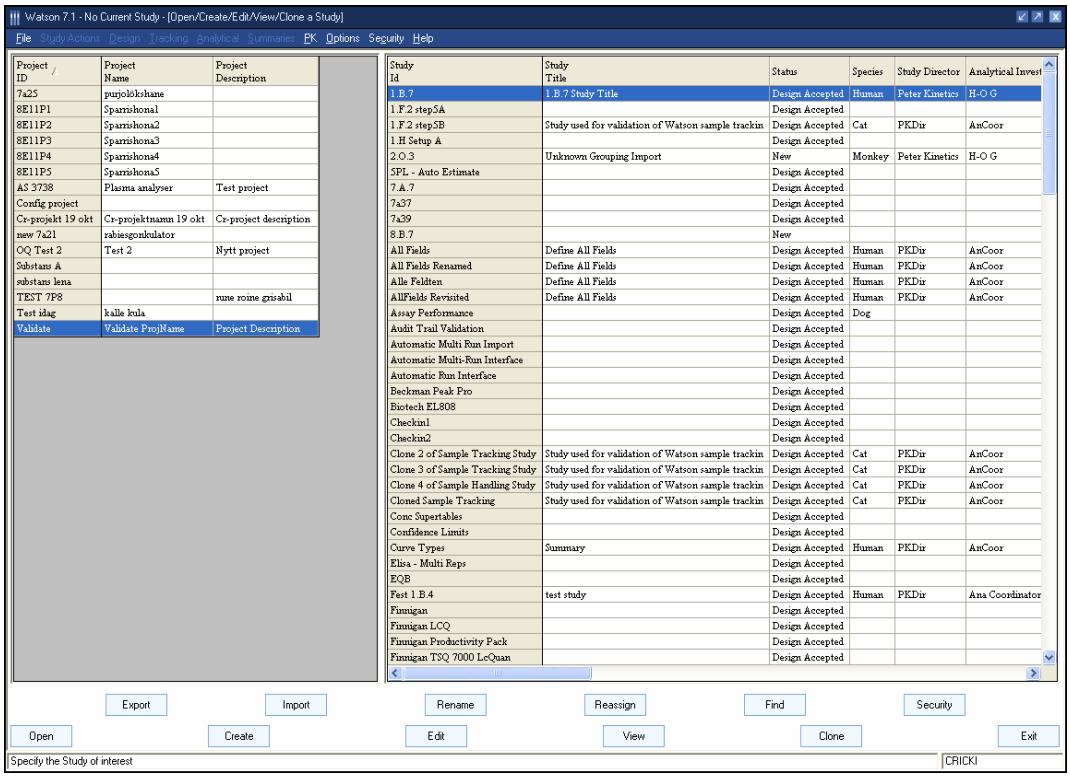
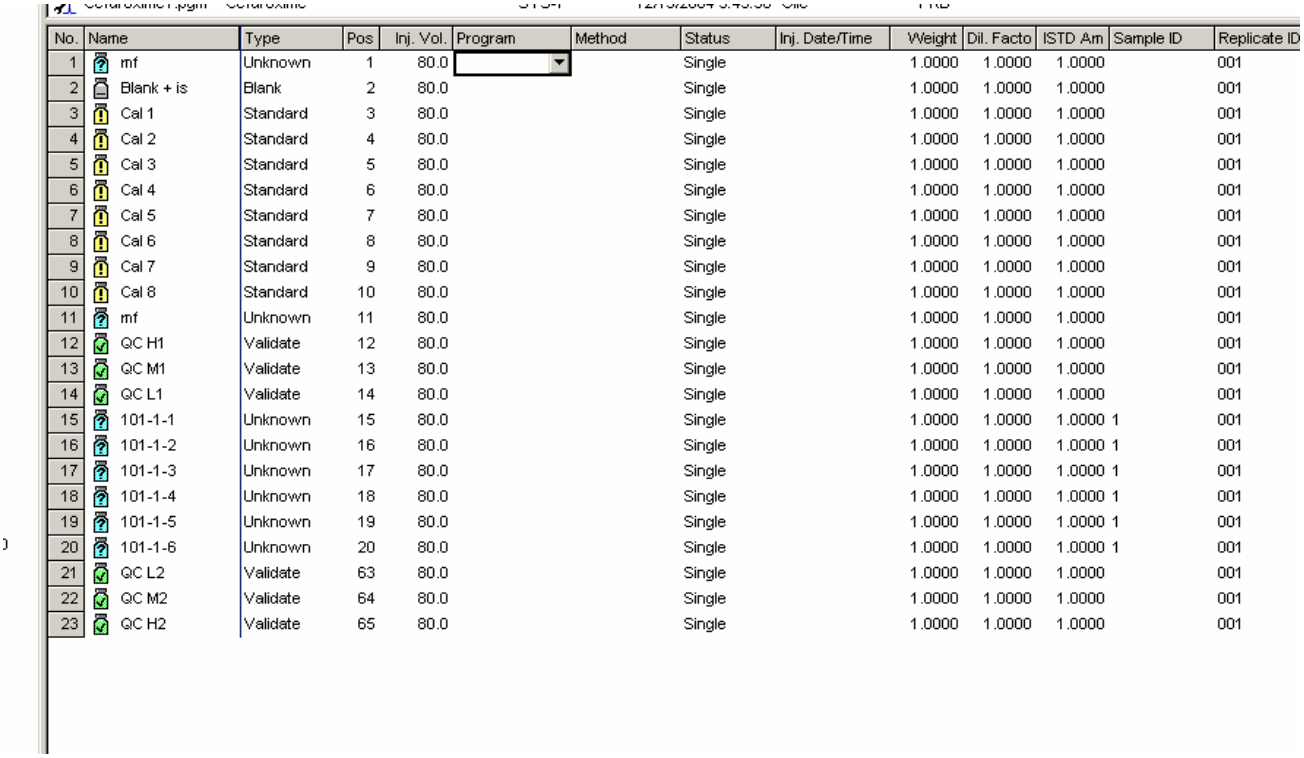


Figure 6.1 This shows all registered projects and the studies belonging to the highlighted project.

If the sample list has arrived in advance, the Watson LIMS sample list can be prepared and the samples identified and marked as “Not received”. This mode will upon arrival be switched from “Not received” to “OK”, which will make the samples available for handling. There are two ways of sample check-in; as a group or as individual samples. If an electronic sample list is available from the customer, a direct import into Watson LIMS can be made during check-in of samples. If this is not achievable, it is possible to simply fill sample columns as long as the samples are numbered logically. Information regarding treatments, doses, gender, and volume and so on can be linked to every sample, as well as the sample storage location. This is displayed by the freezer id, box number and rack. Whenever a sample is moved, the location information needs to be updated.

The more automated procedure during sample receipt does not eliminate the manual control of sample contents, performed in order to check that the received samples are the same as stated on the attached sample list.

Whenever the study samples are checked in, it is possible to plan an analytical run by designing a work list in the instrument software of interest; Chromeleon or MassLynx. This list includes assay samples: blank, calibration, and quality samples (in the beginning of the batch and at the end of the batch to confirm analysis quality consistency), and the study samples of current batch.



No.	Name	Type	Pos	Inj. Vol.	Program	Method	Status	Inj. Date/Time	Weight	Dil. Facto	ISTD Am	Sample ID	Replicate ID
1	mf	Unknown	1	80.0			Single		1.0000	1.0000	1.0000		001
2	Blank + is	Blank	2	80.0			Single		1.0000	1.0000	1.0000		001
3	Cal 1	Standard	3	80.0			Single		1.0000	1.0000	1.0000		001
4	Cal 2	Standard	4	80.0			Single		1.0000	1.0000	1.0000		001
5	Cal 3	Standard	5	80.0			Single		1.0000	1.0000	1.0000		001
6	Cal 4	Standard	6	80.0			Single		1.0000	1.0000	1.0000		001
7	Cal 5	Standard	7	80.0			Single		1.0000	1.0000	1.0000		001
8	Cal 6	Standard	8	80.0			Single		1.0000	1.0000	1.0000		001
9	Cal 7	Standard	9	80.0			Single		1.0000	1.0000	1.0000		001
10	Cal 8	Standard	10	80.0			Single		1.0000	1.0000	1.0000		001
11	mf	Unknown	11	80.0			Single		1.0000	1.0000	1.0000		001
12	QC H1	Validate	12	80.0			Single		1.0000	1.0000	1.0000		001
13	QC M1	Validate	13	80.0			Single		1.0000	1.0000	1.0000		001
14	QC L1	Validate	14	80.0			Single		1.0000	1.0000	1.0000		001
15	101-1-1	Unknown	15	80.0			Single		1.0000	1.0000	1.0000	1	001
16	101-1-2	Unknown	16	80.0			Single		1.0000	1.0000	1.0000	1	001
17	101-1-3	Unknown	17	80.0			Single		1.0000	1.0000	1.0000	1	001
18	101-1-4	Unknown	18	80.0			Single		1.0000	1.0000	1.0000	1	001
19	101-1-5	Unknown	19	80.0			Single		1.0000	1.0000	1.0000	1	001
20	101-1-6	Unknown	20	80.0			Single		1.0000	1.0000	1.0000	1	001
21	QC L2	Validate	63	80.0			Single		1.0000	1.0000	1.0000		001
22	QC M2	Validate	64	80.0			Single		1.0000	1.0000	1.0000		001
23	QC H2	Validate	65	80.0			Single		1.0000	1.0000	1.0000		001

Figure 6.2 An example of a Chromeleon worklist, though including fewer study samples than an average batch.

6.4.2 Report Compilation

The instrument generated data are imported back to Watson LIMS from either MassLynx or Chromeleon as areas respectively heights of chromatograms. These data are then integrated within Watson LIMS to determine the correct quantity of analyzed substance. Using this information, predefined tables, graphs and statistics such as sample concentrations and regression curves, are calculated within Watson LIMS. These are chosen to suit the desires of the customers of Quintiles AS, and are therefore of highest concern to be included in the final report. Many other results and reports may easily be generated within Watson LIMS if wanted. As customers sometimes have additional wishes of certain result tables etc, this availability makes it possible for Quintiles AS to satisfy their

customers and give them good service. Predefined report templates then compile the final report. These will look as the ones used today, and are designed to directly include generated graphs, tables and other standard report information as for example GLP statements, pages of contents and QA statements into the final report, sorted under the correct rubric. This means that a lot of work regarding present report writing will be simplified using Watson LIMS. However, even though much of the contents will be automatically compiled there will be some detail modifications and also, most probable, including of specific customer requests regarding study information, figures and tables.

6.4.3 Internal Quality Control

One important reason for carrying out the internal quality control of today is the easiness of missing a reanalyzed sample value during the generation of the report data table. This mistake can not be made with the use of Watson LIMS, since it has the ability to double-check all values regarding value out of bound, several values belonging to one sample, and other predefined criteria. In case this happens, Watson LIMS immediately gives a warning or force the user to take a statement. Samples needed to be reanalyzed will be flagged in the tables, so that they easily can be noticed. All data transferring will automatically be made within Watson LIMS, which means that tables will not be "copied and pasted" and therefore not exposed to accidental copying mistakes.

The consequences of this, is that as long as Watson LIMS is working with no complications, there will be no need for an internal quality control, since there no longer will be any manual data handling within the bioanalysis process. The time spent on internal quality control today can thus be saved in all studies.

6.4.4 QA Control

The QA auditor's working assignments is expected to change drastically with the introduce of Watson LIMS. Exactly how different tasks will be redesigned is difficult to say today since the new system is not yet in use. The goal is however to eliminate several of the manual steps of report control, where the data audit is a time-consuming procedure. This should theoretically work since all risks for data transferring mistakes can be avoided using Watson LIMS. A part-goal is to make it possible to sort all generated data from all batches, including reanalyzed sample values which data are not in the correct order, by subject number. Eliminating browsing through data tables searching for specific samples will save QA time during data audits.

Another QA working assignment, which will change, is the general check of the report. Today all information, manually generated in the report by an analytical investigator, is controlled. This step will, using Watson LIMS, not be needed since the system keeps track of all actions being performed within a study and automatically generates information such as initiate date, analysis start date, bioanalysis regulation conditions etc in the report.

There is also a desire from QA that Watson LIMS should have the ability to block used Excel formulas of today to avoid mistakes during calculations of statistics. This concern will be eliminated due to the reason that needed statistical calculations will be performed within Watson LIMS and automatically introduced into the report Word template. This means that QA does not have to check all Excel calculated values in the report to confirm correctness, which will decrease the work with each study report drastically.

7 RESULTS AND ANALYSIS

In this chapter discussions regarding differences in the bioanalysis process between current system and the future Watson LIMS system, will be carried out. Since Watson LIMS in this moment not yet has been implemented, it is difficult to estimate exactly how this system will affect all process steps. Therefore the results will be speculative and are mainly aimed as eye-openers and discussion platforms, when implementing Watson LIMS. I have chosen to separate the different aspects and process steps to clearly point out certain facts. The reader should be aware that these chapters in reality are tightly intertwined and are often consequences of each other. One common example of this is how the usability often is affected, sometimes negatively, as a result of security issues.

7.1 How will the security be affected?

In the pharmaceutical industry, nothing is more important than the security of the patients and the correctness of the clinical trial results. One mistake or step from routines and regulations may cause devastating consequences for a person and for the involved drug- or CRO company. For that reason, the activity in this industry is completely governed by security concerns.

7.1.1 General Aspects

Quintiles AS main reason for the investment in Watson LIMS is to satisfy their customers' desires on increased security in clinical trials. The system will definitely reach this goal, but some general aspects of security need to be discussed and considered during performance of the operation qualification. One concern, which needs to be discussed, is how to use the Watson LIMS user roles and access system. Watson LIMS requires all users to hold a type of user role, which gives the user access to specific data handling within a study. If a user is allotted a role with more liability to perform Watson LIMS tasks than he or she has the competence for, mistakes can be made as changing values or deleting information. To ensure the highest security, all users ought to be assigned a role where only the needed duties are allowed to be preformed and only in the studies where the user is assigned. An adjustment is here needed to be done; how strict can the system treat a person's system availability to ensure security, without hinder the person from accomplish his work? When a user does not have access to certain tasks, these menu choices will not be displayed in Watson LIMS. This is mainly a security guarantee, which makes it impossible to perform these tasks, but it also works as a good pedagogic measure.

7.1.2 Sample Receipt

In this step, the security is basically affected regarding the order of samples in the freezers. There are today possibilities that the samples are forgotten to be logged in the log book, or that they are logged in incorrectly, for example on the wrong rack in a freezer. Another case considers the act of moving samples between freezers and forgetting to log out the study of interest by noting where the samples are located after the removal. These mistakes can cause troubles when getting the samples for laboratory analyze, especially if the study is short of time and no time really can be wasted on sample track audit. Using Watson LIMS will prevent these scenarios from happen since the system automatically controls that no such mistakes can be carried out. It attends the user that, for example, this rack is occupied and is not possible to store samples in. If, however, samples are lost, there is a function within Watson LIMS which offers a complete track audit report of any requested sample. This makes it easier to sort out where the samples are located.

7.1.3 Report Compilation

As regards the security of the report compilation, the implementation of Watson LIMS can only result in a security increase. The issue of manually created data tables and statistical calculations will in the future be automatically generated and introduced into the report template of current interest, which means that a great deal of the risk of human mistakes can be avoided. However, certain customers have

their own special requirements of inclusion of certain tables, graphs or study information into the report. This forces the compiler of the report to manually create and import such objects, which generates a risk of mistakes in data handling. This will, just as today, be controlled by both the principal investigator and by the QA auditor of Quintiles AS.

7.1.4 Internal Quality Control

The security will not be affected negatively by the elimination of the internal quality control; it will rather increase with the implementation of Watson LIMS. The quality control will now be carried out automatically within the computer system, which will eliminate current manual procedure where there always is a risk of human mistakes. This generates a considerable improvement in security.

7.1.5 QA Control

Regarding the security of using the system, it will in general increase using a LIMS system. Many of the quality controls that today are manually performed by the QA auditor, as the data audit, will in the future be automatically checked within the computer system. For example the risk of including calibration- and quality control sample values which are out of bound will be eliminated, since these according to set criteria in Watson LIMS can be automatically excluded from the data table. These consequences drastically increase the security since it eliminates the matter of human mistakes. Though, after a discussion with Quintiles AS QA auditor, it has become obvious that there are some concerns that need to be discussed and gained awareness about before starting to use Watson LIMS in bioanalysis studies.

QA's major concern regards the flow of data, when data leaves Quintiles AS validated Watson LIMS system, to be transferred to other external parties such as customers and other Quintiles departments, as for example the DM department. How do you make sure that the contents of data being transferred to and from external systems are identical? If an interacting system is not validated, there is a risk of following transfer troubles within following three major areas:

Security:
- Loss of data
- Alteration of data
- Verification of data authentication
- Cryptography of data transmission is needed

Integrity:
- Data transmitted must be the same as data received
- Format / metadata (must represent a consistent meaning for all actors)

Signature:
- Verify identity and authorization of sender. Who wrote the data and who sent it?

The security concern treats the problem of an eventual sudden interrupt in data transmission, in case of a computer breakdown. This risk is small, but could in case of occurrence cut off for example a data table in half without the receiver's or the sender's knowledge. This mistake could cause large problems if not detected relatively immediately. The integrity area deals with the consciousness of knowing that the receiver really gets the same data as transferred. This problem is most likely to occur when data are being transferred between unvalidated and validated systems. The best way to prevent this from happen is to make sure that validated systems as Watson LIMS are not able to import data from unvalidated systems. It is also of importance to confirm that all involved actors taking part of the same data, understand all information in a consistently meaning. Misunderstandings of data and report information can cause large troubles, which in the end may lead to a delay of the clinical trial.

The last concern regards the issue of signatures. How can you assure the identity of the person who sent the report and how can you confirm that the person who is said to have written the report is the one who wrote it? To guarantee full security regarding this concern, there are special functions within Watson LIMS, which can be used. An electronic signature requires the sender or handler of electronic data, to verify his identity in the system to be able to perform a system based task. This may be done using a personal password, using a personal password combined with a user explanation of why to use the task, or by letting the system "silently" register a user's actions and performances in the system. This function has been discussed to be implemented at Quintiles AS when changing to the new Watson LIMS system, as it is an optional function within the system. However, using electronic signatures means an extensive qualification work which involves going through each Watson LIMS function to define whether a signature will be demanded or not. This extra security issue is strongly recommended by FDA guidelines, but not explicitly required neither by FDA nor the OECD GLP guidelines. Since Quintiles AS is ruled by the OECD guidelines, a decision has been taken to not use electronic signatures since the incentive to do the extra qualification work is not yet strong enough. If the customer's requirements will come to a change, a new consideration of electronic signatures will be made.

The following figure 7.1 is a schematic demonstration of the different systems that Watson LIMS will interact with. The data transferring process between these systems need to be validated in order to be trusted as secure.

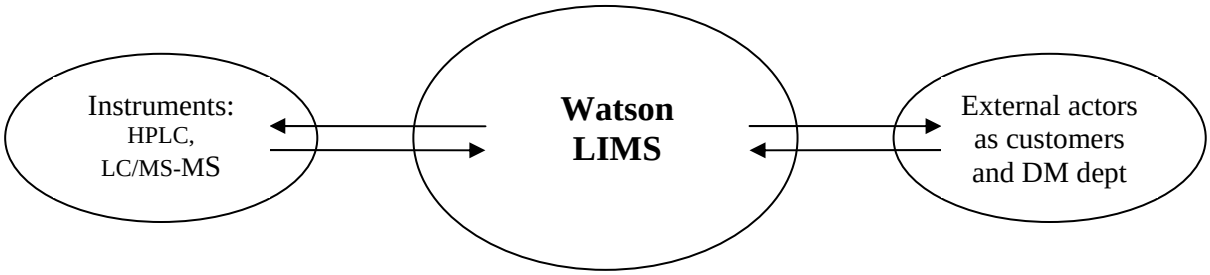


Figure 7.1 This shows Watson LIMS' interactions with Quintiles AS instruments and external actors.

QA also gives attention to the question of how to make sure that all actors always are managing the last version of a report. Is there a need for an implementation of new rules and routines in relation to the start of using Watson LIMS? Eventually the last updated report version always have to be printed out and put in the study *Main Binder* to prevent use and spread of an old report version? This is an issue that needs to be defined and considered.

The QA control of today regarding the Excel calculations will be eliminated due to Watson LIMS automatisation of statistics generation. This of course increases the security since the matter of human mistakes will be avoided.

7.2 How will the efficiency be affected?

During the spring of 2004, Quintiles AS was applying investment money to a Watson LIMS system, from their parent company. A *Proposal Detail Description* was written on May 3rd 2004, which among other things explained an approximation of time saved in the bioanalysis process. This document states that a Watson LIMS system would save 0.5 days per analytical study during the first year of usage (2005), which results in a total work decrease of 0.5 employees per year. When the system has been in use one year, this figure is assumed to change to 1.5, which then means a good save in the Quintiles AS budget. As this far concerned, this estimation seems to me somehow too opportunistic. Another argument stated in the protocol, is that a Watson LIMS would improve the efficiency of the bioanalysis workflow, according to less time spent on for example report writing, and better advantage taken of Quintiles AS increased capacity of LC-MS/MS instruments. This results in an availability of analyzing more samples and thereby having involvement in more studies. This estimation of time-saving was carried out during the negotiation of a Watson LIMS purchase, before actually knowing much about

how the system would affect the Quintiles AS activity. Today Watson LIMS is being implemented and I have carried out a rough estimation of how much time the new system can spare different stages of the bioanalysis process, in each study. The most time per study will be saved when studies are large and include many samples. This is due to the reason that current compilation of data tables and statistics demand extra time the more samples the study includes, which will not have any impact when using Watson LIMS. An average sized study is estimated to take a total time of 20 days today, as it will take 16.5 days using Watson LIMS.

Two timetables are showing a comparison between the current system and the future, regarding estimated time spent on bioanalysis steps. The first figure 7.2 includes only the steps where the time spent on different steps will differ between the systems.

Specific step in the bioanalysis process:	***Estimated time in today's bioanalysis process: (1 study/500 samples)***	***Estimated time using Watson LIMS: (1 study/500 samples)***
Study Sample Receipt	1 day	1 day
Report Compilation	4 days	1 day
Internal Quality Control	1 hour (2 persons needed)	Eliminated step
QA Control	6 hours	3 hours

Figure 7.2 A comparison regarding efficiency differences between today's system and the new.

The following figure 7.3 considers all steps in the total bioanalysis process including the steps which will not change according to time taken. It also estimates the total time spent on a study.

Specific step in the bioanalysis process:	*Estimated time in today's bioanalysis process: (1 study/500 samples)*	*Estimated time using Watson LIMS: (1 study/500 samples)*
Study Sample Receipt	1 day	1 day
Protocol Compilation	1 day	1 day
Preparation of QC and calibration samples	1 day	1 day
Analysis Set-up	1 day	1 day
Laboratory Analysis	11 days	11 days
Report Compilation	4 days	1 day
Internal Quality Control	1 hour (2 persons needed)	Eliminated step
QA Control	6 hours	3 hours
Total time per study:	**~ 20 days**	**~16.5 days**

Figure 7.3 A time estimation considering all bioanalysis steps.

7.2.1 General Aspects

The goal of increasing the efficiency of study analyzes was the second biggest incitement to the investment of a Watson LIMS system. This goal will hopefully be achieved, even though it will not be reached during the first year of use. An increased efficiency means that Quintiles AS will be able to analyze more samples per year, providing all other workflow conditions are optimal. This makes it important to keep a correct balance of the number of instrument and apparatus at the laboratory, to avoid bottleneck problems.

However, as turning out to be a common problem, the total implementation process is taking longer time than expected. The first procedure though, the *Installation Qualification*, took actually shorter time than expected. Also the next procedure, the *Operation Qualification*, was more extensive but still did not take longer time than planned for. These implementation tasks have taken the time of in average one full-time employee from August until December. During some periods though, there have been up to four persons working full-time with the *Operation Qualification* of Watson LIMS, which is more than planned. The last procedure, the *Performance Qualification*, is the main reason for the delay of the implementation. Quintiles AS can start this procedure as soon as they have been given the *Performance Qualification Plan*, which should be stated by the Thermo Electron Corporation, but has until today not appeared and is already delayed by one month.

Another issue, which has been changed from the original plans, is the matter of the employee education. This was planned to start during the fall of 2004, but has now been postponed until the beginning of 2005. One concern is that the education probably is needed to be more extensive and longer lasting than first thought, and maybe also has to be carried out in smaller groups. This is due to the reason of Watson LIMS being more complicated and comprehensive than first considered. Also the plan of Watson LIMS

being in fully use in customer studies in January 2005, is postponed for some month since the installation process has not yet been completed. As there are still only a few persons who know how to handle the system, the start-off will probably get slower than planned.

7.2.2 Sample Receipt

This step of the bioanalysis process is an uncertain time-saver, at least during the learning period of the system. As the routines become clearer, the process will probably be more efficient. However, the step should be considered as a preparation and investment of time, to be able to perform the following bioanalysis steps faster and more secure, compared to the process of today. If the sample list is sent to Quintiles AS electronically, which it ought to be in the future, it can conveniently be imported straight into the Watson LIMS login function. Adding extra information about the study and the samples will take more time than today, but will also increase the security regarding the study, as the documentation of the study will be more complete. When logging in the samples in Watson LIMS, their freezer location will also be registered. This part of the sample receipt procedure will presumably be more efficient than today, since Watson LIMS shows were free freezer location is available. This eliminates the step of manually searching through the freezers both in the laboratory and in the basement located freezers, sometimes needing to store the study samples into different freezers due to deficient room. This search sometimes takes much time, even though the analytical investigators often has an idea of where free storage area may be available.

The possibility of checking up free freezer room from the personal computer will also be of advantage when study samples are needed to be moved from one freezer to another, when for example moving them to a long-time storage. Also in this case, time can be saved.

7.2.3 Report Compilation

Present report writing is taking much time of the total assigned time of the bioanalysis study. A 500 samples large study is taking approximately five days of report compilation, including the time of internal quality control and error tracing. Watson LIMS is estimated to shorten this time to one day. This decrease is above all due to the reason that the report to a much larger extent will be generated more automatically concerning the data table, statistics calculations and other report information such as different study dates. The statistics of interest for the report will be calculated within Watson LIMS, and then directly imported into the right chapters into chosen report template, which also will be available within Watson LIMS. The system guarantees that no internal quality control or error tracing should be needed, since the system has an in-built function of double-checking all sample information, and highlighting samples where data fall outside certain specified criteria. The elimination of the internal quality control, where two persons are needed, will shorten the report writing by approximately 45-60 minutes.

Although much of the report will be generated automatically, there will always be some extra work to be performed manually by the analytical investigator. This may for example include adaptations of the report wording to suit the current customer. The report generation step is the procedure of the bioanalysis process where Quintiles AS is expecting to save the most time in proportion to current situation.

7.2.4 Internal Quality Control

The time taken today for the internal quality control depend on whether all values are corresponding between the tables or if many values are not, which often causes extra time spent on error tracing. For a medium large study including 500 samples, the time spent for two persons on internal quality control range between 45-60 minutes. Since this step will be completely eliminated with the implementation of Watson LIMS, all this time will be saved.

7.2.5 QA Control

Today the QA auditor is checking approximately 25 % of all raw data generated from the instruments against the data table included in the report, a so-called data audit. A study consisting of 500 samples takes a minimum of two hours to check, and a maximum of four hours. Using Watson LIMS this procedure is not needed to be performed, due to the automatisation of the data table creation. The QA auditor is also carrying out a general control of the report, which today is taking from three hours up to two days per study. A lot of the information being checked as dates etc will be automatically generated in the report by Watson LIMS, resulting in large timesaving for the QA auditor. An estimation of the total time Watson LIMS will save the QA auditor is half of the time spent on present studies, which means three hours per study.

An aspect, which will not be possible to make more efficient using Watson LIMS, regards the many individual report requirements of the customers. These accords to extra statistics calculations, tables or information, which are not included into the standard report templates and hence have to be manually generated by the analytical investigator. Therefore, QA also in the future will have to control these parts of the report to ensure that no mistakes have been carried out. To summarize, several QA procedures will with the implementation of Watson LIMS be eliminated or simplified, though there will in most study reports always be some parts needed a manual check by the QA auditor.

7.3 How will the usability be affected?

The usability of the Watson LIMS system is a central issue to reflect upon. A system which replaces an existing, working system should preferably have an improved usability, to enhance the process workflow. Since the system is not yet in use, it is difficult to point out good or bad usability affects. However, some speculations can be made. Even if the system supplies all needed functions for the process, the design, logics, appearance and pedagogic representation is not always of satisfaction for the users. The aspect of such usability problems should be considered seriously, since this will affect how the users will apprehend the new, exhaustive computer system. The integration of Watson LIMS into the Quintiles AS activity will be affected by the employees' attitude to the system, whereas their viewpoints have to be regarded with sincere consideration. One way to prevent negative attitudes from being spread is to provide the users extensive information about the new system, and to give them such a good education in the system as ever possible.

The implementation will change some of the working routines for the analytical investigators. If the Watson LIMS system turns out to be difficult to learn, some employees might eventually, in the beginning at least, carry out bioanalysis studies together with someone else who knows the system well. This is a proposal to avoid unfamiliar routines for a person, as for example the new sample login procedure.

7.3.1 General Aspects

Some comments about the Watson LIMS system have already become clear by the persons involved in the system implementation. A common aspect is the matter of the Watson LIMS system turning out to be less user-friendly than first thought. There are opinions about the layout and design, which gives an unaccustomed user a somehow confused impression. The system offers no distinct, logic workflow, which can make it difficult for the user to retain efficiency. Watson LIMS holds a large range of functions, which is naturally of great advantage for performing extra calculations and tables, which may be requested from customers. However, the big variety of functions can cause insecurity during task performances since the task wanted to operate, may be difficult to identify among all others. There are also in some cases possibilities to perform a task in different ways, as the same function can be reached through different menus and headings. Another concern is the lack of a good user help function, available during the use of Watson LIMS. There does exist a help function in the system, but when called for only the extensive *Watson Bioanalytical LIMS User Manual* appears as a pdf document, and no specific help regarding the current treated function is available. Two helpful user accessories are included as appendices in *Watson Bioanalytical LIMS User Manual*, which offer short, easy-to-

understand instructions; *Quick Start Guide For Setting Up A Study In Watson* and *Quick Start Guide For Processing Raw Data Using Watson*. Regarding freezer login and report generation there are still instructions missing, but these will eventually be established by persons at Quintiles AS in connection to the user start of Watson LIMS.

Due to the system offering more functions than premeditated and having a more complicated approach than first thought, it will eventually take more time than considered to teach the users the system. To make the implementation as convenient as possible, it will be of great importance to give all persons who in some way will be affected by the Watson LIMS, an adequate and extensive education.

If the users, despite some difficulties, learn the system successfully Watson LIMS is
well suited to go with Quintiles AS bioanalysis process. The range of available study documentation and report material will increase dramatically and there will be good opportunities to fully satisfy the customer's desires.

7.3.2 Sample Receipt

Some of the sample receiving routines will work as they do today, as for example the manual checking of agreement between received samples and sample lists. Other parts will change radically, like the log-in and location registration of samples in Watson LIMS. This may in the beginning be considered as a more time-consuming and complicated practice than the one of today, which probably will be the case. As the procedure becomes a matter of routine, the time taken will decrease and the attitudes regarding the sample receipt will probably become more positive.

Concerning the actual usability of the Watson LIMS, all needed functions are available and widespread information may be stored in connection to all samples and to the study. The analytical run is planned and a work list is created, which is exported to MassLynx or Chromeleon to be used directly by the system software. An extensive registering in the beginning will make the workflow later on more straightforward, complete, fast and secure.

7.3.3 Report Compilation

Regarding the procedure of report generation, many of the current tasks will be carried out in an automated manner. This means that a predominant part of the report information, calculations and data tables will be directly included into the report template, and just a few manual adjustments are needed to be executed by the analytical investigator. The report work will be less heavy and the users will probably apprehend the new process as convenient. A consequence of the increased efficiency is that the analytical investigators in the near future will spend less time in front of the computers in their offices during report writing. As more studies will be available to analyze each year due to increased bioanalysis workflow, it means that the proportional time for them spent in the laboratory compared to the office will grow. This aspect is likely to be viewed with different opinions; some may regard it as relieving to get a shorter period of sometimes stressful report writing, as others will miss the period of serenity in the office. However, most of the analytical investigators seem to appreciate the current variation of working tasks, why this matter is important to keep in the future Quintiles AS activity.

7.3.4 Internal Quality Control

This step will be eliminated with the implementation of Watson LIMS. As the procedure is taken some time from two persons every analyzed study, and is not much appreciated, most persons will not miss the internal quality controls.

Some of the opinions from the employees run as follows:

> *"Not much fun, but at least the procedure is quite fast."*
>
> *"I don't mind carrying out the internal quality control, but I also won't miss it."*

"It feels like an extra security when someone but you has checked the values."

7.3.5 QA Control

Exactly how much the work of the QA auditor will change is difficult to predict today. Nevertheless, with a working Watson LIMS several of the manual QA controls will be eliminated, which saves him/her time from performing routine tasks. This means that the QA auditor can put more effort into complicated problems, which will increase the work stimulation.

7.4 The choice of LIMS system

When Quintiles AS, about one year ago, had taken the decision to invest in a computer system to increase the activity's security and efficiency, several different opportunities showed. By some investigations and considerations it was decided to concentrate on the various LIMS systems and especially two kinds were of interest for the activity. These two are the Watson LIMS, which is built specifically to suit bioanalysis activities, and the LabWare LIMS, which is a toolbox that gives the opportunity to construct the system adjusted to the customer's very specific activity. The last system seems at first to be the best choice since no adaptations of the system have to be performed and all needed functions can be included into the system. This is normally the procedure using the theories of Human Computer Interactions, described in the theory chapter of this thesis. As another department at Quintiles had invested in this kind of system some year before, the responsible persons at Quintiles AS learned that this system requires a lot of expensive time from a LIMS consultant to map the activity of the department in detail and then construct the system. They also learned that this project is much further complicated than first believed and causes a lot of troubles, which delays the implementation process significantly. Due to these reasons Quintiles AS chose to install the Watson LIMS system, which was known to work well with bioanalysis activities, even though some configurations of the system had to be carried out.

Thus, the decision to choose the Watson LIMS system was not taken from a strict Human Computer Interaction point of view. This leads to the conclusion that similar problems in the future might be studied in a different theoretical context, such as through a more distinct socio-technical perspective.

8 CONCLUSIONS

The objective of this master thesis is to study how the implementation of a Watson LIMS computer system will affect the process of the bioanalysis activity at Quintiles Analytical Services. The influence of the implemented system has primarily been studied according to the aspects of the bioanalysis security, efficiency and usability and focus are set on procedures where today and the future system will differ the most. Since the Watson LIMS system is not yet in use, the conclusions of this thesis are partly speculative.

The main conclusions in the areas of security, efficiency and usability are:

- Security issues -

- The risks to accidentally manipulate the Watson LIMS functions incorrectly will strongly depend on the employees' user roles.
- Watson LIMS ensures track control of stored samples in freezers.
- Watson LIMS eliminates the internal quality control procedure, since it will not be needed due to security issues.
- Watson LIMS offers increased security regarding the final report contents, due to fewer manual statistical calculations and table generations.
- Careful attention has to be paid to ensure that Watson LIMS only interacts with validated systems, to confirm data transferring security.

- Efficiency issues -

- A 500 samples study takes today a total of approximately 20 days to complete, compared to estimated 16.5 days using Watson LIMS.
- Watson LIMS will reduce the report compilation procedure from approximately 4 days to 1 day.
- The Quality Assurance auditor will have to spend less time per study using Watson LIMS. (3 hours instead of 6 hours)
- The estimated time to be saved during the first year of use, is not realistic.

- Usability issues -

- Watson LIMS will result in partly changed work routines for all Quintiles AS employees.
- Watson LIMS is to several aspects less user-friendly than expected.
- It is very important that the employees get an adequate and extensive education in Watson LIMS. This will be of great importance to their first impression of the new system.

- Shorter time of report compilation may in the future result in more time spent in the laboratory. Is this appreciated among all employees? This question needs to be considered and dealed with to retain the employees' work satisfaction.

- The elimination of the internal quality control seems in general to be appreciated by the employees.

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9.3 Primary sources

Following persons have during the master thesis project been available for questions and support.

Björsberg, Annika, *Analytical Investigator*, Quintiles AS, continuous interviews regarding today's bioanalysis activity.

Ekman, Lena, *Principal Investigator and Watson LIMS Project Manager*, Quintiles AS, continuous interviews regarding today's bioanalysis activity and the Watson LIMS system.

Gustafsson, Hans-Olov, *Chemist, Scientific Computing*, Quintiles AS, continuous interviews regarding the Watson LIMS system.

Hagberg, Olof, *Scientist Mass Spectrometry (Analytical Investigator) and Watson LIMS superuser*, Quintiles AS, continuous interviews regarding today's bioanalysis activity and the Watson LIMS system.

Pham, Catherine, *QA Auditor*, Quintiles Phase I Services, 2004-10-26 and 2005-01-24, interviews.

Tyrefors, Niklas, *Senior Scientist Mass Spectrometry*, Quintiles AS, August-December 2004, continuous interviews regarding the Watson LIMS system.

10 APPENDICES

A. AS Bioanalysis Today – Textual Task Hierarchy

1) Sample receipt

a) Identification, condition and total number of samples are controlled.

b) Sample boxes are packed into freezers.
i) Non-occupied freezer storage is searched.
ii) Sample boxes are put into racks in freezer(s).
iii) Study is logged in to the freezer(s) in the respective log book.

c) Signing of the Sample Receipt document.

d) Confirmation is sent to customer.

2) Sample storage in freezers

a) Changing of sample freezer location (eventually).
i) Free freezer space is searched.
ii) Sample boxes are placed into free freezer(s).
iii) Study is logged out from former freezer(s) and logged into new freezer(s).

3) Project plan creation

a) Analytical project protocol (File Server; G:\Departments\Analytical Services\Templates\Bioanalysis\Studie\Analytical project planl-vx.dot)

4) Study work-up at the laboratory

a) Samples are collected from freezer(s)
i) Find out freezer location (in Study's Main binder; *Sample Receipt*).
ii) Sample-boxes are taken out from freezer(s) and the study is logged out.

b) The samples are worked up at the laboratory (50-200 samples per batch).

5) Study is analyses at the instrument of current interest

a) The instruments autosampler is loaded.

b) Sample list is built in the instrument software.

c) Instrument is analyzing the samples.

d) Sample evaluation
i) Calibration curves and data tables are constructed and chromatograms are evaluated.
ii) Samples are eventually reanalyzed, starting with sample work-up (4).

e) Results are saved in Qtree/Freja/Biodata/Utility/personal file.

6) Report compilation

a) The results are copied and exported to Excel from the personal workstation (Qtree/Freja/Biodata/Utility/personal file).

b) The report is compiled in accordance to the template layouts of reports, which are stored in the File server; G:\Departments\Analytical Services\Templates\Studie\Analytical report-vx.dot.

7) Internal quality control

a) The person in charge of the study and a second person are controlling the results by double-checking the values according to SOP: AS-17001/04.

i) The second person confirms the correct values by signing next to them.
ii) Any non-agreeable values are marked as samples needed to be re-analyzed or checked.
iii) Finally the two persons confirm the internal quality control by signing the *Internal QC document*.

b) Possible reanalysis

i) Go to step 4, starting with sample work-up at the laboratory.

8) QA control

a) The QA auditor is controlling the report.

b) The analytical investigator is correcting any mistakes found by the QA auditor.

9) Report is sent to customer

a) Result tables (Excel or text files) will be sent to the customer as a printed, signed report copy, when requested.

10) Archiving

a) Main binder and all raw data will be archived when the report has been finalized.

11) Study samples are sent back to customer or discarded

a) Samples are collected from freezer(s)

i) Find out study-sample freezer location (in Study Main binder; *Sample Receipt*).
ii) Sample boxes are taken out of freezer(s).
iii) Study is logged out from freezer(s).

b) Pack sample boxes into chest freezers

c) Sample Sending document is signed and sent to customer together with the study

d) Chest freezers are delivered to customer by a shipping agency

B. AS Bioanalysis using Watson LIMS – Textual Task Hierarchy

1) Sample receipt

a) Identification, condition and total number of samples are controlled.

b) Samples are logged in to freezer(s).
i) Non-occupied freezer storage is searched in Watson LIMS.
ii) Sample boxes are put into racks in freezer(s).

c) Study is logged in to Watson LIMS (and freezers are registered).
i) Information regarding treatments, doses, gender etc. is registered.
ii) Name of the Principal Investigator and Analytical Investigator are given.
iii) The freezer(s) and specific racks of the study are registered.

d) Signing of the Sample Receipt document.

e) Confirmation is sent to customer.

2) Sample storage in freezers

a) Changing of sample freezer location (eventually).
i) Free freezer space is searched in Watson.
ii) Sample boxes are placed into freezer(s).
iii) Study is logged out from former freezer(s) and logged in to new freezer(s), in Watson.

3) Project plan creation

a) Analytical project protocol (File Server; G:\Departments\Analytical Services\Templates\Bioanalysis\Studie\Analytical project planl-vx.dot)

4) Study work-up at the laboratory

a) Samples are collected from freezer(s).
i) Find out freezer location of the study-samples in Watson.
ii) Samples are taken out from freezer(s).
iii) Study is logged out from freezer(s) in Watson.

b) The study is worked up at the laboratory.

5) Study is analyses at the instrument of current interest

a) Work list will be created within Watson and exported as a sequence file to the instrument programs MassLynx or Chromeleon.
i) Depending on if it is a study batch or a method validation batch, the sequence/batch will be given the name: study number, prefix “B” or “V” and a serial number. Ex. 24044B4.

b) The instruments autosampler is loaded with samples.

c) Instrument is analyzing the samples.

d) Sample evaluation
i) Data, diagrams, chromatograms etc are evaluated.
ii) Samples are eventually reanalyzed, starting with sample work-up at the laboratory, step 4. Samples may also be reinjected into the instrument.

e) The sequence with integrated areas or heights of the chromatograms is imported back to Watson.

6) Report compilation using Watson LIMS templates

a) Regression and calculations of concentrations will be performed within Watson LIMS.

b) Predefined tables and figures will be prepared when all analytical runs are completed.

c) Reanalysis will be performed according to predefined criteria; which samples to reanalyze and which sample values to report.

7) QA control

a) The QA auditor is controlling the report.

b) The analytical investigator is correcting any mistakes found by the QA auditor.

8) Report is sent to customer

a) Result tables (Excel or text files) will be exported from Watson LIMS and sent to customer when requested.

9) Archiving

a) Main binder and all raw data will be archived when the report has been finalized.

10) Study samples are sent back to customer or discarded

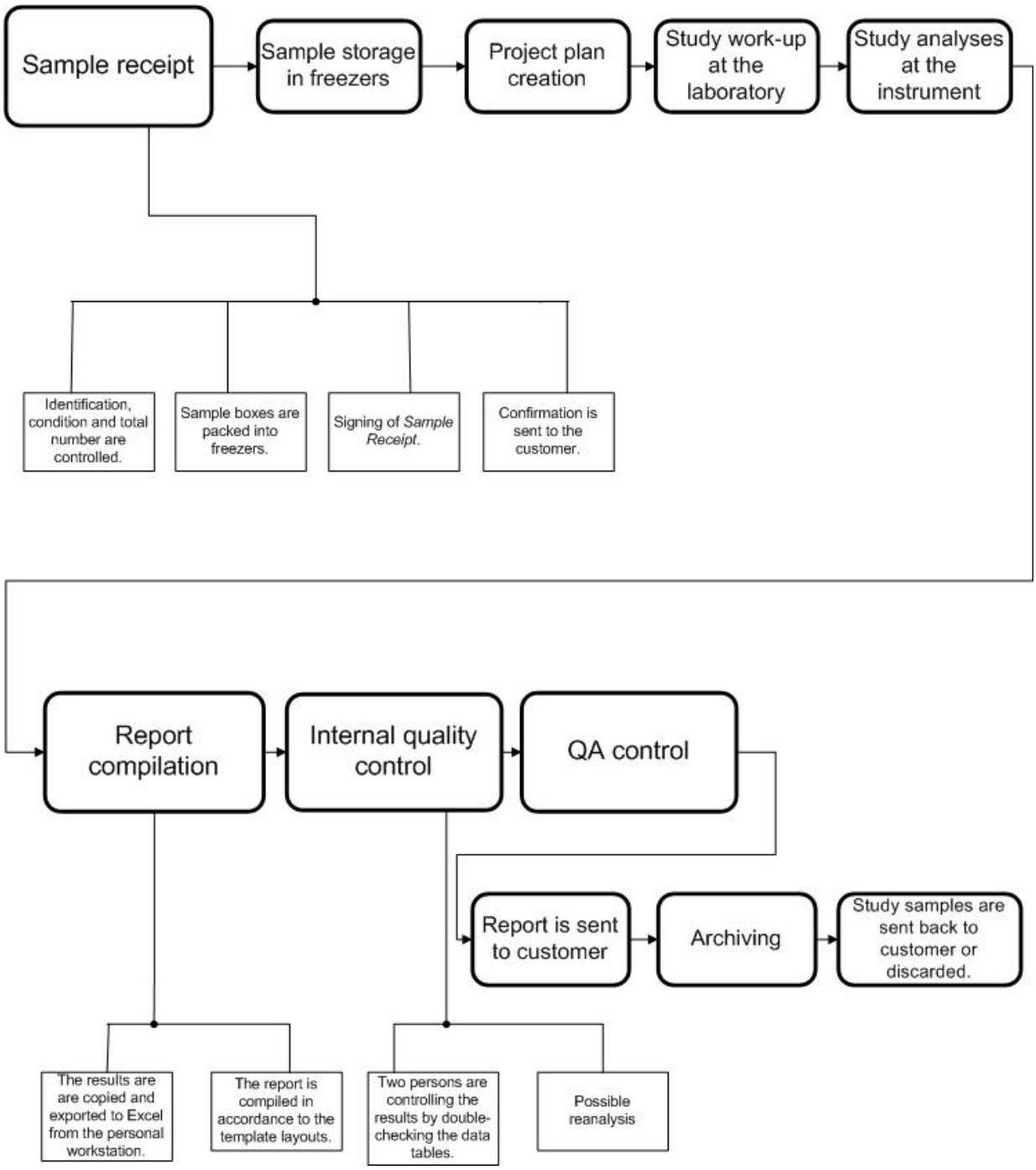
a) Samples are collected from freezer(s).
   i) Find out freezer location within Watson LIMS.
   ii) Sample boxes are taken out of freezer(s).
   iii) Study is logged out from freezer(s) in Watson LIMS.

b) Pack sample boxes into chest freezers.

c) Sample Sending document is signed and sent to customer together with the study.

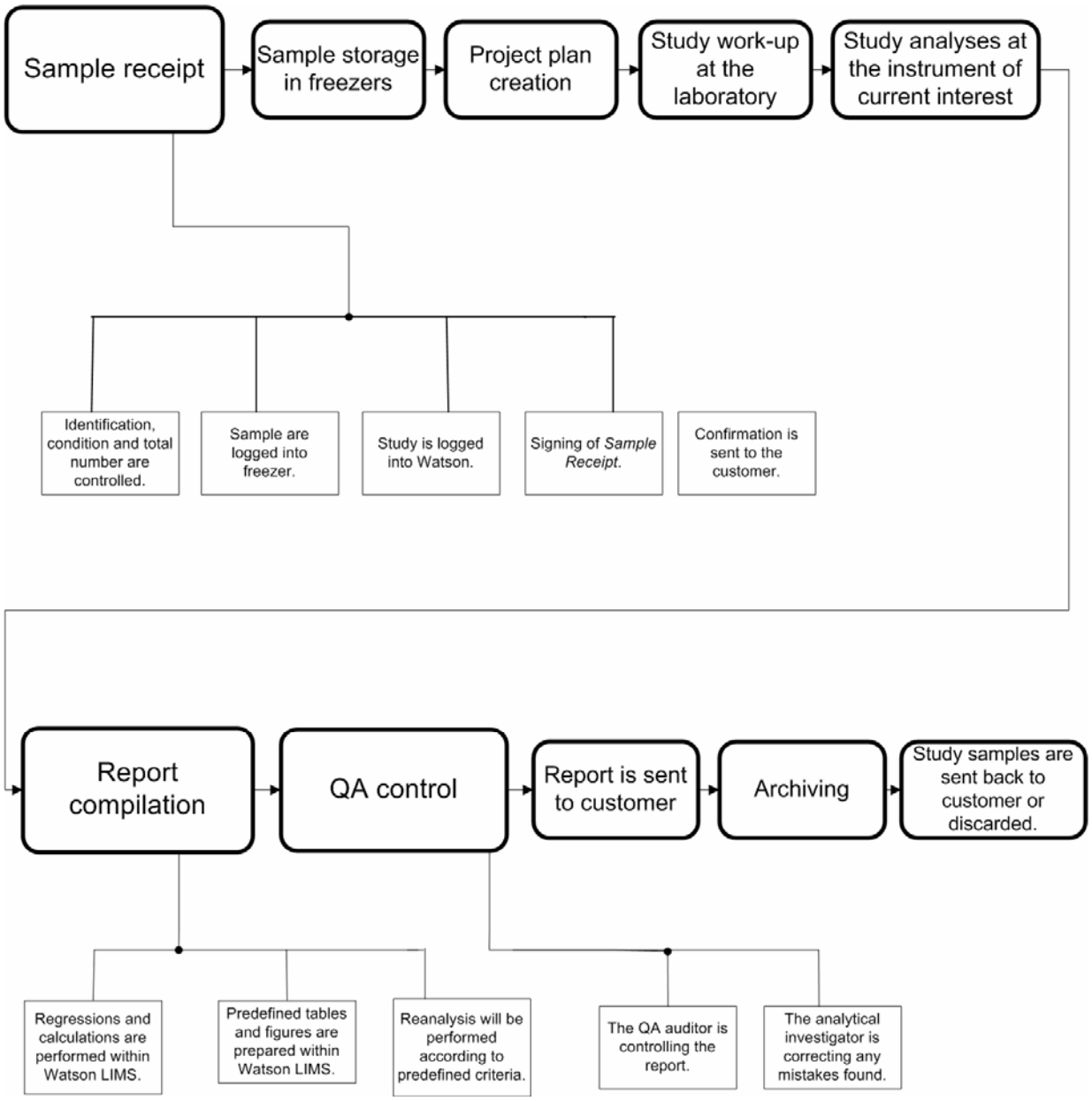
d) Chest freezers are delivered to customer by a shipping agency.

C. AS Bioanalysis Today - HTA diagram



This diagram shows the workflow of the current used bioanalysis system. To study more details, see appendix A.

D. AS Bioanalysis using Watson LIMS - HTA diagram



This diagram shows the predicted workflow of the bioanalysis system when using Watson LIMS. To study the workflow in more detail, see appendix B.