

# Risks in the chemotherapy process and possibilities for improvement

*AnnSofie Fyhr*



LUND UNIVERSITY

Ergonomics and Aerosol Technology  
Department of Design Sciences  
Lund University

Licentiate Thesis

ISBN 978-91-7473-144-6

ISSN 1650-9773 Publication 44

ISRN LUTMDN/TMAT-2031-SE, EAT 2011

© AnnSofie Fyhr

Printed by Media-Tryck, Lund, Sweden

*The goal is nothing compared to the path*



## ABSTRACT

Medications are of considerable help if healthcare providers are able to administer them to patients safely and appropriately. The medication use process is complex and a team of professionals – doctors, nurses, and pharmacists – work together with the patient for optimal treatment effect. The process involves many sub-processes and in every step there is a possibility for an error. Cytotoxic drugs have high toxicity and a narrow therapeutic index, which means that there is little difference between a lethal and therapeutic dose. The use of such drugs may entail great risks for the patient.

The general aim of the research presented in this thesis is to identify these risks and to identify actions and strategies for improving safety in the chemotherapy process. The research focuses on errors in the medication use process of parenteral cytotoxic drugs and how to prevent them. The main objectives are:

- To proactively disclose system weaknesses in the process of prescribing and administering cytotoxic drugs in order to suggest interventions.
- To identify the characteristics of the medication errors involving cytotoxic drugs in Sweden in order to gain increased knowledge about them.

Two approaches have been applied: a proactive one using the disturbance effect barrier (DEB) method, and a retrospective one using a qualitative analysis of the data.

The proactive method revealed system weaknesses mainly at the stage of prescribing and the medication use process was found to involve great risks for the patient. In the retrospective analysis, the most commonly involved drug was fluorouracil and the platinum containing drugs were the ones that often caused serious consequences for the patients. The most common error types were too high doses and use of the wrong drug. Fully 40% of the errors occurred at the prescribing and transcribing stage. All of these were delivered to the patient causing temporary or life-threatening harm. Fully 40% of the errors occurred at the preparation stage and were made by pharmacists. The rest of the errors occurred during preparation or administration by nurses.

The stage of prescribing by doctors was identified as a major risk. The most commonly identified error types were wrong dose, drug or patient. This indicates that there are possibilities for improvements, such as by using computerised prescriber order entry (CPOE) systems and bar coding for identification of drug and patient. Other strategies for improvement of the chemotherapy process have been suggested in the literature. Among these are standardisation of prescribing vocabulary, multidisciplinary co-operation, working with pharmaceutical manufacturers, and education of the patients.

As described in this thesis, the chemotherapy process is complex and involves a great deal of risks for the patients. There is great awareness of the risks and there are many suggestions for actions and strategies for improvements. Some of these needs to be further evaluated and implemented for better safety for the patients.

## SAMMANFATTNING

Läkemedel är till stor hjälp om vårdgivarna kan förse patienterna med dem på ett säkert och riktigt sätt. Läkemedelsprocessen är komplex och ett team av professionella – läkare, sjuksköterskor och farmaceuter – arbetar tillsammans med patienten för att få optimal behandlingseffekt. Processen innehåller flera sub-processer och i varje steg finns möjligheter för fel. Cytostatika har hög toxicitet och ett smalt terapeutiskt fönster, d.v.s. liten skillnad mellan dödlig och terapeutisk dos, och användningen kan innebära stora risker för patienten.

Övergripande mål för denna avhandling är att identifiera risker och att identifiera aktiviteter och strategier som kan öka säkerheten i cytostatika processen. Forskningen i denna avhandling fokuserar på felen i läkemedelsprocessen med parenterala cytostatika och hur man ska kunna förhindra dem. Målen är följande:

- Att proaktivt avslöja systemsvagheter i processen ”ordinera och administrera cytostatika” för att kunna föreslå interventioner.
- Att identifiera egenskaper hos medicineringsfel med cytostatika i Sverige för att er hålla en ökad kunskap om dem.

Två olika tillvägagångssätt har använts, en proaktiv med användande av störning effekt barriärer (SEB) metoden och en retrospektiv kvalitativ analys av data.

Den proaktiva metoden avslöjade systemsvagheter främst i förskrivningssteget och processen innebar stora risker för patienten. I den retrospektiva analysen var fluorouracil det mest inblandade läkemedlet och läkemedlen innehållande platina var de som ofta orsakade allvarliga konsekvenser för patienterna. De vanligaste feltyperna var för höga doser och användande av fel läkemedel. Drygt 40 % av felen uppstod vid ordinationen eller vid överföring av ordinationen till en rekvisition. Samtliga av dessa gavs till patienterna och medförde tillfällig eller livshotande skada. Drygt 40 % av felen uppstod vid beredning av farmaceuter. Resterande fel inträffade vid beredning eller administration av sjuksköterskor.

Ordinationssteget som görs av läkare identifierades som en stor risk. De vanligaste feltyperna som identifierades var fel dos, fel läkemedel eller fel patient. Detta betyder att det finns möjligheter till förbättringar, exempelvis genom användande av datorstöd vid förskrivning och streckkod för att identifiera läkemedel eller patient. Andra förbättringsåtgärder har föreslagits i litteraturen. Bland dessa finns standardisering av begrepp som används vid ordination, multidisciplinärt samarbete, arbete med läkemedelstillverkare och utbildning av patienterna.

Som beskrivits i denna avhandling är cytostatikaprocessen komplex och kan innebära risker för patienterna. Det finns stor medvetenhet om dessa risker och det finns många förslag till aktiviteter och strategier för förbättringar. En del av dessa behöver utvärderas och implementeras för bättre säkerhet för patienterna.

## ACKNOWLEDGEMENTS

Many people have contributed in one way or the other to this thesis. Thanks to you all!

Some deserves special thanks:

Roland Akselsson for his great knowledge, patience and thoroughness in reading all my manuscripts.

Åsa Ek for her fantastic ability to find a structure in the writing and for all help.

Gerd Johansson for welcoming me to the department and managing a whole lot of things.

Sven Ternov for introducing me to this field and leading me on to this broad path.

Jonas Borell and Christofer Rydenfält for fruitful discussions.

Sidney Dekker for challenging discussions.

Eileen Deaner for improving my English.

All colleagues at the Ingvar Kamprad Design Centre for good company and discussions during coffee breaks and lunches.

Bengt-Åke Petersson, former head of the Hospital Pharmacy in Lund, who always believed in and encouraged me.

Lina Mobärg, business manager Skåne, Apoteket Farmaci AB, for giving me leave of absence allowing me to complete this thesis.

All colleagues at the Hospital Pharmacy in Lund, both those still working and those who have left. Together we made great progress.

My family, Peter, Pontus and Malin – YES! And our dogs – Millie and Axa – always keen on a long walk.

This research has been funded by the Swedish Academy of Pharmaceutical Sciences, Apoteket AB, and the Swedish Ministry of Health and Social Affairs together with the Swedish Ministry of Education and Research. Their support is gratefully acknowledged.

## LIST OF INCLUDED PAPERS

### Paper I

System Weaknesses in the Process of Treating Patients with Cytotoxic Drugs.  
Ternov S, Fyhr A, Akselsson R. *Ergonomics and Aerosol Technology*,  
Lund University, Sweden. Manuscript.

### Paper II

Characteristics of Medication Errors with Parenteral Cytotoxic Drugs.  
Fyhr A, Akselsson R. *Ergonomics and Aerosol Technology*, Lund University, Sweden  
Submitted to *International Journal for Quality in Health Care*.



# CONTENTS

ABSTRACT .....	1
SAMMANFATTNING .....	2
ACKNOWLEDGEMENTS .....	3
LIST OF INCLUDED PAPERS .....	4
CONTENTS .....	5
INTRODUCTION .....	7
AIM OF THE THESIS.....	8
THEORETICAL FRAMEWORK.....	8
The complexity of the medication use process.....	8
Legislation and methods used for analysis of adverse events in healthcare in Sweden .....	10
The terminology used in medicine for incidents and accidents.....	12
Literature review on medication errors in the chemotherapy process .....	13
Different accident models.....	18
Accident model used in this thesis.....	20
METHODS AND DATA .....	21
Research background .....	21
Prospective analysis of system weaknesses.....	22
Retrospective qualitative analysis of incidents .....	23
RESULTS.....	23
DISCUSSION .....	24
The risks in the chemotherapy process.....	24
The methods used .....	26
Actions and strategies for improvement in the chemotherapy process.....	27
Need for future research.....	30
REFERENCES .....	31



## INTRODUCTION

Betsy Lehman, a 39-year-old healthcare reporter, died of a drug overdose during treatment of metastatic breast cancer (Cohen et al., 1996). According to the investigational protocol, the prescribed cyclophosphamide dose was “4 g/sq m over four days”. This ambiguous order was misinterpreted by a number of health professionals. What should have been ordered was a daily dose of one g/sq m for four days in a row. Instead, the patient received 6.52 g of cyclophosphamide per day for four consecutive days, for a total of 26.08 g instead of 6.52 g. This tragic event together with other case reports led to unprecedented publicity and may have been the starting point in the USA in the mid-1990s of discussions on how to prevent medication errors in cancer chemotherapy (Cohen, 2007b).

Medication errors (MEs) involving parenteral cytotoxic drugs also received media attention in Sweden in the mid-1990s. Examples are a child’s death due to unintended administration of vincristine intrathecally; another child’s death due to the use of total doses for 3–4 days as doses per day (the same type of error as in the Lehman case), and two women who received a too high dose of carboplatin due to a calculation error.

In general, when an individual accesses the healthcare system, they expect that the care and treatment they receive will be safe. However, this is often not the case as many patients experience harm during their time as a patient. The incidence of adverse events in Swedish hospitals was examined in a medical record review study (Soop, Fryksmark, Koster, & Haglund, 2009). The study was performed from 2003 to 2004 at 28 hospitals. The rate of preventable adverse events was nearly 9%. Extrapolated to the 1.2 million annual admissions, the result correspond to 105,000 preventable adverse events and 630,000 extra days of hospitalisation in Sweden. Problems in drug treatment account for about 27% of these adverse events (wrong medication 3%, failure or delay of drug treatment 9%, wrong dose 7%, and adverse drug reaction 8%). This would be approximately 28,000 adverse events due to drug treatment per year.

In earlier studies from other countries with the same method, the rate of adverse events found in acute care hospitals varied from 3 to 17% (Ödegård, 2006). Extrapolation to annual admissions in the actual country together with total national costs have worked as a wake up call for people working in healthcare and for politicians, resulting in a focus on and programmes for improvements. In 2000 the Institute of Medicine (IOM) published their report, *To Err is Human* (Kohn, Corrigan, & Donaldson, 2000). The response to the report made medical errors a leading public health issue and laid the groundwork for improvements in patient safety (Cohen, 2007a).

It has been extrapolated from the Swedish study that in approximately 3000 cases, preventable adverse events may have contributed to a fatal outcome (Soop, et al., 2009). As a comparison, statistics from Sweden reveal that about 270 persons died in traffic road accidents in 2010 (Swedish Transport Administration, 2011). Traffic road accidents and an improvement strategy have been in focus for more than a decade with an expressed “zero-vision”, to decrease the number of deaths in road accidents. Many stakeholders, government, authorities, the car industry and academia have been working together towards a common goal. Healthcare needs a similar goal for real improvements.

Cytotoxic drugs are highly beneficial medications, but they must be used carefully because of their high toxicity and narrow therapeutic index, which means that there is little difference

between lethal and therapeutic doses. Medication errors with these drugs are potentially fatal and should therefore be prevented. The system's weaknesses contributing to MEs should be sought out and when identified, actions and strategies can be suggested to prevent these MEs. We need to identify the risks and find opportunities for improvements in the chemotherapy process. The purpose of this thesis is to investigate these issues.

The author of this thesis has a background that may be of interest. I have a Master of Science in Pharmacy from Uppsala University and am a Registered Pharmacist. I have more than 30 years of work experience starting with ten years in the pharmaceutical industry including process development and the production of small volume parenterals as well as R&D. For nearly 20 years now, I have been supervisor of the pharmacy preparation service at the Hospital Pharmacy, University Hospital in Lund, Sweden. This includes oncology preparations, which means that I possess both theoretical and practical knowledge in the domain.

## **AIM OF THE THESIS**

The medication use process of parenteral cytotoxic drugs is considered to have great risks for the patient. The general aim of this thesis research is to identify these risks and to identify actions and strategies in order to improve the safety in the chemotherapy process.

The research presented in this thesis focuses on errors in the medication use process of parenteral cytotoxic drugs and how to prevent them. The main objectives are:

- To proactively disclose system weaknesses in the process of prescribing and administering cytotoxic drugs in order to suggest interventions.
- To identify the characteristics of the medication errors involving cytotoxic drugs in Sweden in order to gain increased knowledge about them.

## **THEORETICAL FRAMEWORK**

In the theoretical framework, the following aspects related to the current research will be considered:

- The complexity of the medication use process.
- Legislation and methods used for analysis of adverse events in healthcare in Sweden.
- The terminology used in medicine for incidents and accidents.
- Literature review on medication errors in the chemotherapy process.
- Different accident models.
- Accident model used in this thesis.

### **The complexity of the medication use process**

Medications are of considerable help if healthcare providers are able to administer them to patients safely and appropriately. Yet, healthcare providers are humans and, as such, fallible. Drug treatment can be seen as a process involving a team of professionals: doctors, nurses, pharmacists, and the patient. There needs to be good communications, both written and verbal, about the medications in the team and between the team and the patient. The process contains many sub-processes and in every step there is a possibility for error: drugs can be mixed-up, doses can be miscalculated, wrong strengths of drugs can be picked, preparations

can be erroneous, and patients can be mixed-up. There are about 10,500 medicinal products for humans authorised for marketing in Sweden. They are available in different forms (e.g. as tablets or injections) and in different strengths (Medicinal Products Agency, 2011). The general medication use process has been described as follows (Kohn, et al., 2000):

*Prescribing (doctor)*

- assessing the need for and selecting the correct drug
- individualising the therapeutic regimen
- designating the desired therapeutic response

*Dispensing (nurse or pharmacist)*

- reviewing the order
- processing the order
- compounding and preparing the drug
- dispensing the drug in a timely manner

*Administering (nurse or the patient)*

- administering the right medication to the right patient
- administering the medication when indicated
- informing the patient about the medication
- including the patient in the administration

*Monitoring (nurse, doctor or the patient)*

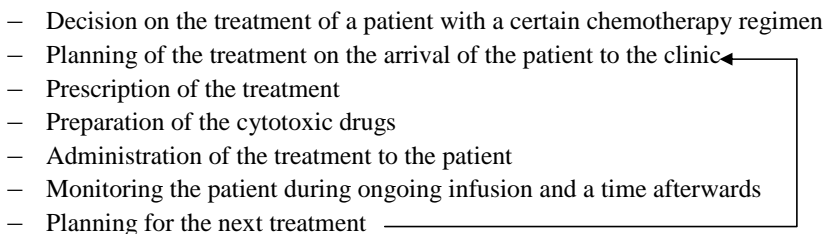
- monitoring and documenting patient's response
- identifying and reporting adverse drug events
- re-evaluating drug selection, regimen, frequency and duration

*Systems and management control (nurse and doctor)*

- collaborating and communicating amongst caregivers
- reviewing and managing patient's complete therapeutic drug regimen.

A commonly used expression to get this process right is: “The **Five Rights** of Medication Safety,” that is, “Right Patient, Right Drug, Right Time, Right Dose, Right Route” (Institute for Safe Medication Practice, 1999). “Route” here means the correct way of delivery of the medication, such as orally or by an intravenous infusion.

The parenteral cytotoxic medication use process can be described as follows:

- Decision on the treatment of a patient with a certain chemotherapy regimen
  - Planning of the treatment on the arrival of the patient to the clinic
  - Prescription of the treatment
  - Preparation of the cytotoxic drugs
  - Administration of the treatment to the patient
  - Monitoring the patient during ongoing infusion and a time afterwards
  - Planning for the next treatment
- 

The doctor is responsible for decision, planning and prescription. Preparation is mostly done by pharmacists. Administration and monitoring is done by nurses. Monitoring can be done by doctors too. Planning for the next treatment is done by doctors. It is an iterative process: the patient will return for the next treatment according to the protocol after one to three weeks.

About 50 different cytotoxic drugs, including monoclonal antibodies, are used for parenteral administration in Sweden today (Swedish Association of the Pharmaceutical Industry, 2011). These drugs are administered in a wide variety of cancer therapies, both for curative and palliative care, and they are used in the treatment of small children up to elderly people. They can be used as a single drug given once a week to once every third week. Combinations of drugs are also used in complex regimens over several consecutive days repeated after 2 to 3 weeks. For most of the drugs, the dose is based on body surface area or other patient-specific factors (e.g. weight or renal function). Most cytotoxic drugs have a narrow therapeutic index so that a small increase in dosage is associated with a large increase in the likelihood for severe adverse effects, and a small decrease in dosage may result in therapeutic failure. At the same time, for some of these drugs, such as cytarabine, and methotrexate, dosages vary widely depending on the condition being treated, how the drug is used, and the use of supportive therapy. Cytotoxic drugs, given parenterally and orally, are classified as “high-alert medications” according to the Institute for Safe Medication Practice (ISMP) (2011).

## **Legislation and methods used for analysis of adverse events in healthcare in Sweden**

### ***Background***

Sweden has about nine million citizens. There are about 65 hospitals varying in size, seven of which are university hospitals. In 2008 about 42,000 people were diagnosed with cancer for the first time; of these 330 were children (<20 years) (Swedish Cancer Society, 2010). Approximately 350,000 parenteral cytotoxic preparations were prepared in 2008. Most of them, 330,000, were prepared by hospital pharmacists and the rest by nurses in the unit (Svedmyr, 2011). Pharmacists in Sweden can be educated on two levels: master’s and bachelor’s. Legislation requires that pharmacists have at least a bachelor’s degree for preparation of cytotoxic drugs. At the time of the studies presented in this thesis, hospital pharmacies were run by a governmental company, Apoteket AB, which is an external partner to healthcare.

There are several authorities that regulate and influence the work carried out in healthcare in Sweden. The agency with the greatest influence is the Swedish National Board of Health and Welfare (NBHW). It is a government agency under the Ministry of Health and Social Affairs. NBHW issues regulations in accordance with national legislation that healthcare providers must follow. According to the legislation (SOSFS 2005:12) (National Board of Health and Welfare, 2005), a management system for quality and patient safety in healthcare has to be in place. The aim of these systematic quality efforts is to prevent adverse events. The healthcare providers are required to set up rules and procedures for how to identify, analyse and assess risks, and to suggest improvements. The management system must contain procedures for incident reporting as well as for risk and incident analysis.

### ***Incident reporting systems***

All hospitals and pharmacies in Sweden have local incident reporting systems, most of them now computerised. The incidents reported by hospital staff are assessed by a person appointed by the management. If the incident is judged to be serious, it is sent to the medical director at the hospital who is responsible for the final decision to report or not report to the NBHW according to the lex Maria Act (legislation and regulations on injuries in the healthcare sector) (National Board of Health and Welfare, 2011a). For the pharmacies, the final decision has been centralised to the quality department. In 2008 a total of 1,102 incidents were reported

according to lex Maria (National Board of Health and Welfare, 2011c). About 250 (23%) of these involved a medication (Fryksmark, 2011). Until the end of 2010, the Swedish Medical Responsibility Board (HSAN) was the national authority that assessed medical negligence. If healthcare staff was at fault the Board could take disciplinary action against them, issuing admonitions or warnings. The patient, a close relative or the NBHW could file a complaint to the Board. Since 1 January 2011, a new patient safety law has been in force: Patientsäkerhetslagen (The Patient Safety Act) (National Board of Health and Welfare, 2011b). All serious incidents reported from healthcare along with complaints from patients and close relatives are to be reported to and investigated by the NBHW.

### ***Handbooks in Sweden***

To be able to work systematically with quality there is a need for different tools. A search was carried out to locate such tools already used in healthcare around the world. In 2005 a Swedish handbook for risk and incident analysis for patient safety was introduced (National Board of Health and Welfare, 2009b). The purpose of an incident analysis is to find shortcomings in the organisation, for instance in communication, co-operation, equipment, and procedures. The method described in the handbook was inspired by the root cause analysis (RCA) that has been used in the USA, UK, and Denmark. For the risk analysis a proactive method inspired by the Healthcare Failure Mode Effect Analysis (HFMEA) is used. Good support for the handbook came from the National Centre for Patient Safety Department of Veterans Affairs, USA. The handbook was introduced at Swedish hospitals and teams of investigators were educated. Since the introduction of the handbook, it has been used for many analyses of serious incidents, often before a decision to report or not according to lex Maria.

A few years after the favourable reception of the first handbook, two new ones were introduced. One on measuring adverse events with the help of the Global Trigger Tool (GTT) (Institute for Healthcare Improvement Innovation, 2008), and one on measuring the safety culture (National Board of Health and Welfare, 2009a).

### ***Man-Technique-Organisation (MTO)***

Methods directed at the interplay between (hu)Man-Technique -Organisation (MTO) commonly used for industrial application have also been used in healthcare. The MTO analysis was used for the tragic incident where a little girl died from an overdose of lidocaine in 2002 (Ödegård, 2007). The incident was also described by Dekker (2007). The MTO analysis has been used in the analyses of eight consecutive accidents reported to the NBHW in Sweden by Ternov and Akselsson (2005). The MTO method is a structured way of gathering and analysing information. In their article, the following elements were included in the analysis:

- “Detailed mapping of the event, plotted against a time axis
- Causal analysis for inappropriate or faulty actions in the sequence
- Identification of situational factors
- Barrier analysis: analysis of the role of barriers in the actual context for not being able to stop the chain of events leading up to the accident.”

Ternov and Akselsson point out that the cause analysis is the difficult part. Basically it consists of asking “why” a sufficient number of times and tracing a causal chain backwards (upwards) within the organisation. The question is: When should one stop asking the question

“why”? (i.e. How should the stop rule be defined?). A preliminary analysis is made from a written accident report. The personnel and managers involved are interviewed in the next step, and the results from the cause and barrier analysis are modified according to this new information. The final report is then written.

## **The terminology used in medicine for incidents and accidents**

The terminology and definitions vary when reading the literature about incidents and accidents in medicine and in the medication use process. In a recent article by Lisby, et al. (2010), they carried out a systematic literature review of definitions and characteristics of MEs. They concluded that there was inconsistency in defining MEs and that it appeared that definitions and methods of detection were subject to the individual researcher’s preference.

The interconnections between different terms also vary, making it difficult for the reader to fully comprehend. This was observed by Yu, et al. (2005) who concludes that the multiplicity of terms, definitions and, most importantly, functional meanings demonstrates an urgent need for agreement on standardisation of nomenclature describing medication related occurrences. This is an essential prerequisite to enable meaningful analysis of incidence data and the development of medication safety improvement strategies. They are not alone in having problems with the terminology to describe errors and patient harm associated with medications. In a recent article in Sweden by Nydert (2011), the terminology and methods needed to promote drug safety were discussed. Nebeker, et al. (2004) used a case study of a patient with multiple adverse events to clarify key terms. Some of the key terms and definitions used in the current research are as follows:

*An error* is defined “as the failure of a planned action to be completed as intended (i.e. error of execution) or the use of a wrong plan to achieve an aim (i.e. error of planning)” (J Reason, 1990).

*A medication error (ME)* can be defined as “a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient” (Ferner & Aronson, 2006) or as “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use” (National Coordinating Council for Medication Error Reporting and Prevention, 2011). This means that an ME can occur in any of the stages of the medication use process as described earlier. Most MEs do not harm the patients. Some authors estimate that less than 1% of MEs result in harm (Bates, Boyle, Vander Vliet, Schneider, & Leape, 1995).

*An adverse event (AE)* can be defined as “an injury resulting from a medical intervention, or in other words, it is not due to the underlying condition of the patient” (Kohn, et al., 2000).

*An adverse drug event (ADE)* can be defined as an “injury resulting from medical intervention related to a drug” (Kohn, et al., 2000). In the patient safety literature, the term ADE usually denotes a causal association between the drug and the event. It also means that the patient is harmed by the event. An example would be a double dose of a cytotoxic drug given by mistake – this would be considered both an ADE and an ME. It gets even more complicated when authors like Morimoto, et al. (2004) discuss preventable or potential ADEs.



An *adverse drug reaction (ADR)* can be defined as “a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function” (European Medicines Agency, 1995) or as “injuries caused by a drug administered at usual doses” (Nebeker, et al., 2004). This is an inborn property of the drug itself and some patients react in one way or another. An example would be an allergic reaction to an antibiotic. If this is an unknown reaction to healthcare and the patient, it would be classified as an ADR. If the allergy was known to healthcare it would also be classified both as an ME and an ADR.

Other terms are used, for example, “a *sentinel event*” is used for “an unexpected occurrence involving death or serious physical or psychological injury, or the risk thereof” (Joint Commission, 2011).

From these different definitions it can be seen that there are interconnections between ME, ADE and ADR. This has been described in different ways. One view (Otero & Schmitt, 2005) is presented in Figure 1. Others can be found (Aronson, 2009; Nebeker, et al., 2004).

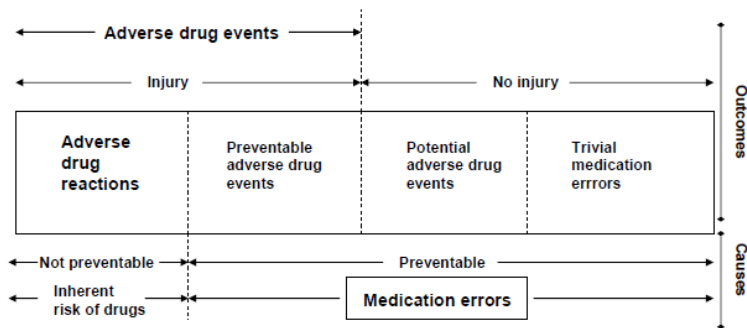


Figure 1. Relationship between adverse drug events, adverse drug reactions, and medication errors, from Otero and Schmitt (2005). The area of each section does not reflect the magnitude of the corresponding incident.

## Literature review on medication errors in the chemotherapy process

### *What we know about medication errors and adverse drug events in general*

There are many articles on ME and ADE in general. Some relevant articles are reviewed here. In a retrospective analysis of mortalities associated with ME from the USA, they analysed more than 5000 case reports sent to the Food and Drug Administration 1993-1998 (Phillips et al., 2001). Sixty-eight percent resulted in serious patient outcome and nearly 10% were fatal. The most common type of errors resulting in patient death involved administering an improper dose (mostly overdose) (41%), administering the wrong drug (16%), and using the wrong route of administration (10%). The most common drug categories involved in the fatal errors were central nervous system agents (e.g. opiates) and antineoplastic agents (cytotoxic drugs).

In a study of serious ADEs reported to the Food and Drug Administration, 1998-2005, they found a marked increase in reported deaths and serious injuries associated with drug therapy over the study period (Moore, Cohen, & Furberg, 2007). A relatively few drugs accounted for most of the severe events: 298 drugs (20%) accounted for more than 400,000 of all reported study events (87%). This is an example of the quality assurance rule of thumb that holds that 80% of the consequences spring from 20% of the causes. Among the 15 drugs most frequently identified in fatal and nonfatal serious events is paclitaxel, a cytotoxic drug.

Medication errors identified through solicited error reports in general medicine and specialty units of a major tertiary teaching hospital in the USA were studied to identify prevalent patterns and causes (Winterstein et al., 2004). Two hundred forty reports of MEs were included in the analysis. Of these, 95 represented manifested errors and the rest near misses or averted. Most errors were initiated during prescribing (72%) and were associated with deficits in pharmacotherapy knowledge or with failure to consider critical patient information. Errors initiated during dispensing and administration were mostly associated with performance deficits (e.g. accidental slips and lapses). They found that most of the prescribing errors were not intercepted and reached the patient. About 20% were averted by the pharmacy at dispensing or by nurses at administration.

### ***Medication errors and adverse drug events in chemotherapy***

The research process leading to this thesis has been ongoing for more than ten years. During this time, many articles have been read and collected but not systematically. Thus, working with this thesis was a good opportunity to compile and find the common patterns.

Articles came from three main sources: 1) Articles found and read in the research field. 2) Articles identified by searching the PubMed database. The PubMed search strategy was performed using the following MeSH terms: *medication error; hospital; medication error cytotoxic; medication errors cytotoxic drugs* and with the following limits activated: *humans; English; cancer*. 3) Reference lists in retrieved articles were reviewed to identify additional articles.

The abstracts were read and if the content was of interest, the full articles were printed and read. A decision was then made to include the article in the review or not. Short descriptions of each article were compiled in a table. This was, in turn, classified in different groups of interest.

In a recent literature review article from Switzerland (Schwappach & Wernli, 2010b), they point out, with reference to Müller (2003), that: “While any other class of drugs is susceptible to errors, chemotherapy presents special dangers because: (1) many drugs have a narrow therapeutic index; (2) are toxic even at therapeutic dosages; (3) chemotherapy regimens are highly complex; and (4) cancer patients are a vulnerable population with little tolerance.”

They summarises that errors in administration contribute to a significant fraction to all MEs in chemotherapy. This was supported by a systematic analysis of accidental iatrogenic intoxication by cytotoxic drugs where it was found that most cases with a fatal outcome for the patient involved erroneous drug administration (Zernikow, Michel, Fleischhack, & Bode, 1999).

A brief compilation of the studies on errors in the chemotherapy process is presented in Table 1. During the first ten years, nearly all articles on MEs with cytotoxic drugs involved suggestions for improvements. This could be by standardisation of prescription vocabulary (acronyms, abbreviations, brand names) and steps that should be taken to avoid other sources of confusion in written orders, such as trailing zeros. Another way suggested by many authors was improvement by an interdisciplinary approach, which means doctors, nurses and pharmacists working together. The first study with a proactive risk analysis, using Failure Mode and Effect Analysis (FMEA), came in 2005. This was also the first study on the introduction of Computerised Physician (or Prescriber) Order Entry (CPOE). After this, there have been many studies both using a proactive risk analysis method and evaluation of CPOE. Other methods used for improvements have been described since 2009, starting with telepharmacy and bar coding in preparation. Children or paediatrics were studied in seven of the studies.

Attempts have been made to measure or estimate the ME rate or the amount of ADEs in the chemotherapy process. Depending on the method and process used, the rate of MEs varies from 0.04 to 19%.

In Fernandez (2000) a general procedure for identification and prevention of errors was described, see Table 2. Some of the studies in Table 1 have used this approach for their improvements. It is very reminiscent of Deming's "Plan-do-check-act" method (Frid, 1997).

Table 1. A brief compilation of articles on the chemotherapy process from 1995 to 2010.

<b>Method used</b>	<b>Conclusions / References</b>
Recommendations, experiences	Pharmacists and an oncology nurse give advice on how to improve the system. Standardisation of prescribing vocabulary, clearer communication, multidisciplinary co-operation, working with manufacturers, education of patients, use computerised systems for prescribing, for pharmacists and for alerts. (Attilio, 1996; Berard, Mahoney, Welch, & Rodrigues, 1996; Cohen, et al., 1996; Cousins, Upton, & Cohen, 1995; Greenberg, Kramer, Welch, O'Sullivan, & Hall, 2006; Kohler et al., 1998; Lunik, Peters, & Wilson, 1996; Schulmeister, 2005, 2006, 2008)
Review of literature	Different views depending on different professions among the authors. There are numerous case reports and several summaries of chemotherapy errors leading to death and disability. Vincristine intrathecal installation continues to occur despite decades of case reports. Recommendations are systems analysis, review the process, incident reporting (blame free), multidisciplinary education, educate and empower the patient, new technologies such as CPOE, pharmacist interventions, oncology nurse leadership. (Boyle, Schulmeister, Lajeunesse, & Anderson, 2002; Fernandez, 2000; Schwappach & Wernli, 2010b)
Review of reports, cases	Reviews of cases from databases and cases found in the literature. Serious consequences, most commonly wrong dose or drug. In two of the studies most errors originated in the administering phase. (Mehta, Beltz, & Cousins, 1998; Rinke, Shore, Morlock, Hicks, & Miller, 2007; Zernikow, et al., 1999)
Questionnaire	Mailed to nurses working with chemotherapy; 63% had experienced a medication error in the previous year. Survey sent to patients, 16% had experienced an error in their care. Many of the patients were willing to be involved in error prevention. (Cusano, Chambers, & Summach, 2009; Johnson, Chambers, & Vaida, 2008; Schulmeister, 1999; Schwappach & Wernli, 2010a)
Interdisciplinary, multi-institutional, multifaceted approach	Powerful systems change; simplify, standardise, computerise, learn from errors, education, reduce handoffs, pay attention to human factors; communication and flexibility are vital. (Branowicki et al., 2003; Dinning, Branowicki, O'Neill, Marino, & Billett, 2005; Goldspiel, DeChristoforo, & Daniels, 2000; Womer et al., 2002)
Retrospective study	Analysis of prescription and transcription reveals that too many transcriptions are a source of error. When studying MEs among adults and children in the outpatient setting, the error rate found was 18.8% for children and 7.1% for adults. (Pichon, Zelger, Wacker, Vodoz, & Humbert, 2002; Walsh et al., 2009)
Editorials	Reminds readers of the Lehman case. Need for systemic changes, formation of a multidisciplinary quality improvement committee. Oncologists and allied health professionals should take a leading role in the implementation of measures aimed at reducing errors and patient harm. Pharmaceutical safety studies can lead to strategies for prevention, such as CPOE, improved patient education and participation, pharmacovigilance, and computerised surveillance of ADEs. (Erdlenbruch, Lakomek, & Bjerre, 2002; Holcombe, 1996; Ignoffo, 1996; Nebeker & Bennett, 2005)

FMEA, HACCP	<p>A proactive method to identify risks in the process from prescribing to administration or to identify risks as a part of the process (preparation) or the introduction of CPOE. Three of the studies involved paediatric care. Risks were identified and led to improvements. A patient or parent contributed to the multidisciplinary in the team. In one study they compared scoring procedures using “team consensus” and “mathematical average” and found differences. They conclude that the scoring is a subjective and qualitative process. (Ashley &amp; Armitage, 2010; Bonan et al., 2009; Bonnabry et al., 2006; Kim et al., 2006; Kozakiewicz, Benis, Fisher, &amp; Marseglia, 2005; Robinson, Heigham, &amp; Clark, 2006; van Tilburg, Leistikow, Rademaker, Bierings, &amp; van Dijk, 2006)</p>
Prospective study	<p>Different levels of MEs are reported from 0.04-17.1% depending on what is measured, where and by whom. Improvements are made with pharmaceutical validation, “clinical service centre”, or by introducing CPOE. (Ford, Killebrew, Fugitt, Jacobsen, &amp; Prystas, 2006; Gandhi et al., 2005; Huertas Fernandez, Baena-Canada, Martinez Bautista, Arriola Arellano, &amp; Garcia Palacios, 2006; Limat et al., 2001; Markert, Thierry, Kleber, Behrens, &amp; Engelhardt, 2009; Nerich et al., 2010; Serrano Fabia, Cavero Rodrigo, Albert Mari, Almenar Cubells, &amp; Jimenez Torres, 2005; Slama, Jerome, Jacquot, &amp; Bonan, 2005; Small, Barrett, &amp; Price, 2008)</p>
Before and after intervention	<p>Introduction of standardised chemotherapy order forms lead to significantly reduced prescribing errors. Introduction of CPOE improved the safety of chemotherapy prescriptions markedly recorded by the centralised unit of pharmacy service. The preparation process was also evaluated. (Sano, Waddell, Solimando, Doulaveris, &amp; Myhand, 2005; Voeffray et al., 2006)</p>
Incident reporting	<p>Design and development of a system for paediatric oncology nurse and pharmacists. A technical and a human component formed an integrated system that facilitated a blame-free culture and improved reporting. Ordering errors were the most commonly reported incidents. (France, Cartwright, Jones, Thompson, &amp; Whitlock, 2004)</p>
A case study communication	<p>A mix-up of drugs (navelbine instead of etoposide) during prescription. Detailed analysis of what happened; Sunday, specialised pharmacist not available; many communication-related issues that contributed to the error. (Patterson, Cook, Woods, &amp; Render, 2004)</p>
Technology	<p>Telepharmacy and bar coding for checking preparation process improved the process. Deciding what components of a checklist contribute to effective detection of administration medication errors at the bedside. Specific step-by-step instructions were more effective than abstract reminders in helping nurses to detect errors. Generic drug name pairs identified by three or four methods were considered to provide the highest risk for errors. A proactive system of reviewing LASA. A virtual chemotherapy unit that standardised the ordering and documentation for admissions. (Kovacic &amp; Chambers, 2010; O'Neal, Worden, &amp; Couldry, 2009; Scavuzzo &amp; Gamba, 2004; White et al., 2010)</p>

Table 2. A general procedure for identification and prevention of errors from (Fernandez, 2000).

Steps to error prevention	Examples of mechanisms
Determine what errors are occurring (non-punitive form)	Morbidity/mortality/incident reports, simulation/observational studies
Collect information and prioritise based on severity index (potential or actual errors)	Pharmacy and therapeutics/morbidity/formal chemotherapy review committees
Categorise errors – skill-based, rule-based, knowledge-based, technical	Use human error identification techniques
Categorise latent or contributing factors	Design reports to capture negative and positive influences on error outcome/occurrence
Develop strategies/policies/procedures – prevention, detection, minimising errors	Multidisciplinary input, risk/benefit analysis, national standards
Implement strategies/policies/procedures	Education of and feedback from user groups, need to be functional and understandable
Determine whether strategy is effective	Return to no. 1

## Different accident models

### *Slips, lapses, mistakes, and violations*

Human errors may be classified either by their consequences or by their presumed causes. Causal classifications make assumptions about the psychological mechanisms implicated in generating the error. Much of the understanding is based on the classifications made by Reason (1990). These in turn were based on the classic “Rasmussen’s skill-rule-knowledge framework”. Error can be defined as a failure of planned actions to achieve their desired goal (J. Reason, 1995). There are basically two ways in which this failure can occur:

- The plan is adequate, but the associated actions do not go as intended. There are failures of execution and these are termed “slips” and “lapses”. Slips relate to observable actions and are associated with attentional failures. Lapses are more internal events and relate to failures of memory. Examples would be picking the wrong drug from the shelf, or administering the drug to the wrong patient when two patients have the same name.
- The action may go entirely as planned, but the plan is inadequate to achieve its intended outcome; these are termed “mistakes”. Mistakes can be further subdivided into rule based mistakes and knowledge based mistakes. The failure lies in the mental processes involved in planning, formulating intentions, judging, and problem solving.
  - Rule based mistakes relate to problems for which the person possesses some pre-packaged solution, acquired as the result of training, experience, or the availability of appropriate procedures. The errors may come in various forms: the misapplication of a good rule (could be failure to spot contraindications for the drug), the application of a bad rule, or the non-application of a good rule.
  - Knowledge based mistakes occur in novel situations where the solution to a problem has to be worked out on the spot without help of pre-programmed

solutions. This entails the use of slow, resource-limited but computationally-powerful conscious reasoning carried out in relation to what is often an inaccurate and incomplete “mental model” of the problem and its possible causes.

Among the unsafe acts, together with errors, there are also violations. Violations have been defined by Reason (1990) as “deliberate, but not necessarily reprehensible, deviations from those practices deemed necessary (by designers, managers, and regulatory agencies) to maintain the safe operation of a potentially hazardous system”.

Over the years, different accident models have been used. They have evolved over time and with different researchers.

### ***The sequential accident model – Heinrich domino model***

The accident is described as a result of a sequence of clearly distinguishable events that occur in a specific order, as a set of dominos that tumble because of a unique initiating event. This model is deterministic because the outcome is seen as a necessary consequence of one specific event. Sequential models need not be limited to a single sequence of events but may also include multiple sequences of events, such as the event tree.

The thinking is that there is a final cause – a root cause. Just as there must be a first domino that makes the others tumble, so there must be a first event or occurrence that makes the accident happen. The root cause is usually defined as the combinations of conditions and factors that underlie accidents or incidents, or even as the absolute beginning of the causal chain. A root cause is not only an abstraction, but also an artefact of a specific analysis principle – the stop rule, the criterion for when the analysis should stop.

### ***The epidemiological accident model***

The accident is described analogous to the spreading of a disease, that is, as the outcome of a combination of factors. Some of these factors are manifest and some are latent; accidents seem to happen when a sufficient number of factors come together in time and space. Latent conditions arise from strategic and other top-level decisions made by governments, regulators, manufacturer, designers, and organisational managers. They are present in all systems and are an inevitable part of organisational life. Nor are they necessarily the products of bad decisions, although they may well be (J Reason, 1997).

An active failure is needed for the accident to happen. These errors and violations are committed by the operator in the act, when he or she is actually carrying out the task (e.g., the nurse administering a medication; the surgeon holding the scalpel). Active failures usually have immediate and relatively short-lived effects.

The necessary condition for an organisational accident is the rare conjunction of a set of holes in successive defences. These “windows of opportunity” are rare because of the multiplicity of defences and the mobility of the holes – the metaphor is the Swiss cheese model.

In his book, *Barriers and Accident Prevention*, Hollnagel (2004) discusses different accident models. Here he points out that “Epidemiological models are valuable because they provide a basis for discussing the complexity of accidents that overcomes the limitations of sequential models. ....epidemiological models still follow the principles of the sequential models, i.e., a propagation of effects from a beginning to an end, as indicated by the direction of causality”.

The research by Vincent, et al. (2000) on how to investigate and analyse clinical incidents has had a great influence in healthcare. Their approach is based on Reason’s model of organisational factors as shown in Figure 2.

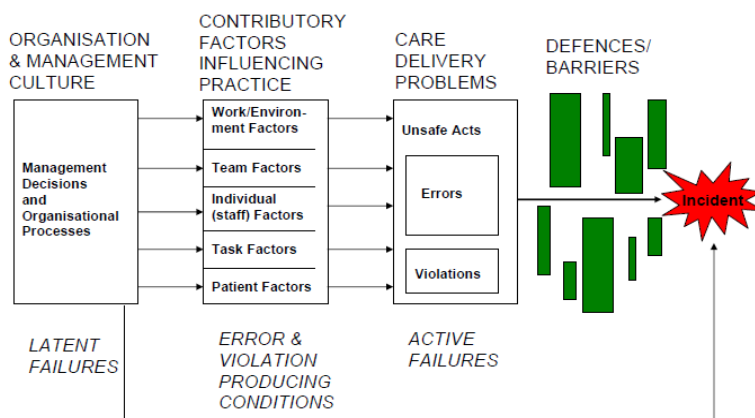


Figure 2. Organisational accident causation model based on Reason’s model of organisational accidents found in *The London Protocol* (Taylor-Adams & Vincent, 2011).

### ***The systemic accident model***

Systemic models have their roots in control theory, in chaos theory, and in the idea of stochastic resonance. The two main ideas in chaos theory are that even complex systems rely upon an underlying order, and that very simple or small events can cause very complex behaviours or events (the butterfly effect). The responses of the system are non-linear, which means that the effect (output) is not proportional to the cause (input).

The systemic view considers accidents as emergent phenomena, which therefore are also “normal” or “natural” in the sense of being something that must be expected. The outcomes of actions may sometimes differ from what was intended, expected or required. When this happens it is more often due to variability of context and conditions than to the failures of actions. The adaptability and flexibility of human work is the reason for its efficiency. Normal actions are successful because people adjust to local conditions, to shortcomings of technology, and to predictable changes in resources and demands. This adaptability and flexibility of human work is also the reason for the failures that occur, although it is rarely the cause of such failures. Actions and responses are almost always based on a limited rather than complete analysis of the current conditions (i.e. a trade-off of thoroughness for efficiency) (Hollnagel, Woods, & Leveson, 2006).

### **Accident model used in this thesis**

From Paper I, *System Weaknesses in the Process of Treating Patients with Cytotoxic Drugs*. The accident model used in this thesis is principally based on the epidemiological model. System weaknesses consist of latent system failures (conditions) and insufficient safety barriers.



- Latent system failures (conditions) can be insufficient maintenance of equipment, inappropriate or outdated equipment, insufficient introduction of new staff, and inappropriate adaptation of working tasks to human cognitive ability.
- Safety barriers are different kinds of hindrances, built into the system. Their purpose is to detect and identify operator errors before they influence the system or, and even better, to prevent the operator from acting in an erroneous way.

Safety barriers can be administrative (e.g. checking of the medication by the nurse prior to administering it to the patient) or technical (e.g. the use of incompatible fittings for different kinds of anaesthetic gases). Barriers can be weak/relative or strong/absolute, depending on their ability to detect and identify disturbances/erroneous acts. Administrative barriers are often weaker than technical barriers.

In a process model view on accidents, these seldom occur because of a single wrong action or single disturbance. Normally, complex systems have sufficient defence barriers that make this very unlikely. Instead, accidents are believed to evolve over time where multiple disturbances interact to the point where the defence mechanisms of the system are insufficient to counteract the negative impact on the system of the disturbances. The system gradually loses control and a system breakdown is imminent.

In Paper II, *Characteristics of Medication Errors with Parenteral Cytotoxic Drugs*, we used incident reports sent to the national authorities. The incidents were investigated by the staff at the authorities. Since the introduction of the Swedish handbook for risk and incident analysis in patient safety (National Board of Health and Welfare, 2009b), local investigations were carried out according to the handbook. These incident analyses were sent to the authorities. The authors of the handbook were inspired by the epidemiological accident model and the method used was the RCA.

## METHODS AND DATA

### Research background

The medication use process for cytotoxic drugs is complex and pharmacy preparation is one of the stages in the process. From everyday work, the thesis author in her profession has experienced errors, sometimes serious, made by doctors in the prescribing stage. There was also a tragic case with overdoses leading to a fatal outcome for a girl at the hospital. This led to contact with an NBHW investigator. Normally at this time, measures of precautions are made after an accident. After discussions, though, we agreed that a more rational approach would be to identify the “system weaknesses” and take actions before accidents happened. The investigator had developed and validated a proactive method for finding system weaknesses in another field and was interested in applying it in healthcare. Besides, at that time there were few proactive methods available in healthcare. The study was performed in 1998. This co-operation resulted in Paper I.

In the summer of 2000 a serious incident occurred at the preparation unit in Lund. A little child received a dose of a cytotoxic drug that was ten times too high three days in a row due to a tenfold calculation error. The incident did not cause any permanent harm to the child. However, the incident had to be reported to the NBHW according to lex Maria. This led to an increased interest from the thesis author of the information gathered in lex Maria reports.

Could this information be used for increased knowledge of the risks and possible improvements? This question resulted in Paper II.

## **Prospective analysis of system weaknesses**

In Paper I the process analysed was the treatment of patients with cytotoxic drugs at an oncological unit at the Department of Oncology, University Hospital, Lund, Sweden. The team of analysts consisted of a pharmacist from the hospital pharmacy (thesis author), responsible for the preparation of cytotoxic infusions at the department of oncology, a safety engineer from the nuclear power industry in Sweden, and a licensed doctor with more than ten years of experience in risk management analysis in healthcare (investigator at the NBHW). The analysis was performed with the DEB method.

### ***The disturbance effect barrier (DEB) method***

The disturbance effect barrier (DEB) method was inspired by a method for retrospective analyse of accidents and incidents, the previously described MTO analysis. The DEB analysis, however, is *proactive* (i.e. no accident/incident is involved). The idea is to be a step ahead of a potential incident/accident. The DEB analysis has been validated for processes in air traffic control (Ternov & Akselsson, 2004). The method starts with a task analysis, which is a detailed mapping of the sequence of operator activities (“Who is doing what?”) for carrying out the designated work task in the chosen (sub-) process. A key tool in the analysis is asking “What happens if...?” questions within operator activities. The management system of the organisation is an important focus for the DEB analysis. Issues such as the appropriateness of procedures and their implementation, the clarity of roles and responsibility for the staff and the management engagement, are assessed during the analysis.

### **The analysis contains the following steps:**

1. *Process description* – A precondition for the analysis is access to a fairly detailed process description.
2. *Choice of sub-processes* – The choice should be made in co-operation with the organisation concerned, using criteria such as risks for system failure and frequency of process disturbances.
3. *Task analysis* – A detailed task analysis is made (i.e. to describe the operator actions during the different working task sequences).
4. *Management system audit* – Part of the management (quality) system is examined for consequence and consistency.
5. *Disturbance analysis* – For each action sequence the question is asked: What would happen if the operator does too little, too much, too late, does nothing, or does it incorrectly?
6. *Validation of hypotheses on disturbances* – The hypotheses are validated by interviewing the operators and, if applicable, by analysing incident/accident reports.
7. *Effects on the system* – For the validated hypotheses on disturbances, the operators are asked: What effects on the system performance might these disturbances have?
8. *Identification of system weaknesses* – Are latent system failures identifiable as contributing causes for these disturbances? Do safety barriers exist in the system that prevents harmful system influence due to these disturbances? If not, how can such barriers be designed?

A flow chart, a “DEB diagram”, is the working tool for the DEB. In this, the action sequences are plotted against a time axis. The results of the different steps in the analysis described above are written in columns under the action sequence that has been analysed.

## Retrospective qualitative analysis of incidents

Considerable information is gathered in incidents reports and if it is thoroughly examined, common patterns may be seen. The purpose of reporting incidents is to learn in order to make improvements. Healthcare providers are legally obliged to report serious injuries and risks of injuries to the NBHW pursuant to lex Maria. Complaints from the patient, relatives or NBHW could be filed with the Medical Responsibility Board (HSAN) until the end of 2010. HSAN was a national authority that assessed medical negligence.

In Paper II, a retrospective qualitative analysis was performed of incidents reported to the national error reporting systems (according to lex Maria or/and HSAN) from 1996 to 2008 involving a cytotoxic drug, administered parenterally at a hospital. A total of 60 case reports met the inclusion criteria and were reviewed. A short description of each incident was compiled in a table with information of report number, drug involved, where it occurred (hospital, pharmacy), what happened, how was it discovered, consequences for the patient, and contributory causes. From this compilation, other tables were compiled to answer the following questions: what cytotoxic drugs were involved, type of error, stage where the error occurred in the medication use process, error detection mechanism, and consequences for the patient.

## RESULTS

### **Paper I: System Weaknesses in the Process of Treating Patients with Cytotoxic Drugs**

This prospective analysis with the DEB method was performed at an oncological unit at the Department of Oncology, University Hospital, Lund. In our analysis we identified the following latent system failures:

1. *The procedures for transfer of information from the manual for chemotherapy protocols to the Cytotoxic Treatment Card (CTC) are inappropriate.*
2. *The procedures for updating the manual for chemotherapy protocols are unsafe.*
3. *The procedures for co-operation between the pharmacy and the Department of Oncology are implicit and not clear.*
4. *The technical equipment (infusion pumps) consists of different brands at different units at the Department of Oncology.*
5. *The procedures for evaluating the results of blood tests are unsafe.*
6. *The procedures of filling in the CTC are unsafe.*
7. *The procedures for tracing the results of blood tests are inappropriate.*
8. *The procedures for marking the CTC with proper patient identity are unsafe.*
9. *Responsibility and authority for the nurses are not defined.*
10. *Necessary competence for the doctors is not properly defined.*
11. *The procedure for monitoring the patient during treatment is unsafe.*

When identifying system weaknesses, the next step was to identify safety barriers in the system that might prevent harmful system influence. The safety barriers were graded 1-4 depending on their capabilities to act as a barrier. A weak barrier was graded 1 or 2; a strong 3 to 4. The grading was based on the information from the incident reporting system. Many disturbances during prescription will be discovered at the preparation unit (pharmacy). Disturbances arising at the preparation unit may be discovered during the process of administering. These barriers were found to be informal (i.e. not agreed upon).

The result revealed that the errors creating the greatest probability for causing harm to the patient are as follows:

1. *Clinical misjudgement of the patient before prescription.*
2. *Misjudgement of laboratory results before prescription.*
3. *Necessary blood tests are not taken.*
4. *Blood test results do not arrive, or arrive too late, to the clinic.*
5. *Errors in prescriptions and errors in filling in the Cytotoxic Treatment Card (CTC).*
6. *Wrong infusion is administered to the patient (wrong drug, wrong amount, or wrong infusion rate).*

We suggested a computerisation that involved all the studied sub-processes for treatment with cytotoxic drugs and proposed a generic checklist that could be used proactively by other departments.

The main process studied – treatment of patients with cytotoxic drugs – was a process that involved great risks and tiny margins for error mitigation. Overall, the results showed that the barriers were weak or nonexistent at the unit. Too many errors were able to defy detection before the effect of the error hit the patient.

## **Paper II: Characteristics of Medication Errors with Parenteral Cytotoxic Drugs**

In this retrospective study, 60 incidents were reviewed that were reported to the national error reporting systems from 1996-2008 involving a cytotoxic drug administered parenterally at a hospital. The most commonly involved cytotoxic drugs were fluorouracil, followed by carboplatin, cytarabine, and doxorubicin. The platinum containing drugs often caused serious consequences for the patients.

In 45% (27/60) of the reports, doses were found that were too high in prescribing and transcribing or preparation. A tenfold error was seen in four cases. Wrong drug used during preparation or prescription was the second largest category, 30% (18/60).

Twenty-five of the medication errors, 42%, occurred when doctors were prescribing or transcribing an order to the pharmacy. All of the preparations were delivered to the patient causing temporary or life-threatening harm. In nearly 50%, these errors were discovered due to adverse reactions from the patient. Twenty-five of the medication errors (42%) started with preparation at the pharmacies. Nurses intercepted the infusion to the patient in these eight cases. The remaining ten cases were due to errors during preparation by nurses (5/60) and administration by nurses to the wrong patient (5/60). The errors were discovered by healthcare professionals and by patients or relatives.

## **DISCUSSION**

### **The risks in the chemotherapy process**

The general aim of the research presented in this thesis is to identify the risks in the chemotherapy process and to identify actions and strategies in order to improve the safety in the process. In Paper I we started with a proactive approach to identify system weaknesses, latent system failures (conditions) and insufficient safety barriers at an oncology unit. We found that the process studied involved great risks and tiny margins for error mitigation. Most of the potentially serious errors were found at the prescribing stage. One strategy for improvement of a process is to redesign it to make it resistant to failures. We therefore

suggested computerisation of the whole chemotherapy process in 1998. This meant the inclusion of all the sub-processes for the cytotoxic medication use process, i.e. prescribing by doctors, preparation by pharmacists, and administration by nurses. This has been done for the oncology department in question and will be described and evaluated in a coming study. It has been reported in the literature that the quality of physician order entry improves with Computerised Physician (or Prescriber) Order Entry (CPOE) systems. The risk of MEs made in prescribing have been reduced; a decrease of 55-80% has been reported (Nerich, et al., 2010). In a systematic review of generic CPOE systems, it was found that the use of CPOE and clinical decision support systems can substantially reduce ME rates (Kaushal, Shojania, & Bates, 2003). They also found that most studies have not been powered to detect differences in ADEs and have evaluated a small number of “home-grown” systems. More research is needed they conclude. Implementing a CPOE system would probably solve some problems but it may also introduce new risks for MEs as demonstrated by Koppel, et al. (2005).

The latent system failures identified in Paper I seemed to be rather generic, such as the transferral procedure of information and necessary staff competency. We therefore proposed a generic checklist to be used in other departments of oncology.

In the retrospective analysis of cases reported to the national error reporting systems (Paper II) we found that the most severe MEs occurred during prescribing and transcribing by doctors. The consequences for the patients were in some cases fatal, in some cases life-threatening, and in some cases no harm resulted. This finding was supported in a study by Gandhi, et al. (2005) on medication safety in the ambulatory chemotherapy setting. In other chemotherapy studies the stage responsible for most of the errors (Rinke, et al., 2007; Walsh, et al., 2009) or the most fatal outcomes was administration (Zernikow, et al., 1999). In our paper we discussed the difference in results and suggested that it may be due to different material, to different definitions in the studies or to national/cultural differences. Studies on general medication use process reveal that prescribing errors are the most frequent source (Koppel, et al., 2005; Winterstein, et al., 2004).

In our study of cases reported to the national reporting systems (Paper II) we found that the most common error types were wrong dose and wrong drug but also wrong patient. Some of the causes behind the events are well described in the literature on medicine such as: tenfold errors, mix-up of drugs due to similarities in drug names or packaging (look-alike, sound-alike – LASA), and patient misidentification.

Based on the findings in this study (Paper II) it is especially important to minimise the potential for errors in the prescribing stage since they are all delivered to the patient and in most cases causing serious harm. This can be accomplished using CPOE not only for prescribing but also for the whole medication use process. Identification of drugs and patients should also be improved by bar coding, for example.

To summarise our findings, both papers and the literature review identify the stage of prescribing by doctors as a major risk. Our study (Paper II) identified wrong dose, wrong drug, and wrong patient as the most common error types. This indicates that there are possibilities for improvements, for example, by using CPOE systems and bar coding for the identification of drug and patient.

## **The methods used**

The methods used in the research presented are one proactive analysis and one retrospective qualitative analysis. The quality of the results from the proactive DEB analysis seems to be very dependent on the composition and understanding of the reference operator team used for validation. The understanding of the purpose of the study among staff for the interviews also seems crucial. The team of analysts and their understanding of the method used and domain knowledge may be important for the results as well. At the time of the study the oncology unit did not have any incident reporting system. The incident reports used in the study came from the preparation unit (pharmacy). The more information that can be gathered, the better the analysis.

The retrospective qualitative method used incidents reported to the national error reporting systems for analysis. The material used – the incident reports – caused some problems and the initial difficulty was to identify all relevant reports. The database where all reports to the national error reporting systems should be filed were incomplete and reporting to the database ended mid-2006. A new database is under construction. We were limited to the content in the written reports which varied with the author and over time. During the 13 years studied there were several changes, such as in treatment protocols, in drugs available, and in the work for improvements of patient safety. Despite this, there is quite a bit of interesting information in the material. Retrospective analyses of chemotherapy incidents reported to national incident reporting systems have been used in other studies (Mehta, et al., 1998; Rinke, et al., 2007)

The purposes differ of the two methods used. The proactive method was applied to one unit of oncology, analysing its process as it was at that time. The recommendations given were aimed at that unit but could also be used by others. The retrospective method used incidents reported to a national error reporting systems over 13 years. The purpose was to find common patterns in the incidents to be able to suggest improvements. The recommendations were general and aimed to be used both nationally and internationally.

### ***Risk analysis***

The proactive method used in healthcare since about 2000 is the Failure Mode and Effect Analysis (FMEA). It has been used for decades in engineering to identify and reduce hazards (Spath, 2003). The technique examines the individual components of a system to determine the variety of ways each component could fail and the effect of a particular failure on the stability of the entire system. It promotes systematic thinking about the safety of a patient care process in terms of the following questions: What could go wrong? How badly might it go wrong? What needs to be done to prevent failures? This is very reminiscent of the DEB method. However, in the FMEA method they use scoring of identified failure modes (potential errors). Ashley, et al. (2010) investigated the scoring procedures using “team consensus” or “mathematical average”. This lead to differences in results and the authors conclude that the scoring is a subjective and qualitative process.

### ***Incident analysis – accident investigation***

The method most used in healthcare for accident investigation is the root cause analysis (RCA). It aims to identify the root causes of problems or events in order to create effective corrective actions that will prevent that problem from reoccurring. Since its introduction in healthcare around 2000 by Vincent, et al. (2000), through what later referred to as the *London Protocol*, it has developed. In an editorial on incident analysis, Vincent (2004) discussed the use of an RCA analysis. He emphasised the following: “. . . the picture that emerges is much more fluid and the notion of a root cause is a gross oversimplification. . . . However, if the

purpose is to achieve a safer healthcare system, then it is necessary to go further and reflect on what the incident reveals about the gaps and inadequacies in the healthcare system in which it occurred. The incident acts as a ‘window’ on the system – hence systems analysis”.

In our retrospective analysis of incidents, some error types like tenfold errors, mix-up of drugs and misidentification of patients occur frequently. The error types have been described in the literature. The question then is why these errors, the causes of which are known, repeat themselves? Why have we not learnt the lessons? Could it be that we spend too much effort on analysis and too little on following up the changes?

In an interesting article by Wu, et al. (2008), they discuss the effectiveness and efficiency of root cause analysis (RCA) in medicine. The RCA process is designed to answer 3 basic questions: What happened? Why did it happen? What can be done to prevent it from happening again? A fourth question, they say, is missing in medicine: Has the risk of recurrence actually been reduced? Wu, et al. claim that follow-up on outcomes is rare and that the interventions implemented have little chance of diminishing risks or harm. They propose that follow-up for implementation and outcome should be a standard element of the process and that it is imperative to develop mechanisms to implement the intervention with the highest probability for success. Not all actions aimed to mitigate risk have equal probability for success. Some, like redesigning a product or process, have a high probability of reducing harm. Others, like re-education or writing a policy, have a low probability of reducing risk (Wu, et al., 2008).

An example of what should be a strong action with high probability of reducing harm is the redesign of a process. Vincristine, a neurotoxic cytotoxic drug, should only be administered intravenously, and never by any other route. Many patients receiving intravenous vincristine also receive other medication via a spinal route as a part of their treatment protocol. This has led to errors where vincristine has been administered via a spinal route, a mistake that has occurred more than 55 times around the world since 1968. An error in Hong Kong in 2007 led to an alert from the World Health Organisation (WHO) (World Health Organization, 2007). The recommendation was that vincristine (and other vinca alkaloids) should only be given intravenously via minibags. Normally small volumes, as in this case, are administered by syringes, but syringes can be mixed-up. A larger volume, like 50-100 mL, is very unlikely to be given spinally by mistake – a forcing function. This information and recommendation was forwarded to Sweden in 2007 (Fyhr & Sjökvist Saers, 2007).

In a study from Sweden, a follow-up of 118 event analyses from healthcare performed with the RCA method was carried out (Elfstrom, Nilsson, & Sturnegk, 2009). On average, three preventive measures were suggested in the analysis and one year later about 65% of these were carried out. The most common preventive measure (45%) was improvements in procedures, routines and guiding principles. The authors conclude that there is a potential for improvements in the work with the analysis. The causes and countermeasures need to be more specific and concrete and include more standardisations and simplifications instead of new routines.

### **Actions and strategies for improvement in the chemotherapy process**

In the literature review there are many articles offering advice on how to improve the process (Attilio, 1996; Kohler, et al., 1998; Schulmeister, 2005). Among these are standardisation of prescribing vocabulary, multidisciplinary co-operation, working with manufacturers,

education of patients and use of CPOE systems. Working with manufacturers may need an explanation. One problem already mentioned is the mix-up of drugs. This can be due to similarity in drug packaging or drug names that look alike or sound alike (Mehta, et al., 1998; Phillips, et al., 2001; Rinke, et al., 2007). The manufacturer of the drugs and the Swedish Medical Product Agency are the ones who are able to make a permanent change, a strong action. Today, actions at the local level have to be taken to handle the similarities, such as purchasing for safety and separate storage of the drugs.

Education of patients should also be commented on. This has been suggested in publications since 1996 (Cohen, et al., 1996; Fernandez, 2000; Nebeker & Bennett, 2005). In a recent article, Schwappach and Wernli state that it has been increasingly acknowledged that patients often observe errors in the administration of drugs and can thus be a valuable resource in error prevention (Schwappach & Wernli, 2010b). The patients need appropriate information, motivation and encouragement to act as “vigilant partners”. In our retrospective analysis of the incidents, we observed a few examples of patients discovering errors in administration.

One approach suggested in several articles was a multidisciplinary co-operation often using the “plan-do-check-act” performance improvement model, also called the rapid cycle change method (Goldspiel, et al., 2000; Scavuzzo & Gamba, 2004; Womer, et al., 2002). This type of co-operation was used for follow-up on errors and to learn from them, to simplify and standardise, to use constraints and forcing functions, to pay attention to human factors, and to improve competencies.

In several articles, the pharmacy preparation and pharmacist intervention were highlighted as important for improved patient safety (Bonnabry, et al., 2006; Lunik, et al., 1996; Serrano Fabia, et al., 2005). The preparation stage comes after the doctors have prescribed and transcribed. Pharmacists are educated to be experts on drugs and can play an important role as another competency in the team, observing inadequacies and errors in the prescriptions. Preparation of the cytotoxic drugs was previously carried out by nurses but is now generally done at the hospital pharmacy. This change was due to different reasons: increased attention to the health risks when working with these toxic drugs, increased efficiency, and reduced costs when preparation was centralised, for example.

Errors can be made at the pharmacy preparation too, as demonstrated in Paper II. Of the 60 reported incidents, 25 of the medication errors started with preparation at the pharmacies. The incidence and risk factors in centralised preparation units have been investigated (Limat, et al., 2001; Martin et al., 2004). The overall and major error rates found were 0.2-0.5% in the Limat, et al. study and 0.1-0.2% in the Martin, et al. study. The risk factors found were drug labelling (dose/bottle and concentration) and workload. In a study by Bonan, et al. (2009), another proactive method for analysis of critical control points in their chemotherapy process was used, the Hazard Analysis and Critical Control Points (HACCP). The team identified 39 critical control points, including 11 of higher importance with a high-risk index. They report a 7.4% rate of non-conformities including prescription errors.

The medication use process with cytotoxic drugs means that there is a direction and a flow of information and preparation as described earlier. The doctor turns in his/her prescription to the pharmacy for preparation. The pharmacy staff read and control (validate) the information, generate their own documentation (batch record and labels for the preparation), and prepare the preparation. This in turn is delivered to the unit where the nurse checks the labelling from the pharmacy to make sure it corresponds to the prescription written by the doctor. There are



three competencies involved in the process, providing great opportunities for checkpoints. In many cases, the pharmacy staff or the nurses intercept errors. This was observed in Papers I and II and has been reported in several studies (Bonan, et al., 2009; Gandhi, et al., 2005; Mehta, et al., 1998; Serrano Fabia, et al., 2005). Multidisciplinary teams' working together has been recommended as an effective way to improve the chemotherapy process.

Use of technologies, other than the CPOE systems, as a mean to improve safety has been highlighted in the last five years. One good example is the use of telepharmacy and bar-code technology in preparation in order to decrease the likelihood of using an incorrect product or quantity of drug (O'Neal, et al., 2009). Another interesting approach was the use of a usability laboratory for evaluation of checklists for detecting MEs at the bedside (White, et al., 2010).

As described in this thesis, the chemotherapy process is complex and involves a great number of risks for the patients. There is great awareness of the risks among those involved in the process and there have been many suggestions of actions and strategies for improvements. Some of these improvements have to be further evaluated and implemented for better safety for the patients.

## **Need for future research**

The material collected from incident reports in the Swedish national error reporting systems will be further analysed to detect system failures and missing barriers or barriers that did not capture the errors. Interesting questions that will be addressed are: Are there any common patterns? What other lessons can be learnt from these MEs and what countermeasures need to be taken?

In co-operation with the Department of Oncology, the Hospital Pharmacy at the University Hospital in Lund and Journalia AB, a computerised system for the entire cytotoxic treatment process has been developed. The lessons learnt from the evaluation and implementation process will be described. The computerised system will be described along with experiences from more than 8,000 treatments of patients.

With the starting point in a serious medication error at the pharmacy preparation unit in Lund, the development process toward safer preparation will be described. This includes the construction of a new preparation unit with participatory design, standardisation of the process and improved training of staff.

## **REFERENCES**

- Aronson, J. K. (2009). Medication errors: definitions and classification. *Br J Clin Pharmacol*, 67(6), 599-604.
- Ashley, L., & Armitage, G. (2010). Failure Mode and Effects Analysis: An Empirical Comparison of Failure Mode Scoring Procedures. *J Patient Saf*, 6(4), 210-215.
- Attilio, R. M. (1996). Caring Enough to Understand: The Road to Oncology Medication Error Prevention. *Hospital Pharmacy*, 31(1), 17-26.
- Bates, D. W., Boyle, D. L., Vander Vliet, M. B., Schneider, J., & Leape, L. (1995). Relationship between medication errors and adverse drug events. *J Gen Intern Med*, 10(4), 199-205.
- Berard, C. M., Mahoney, C. D., Welch, D. W., & Rodrigues, T. D. (1996). Computer software for pharmacy oncology services. *Am J Health Syst Pharm*, 53(7), 752-756.
- Bonan, B., Martelli, N., Berhoune, M., Maestroni, M. L., Havard, L., & Prognon, P. (2009). The application of hazard analysis and critical control points and risk management in the preparation of anti-cancer drugs. *Int J Qual Health Care*, 21(1), 44-50.
- Bonnabry, P., Cingria, L., Ackermann, M., Sadeghipour, F., Bigler, L., & Mach, N. (2006). Use of a prospective risk analysis method to improve the safety of the cancer chemotherapy process. *Int J Qual Health Care*, 18(1), 9-16.
- Boyle, D. A., Schulmeister, L., Lajeunesse, J. D., & Anderson, R. W. (2002). Medication misadventure in cancer care. *Semin Oncol Nurs*, 18(2), 109-120.
- Branowicki, P., O'Neill, J. B., Dwyer, J. L., Marino, B. L., Houlihan, K., & Billett, A. (2003). Improving complex medication systems: an interdisciplinary approach. *J Nurs Adm*, 33(4), 199-200.
- Cohen, M. R. (2007a). The Institute of Medicine report, preventing medication errors: another good day. *Am J Health Syst Pharm*, 64(14 Suppl 9), S1-2.
- Cohen, M. R. (2007b). *Medication errors* (2nd ed.). Washington, DC: American Pharmacists Association.
- Cohen, M. R., Anderson, R. W., Attilio, R. M., Green, L., Muller, R. J., & Pruemer, J. M. (1996). Preventing medication errors in cancer chemotherapy. *Am J Health Syst Pharm*, 53(7), 737-746.
- Cousins, D. H., Upton, D. R., & Cohen, M. R. (1995). Reducing the risks of chemotherapy errors. *The Hospital Pharmacist*, 2(October), 117-120.
- Cusano, F. L., Chambers, C. R., & Summach, D. L. (2009). A medication error prevention survey: five years of results. *J Oncol Pharm Pract*, 15(2), 87-93.
- Dekker, S. (2007). Discontinuity and disaster: gaps and the negotiation of culpability in medication delivery. *J Law Med Ethics*, 35(3), 463-470.

- Dinning, C., Branowicki, P., O'Neill, J. B., Marino, B. L., & Billett, A. (2005). Chemotherapy error reduction: a multidisciplinary approach to create templated order sets. *J Pediatr Oncol Nurs*, 22(1), 20-30.
- Elfstrom, J., Nilsson, L., & Sturnegk, C. (2009). [Incident reporting analyses should be more stringent and involve physicians. A survey of 118 lex Maria cases in Ostergotland]. *Lakartidningen*, 106(48), 3262, 3264-3267.
- Erdlenbruch, B., Lakomek, M., & Bjerre, L. M. (2002). Editorial: chemotherapy errors in oncology. *Med Pediatr Oncol*, 38(5), 353-356.
- European Medicines Agency, E. (1995). Clinical safety data management: Definitions and standards for expedited reporting. Retrieved February 16, 2011, from [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500002749.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf)
- Fernandez, C. V. (2000). Can we prevent cytotoxic disasters? *Br J Haematol*, 108(3), 464-469.
- Ferner, R. E., & Aronson, J. K. (2006). Clarification of terminology in medication errors: definitions and classification. *Drug Saf*, 29(11), 1011-1022.
- Ford, C. D., Killebrew, J., Fugitt, P., Jacobsen, J., & Prystas, E. M. (2006). Study of medication errors on a community hospital oncology ward. *J Oncol Pract*, 2(4), 149-154.
- France, D. J., Cartwright, J., Jones, V., Thompson, V., & Whitlock, J. A. (2004). Improving pediatric chemotherapy safety through voluntary incident reporting: lessons from the field. *J Pediatr Oncol Nurs*, 21(4), 200-206.
- Frid, B. (1997). TQM - en introduktion (TQM - an introduction - in Swedish) (1 ed.): Liber Ekonomi.
- Fryksmark, U. (2011). Lex Maria involving a medicine 2008: Fyhr, A.
- Fyhr, A., & Sjökvist Saers, E. (2007). Ung kvinna dog av vinkristin administrerat spinalt. (Young women died after spinal administration of vincristine - in Swedish). *Lakartidningen*, 104(36), 2529.
- Gandhi, T. K., Bartel, S. B., Shulman, L. N., Verrier, D., Burdick, E., Cleary, A., et al. (2005). Medication safety in the ambulatory chemotherapy setting. *Cancer*, 104(11), 2477-2483.
- Goldspiel, B. R., DeChristoforo, R., & Daniels, C. E. (2000). A continuous-improvement approach for reducing the number of chemotherapy-related medication errors. *Am J Health Syst Pharm*, 57 Suppl 4, S4-9.
- Greenberg, A., Kramer, S., Welch, V., O'Sullivan, E., & Hall, S. (2006). Cancer Care Ontario's computerized physician order entry system: a province-wide patient safety innovation. *Healthc Q*, 9 Spec No, 108-113.

- Holcombe, B. J. (1996). Oncology pharmacy as a specialty. *Am J Health Syst Pharm*, 53(7), 734.
- Hollnagel, E. (2004). *Barriers and Accident Prevention*: Ashgate.
- Hollnagel, E., Woods, D., & Leveson, N. (2006). *Resilience engineering : concepts and precepts*. Aldershot Burlington, VT: Ashgate.
- Huertas Fernandez, M. J., Baena-Canada, J. M., Martinez Bautista, M. J., Arriola Arellano, E., & Garcia Palacios, M. V. (2006). Impact of computerised chemotherapy prescriptions on the prevention of medication errors. *Clin Transl Oncol*, 8(11), 821-825.
- Ignoffo, R. J. (1996). Preventing chemotherapy errors. *Am J Health Syst Pharm*, 53(7), 733.
- Institute for Healthcare Improvement Innovation. (2008). Strukturerad journalgranskning för att identifiera och mäta förekomst av skador i vården enligt metoden Global Trigger Tool. (Structured medical review for identification of adverse events in healthcare with the Global Trigger Tool method - in Swedish): Landstingen i Jönköping, Kalmar och Östergötland samt LÖF.
- Institute for Safe Medication Practice. (1999). The "Five Rights". Retrieved February 16, 2011, from <http://www.ismp.org/Newsletters/acutecare/articles/19990407.asp>
- Institute for Safe Medication Practice. (2011). ISMP's List of High-Alert Medications. Retrieved February 16, 2011, from <http://www.ismp.org/Tools/highalertmedications.pdf>
- Johnson, P. E., Chambers, C. R., & Vaida, A. J. (2008). Oncology medication safety: a 3D status report 2008. *J Oncol Pharm Pract*, 14(4), 169-180.
- Joint Commission. (2011). Sentinel Event Policy and Procedures. Retrieved 20 February, 2011, from [http://www.jointcommission.org/Sentinel\\_Event\\_Policy\\_and\\_Procedures/](http://www.jointcommission.org/Sentinel_Event_Policy_and_Procedures/)
- Kaushal, R., Shojania, K. G., & Bates, D. W. (2003). Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. *Arch Intern Med*, 163(12), 1409-1416.
- Kim, G. R., Chen, A. R., Arceci, R. J., Mitchell, S. H., Kokoszka, K. M., Daniel, D., et al. (2006). Error reduction in pediatric chemotherapy: computerized order entry and failure modes and effects analysis. *Arch Pediatr Adolesc Med*, 160(5), 495-498.
- Kohler, D. R., Montello, M. J., Green, L., Huntley, C., High, J. L., Fallavollita, A., Jr., et al. (1998). Standardizing the expression and nomenclature of cancer treatment regimens. American Society of Health-System Pharmacist (ASHP), American Medical Association (AMA), American Nurses Association (ANA). *Am J Health Syst Pharm*, 55(2), 137-144.
- Kohn, L. T., Corrigan, J., & Donaldson, M. S. (2000). *To err is human : building a safer health system*. Washington, D.C. ; [Great Britain]: National Academy Press.

- Koppel, R., Metlay, J. P., Cohen, A., Abaluck, B., Localio, A. R., Kimmel, S. E., et al. (2005). Role of computerized physician order entry systems in facilitating medication errors. *JAMA*, 293(10), 1197-1203.
- Kovacic, L., & Chambers, C. (2010). Look-alike, sound-alike drugs in oncology. *J Oncol Pharm Pract*.
- Kozakiewicz, J. M., Benis, L. J., Fisher, S. M., & Marseglia, J. B. (2005). Safe chemotherapy administration: using failure mode and effects analysis in computerized prescriber order entry. *Am J Health Syst Pharm*, 62(17), 1813-1816.
- Limat, S., Drouhin, J. P., Demesmay, K., Tissot, E., Jacquet, M., & Woronoff-Lemsi, M. C. (2001). Incidence and risk factors of preparation errors in a centralized cytotoxic preparation unit. *Pharm World Sci*, 23(3), 102-106.
- Lisby, M., Nielsen, L. P., Brock, B., & Mainz, J. (2010). How are medication errors defined? A systematic literature review of definitions and characteristics. *Int J Qual Health Care*, 22(6), 507-518.
- Lunik, M. C., Peters, B. G., & Wilson, A. L. (1996). Quality-improvement processes in an oncology pharmacy service. *Am J Health Syst Pharm*, 53(7), 757-759.
- Markert, A., Thierry, V., Kleber, M., Behrens, M., & Engelhardt, M. (2009). Chemotherapy safety and severe adverse events in cancer patients: strategies to efficiently avoid chemotherapy errors in in- and outpatient treatment. *Int J Cancer*, 124(3), 722-728.
- Martin, F., Legat, C., Coutet, J., Bracco-Nolin, C. H., Jacquet, M., Woronoff-Lemsi, M. C., et al. (2004). [Prevention of preparation errors of cytotoxic drugs in centralized units: from epidemiology to quality assurance]. *Bull Cancer*, 91(12), 972-976.
- Medicinal Products Agency. (2011). Årsredovisning 2010 (Annual Report 2010 - in Swedish). Retrieved April 18, 2011, from <http://www.lakemedelsverket.se/upload/nyheter/2011/Lakemedelsverkets-arsredovisning-2010.pdf>
- Mehta, P., Beltz, S., & Cousins, D. (1998). A review of the national chemotherapy errors database and recommendations for safe administration. *International Journal of Pediatric Hematology/Oncology*, 5(6), 463-473.
- Moore, T. J., Cohen, M. R., & Furberg, C. D. (2007). Serious adverse drug events reported to the Food and Drug Administration, 1998-2005. *Arch Intern Med*, 167(16), 1752-1759.
- Morimoto, T., Gandhi, T. K., Seger, A. C., Hsieh, T. C., & Bates, D. W. (2004). Adverse drug events and medication errors: detection and classification methods. *Qual Saf Health Care*, 13(4), 306-314.
- Muller, T. (2003). Typical medication errors in oncology: analysis and prevention strategies. *Onkologie*, 26(6), 539-544.
- National Board of Health and Welfare. (2005). Ledningssystem för kvalitet och patientsäkerhet i hälso- och sjukvården (Management system for quality and patient safety in healthcare - in Swedish).

- National Board of Health and Welfare. (2009a). Att mäta säkerhetskulturen. Handbok för patientsäkerhet. (To measure safety culture. Handbook for patient safety - in Swedish).
- National Board of Health and Welfare. (2009b). Risk analys & Händelseanalys. Handbok för patientsäkerhetsarbete. (Risk Analysis & Incident Analysis. Handbook for patient safety - in Swedish) (2 ed.).
- National Board of Health and Welfare. (2011a). Avvikelseberättelser i hälso- och sjukvården (Incident reporting in healthcare - in Swedish). Retrieved April 6, 2011, from <http://www.socialstyrelsen.se/patientsakerhet/avvikelseberättelser>
- National Board of Health and Welfare. (2011b). Patientsäkerhetslagen, SFS 2010:659 (Patient Safety law - in Swedish). Retrieved April 5, 2011, from <http://www.socialstyrelsen.se/regelverk/lagarochforordningar/patientsakerhetslag>
- National Board of Health and Welfare. (2011c). Statistik om lex Maria. Retrieved April 5, 2011, from <http://www.socialstyrelsen.se/statistik/statistikefteramne/Sidor/lexmaria.aspx>
- National Coordinating Council for Medication Error Reporting and Prevention. (2011). What is a Medication Error? Retrieved 20 February, 2011, from <http://www.nccmerp.org/aboutMedErrors.html>
- Nebeker, J. R., Barach, P., & Samore, M. H. (2004). Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Ann Intern Med*, 140(10), 795-801.
- Nebeker, J. R., & Bennett, C. L. (2005). Reducing adverse drug events in the outpatient chemotherapy setting: attention must be paid. *Cancer*, 104(11), 2289-2291.
- Nerich, V., Limat, S., Demarchi, M., Borg, C., Rohrlisch, P. S., Deconinck, E., et al. (2010). Computerized physician order entry of injectable antineoplastic drugs: an epidemiologic study of prescribing medication errors. *Int J Med Inform*, 79(10), 699-706.
- Nydert, P. (2011). [Connections between drug management and drug reviews. Correct tools can make the drug management better and safer]. *Lakartidningen*, 108(6), 268-270.
- O'Neal, B. C., Worden, J. C., & Couldry, R. J. (2009). Telepharmacy and bar-code technology in an i.v. chemotherapy admixture area. *Am J Health Syst Pharm*, 66(13), 1211-1217.
- Otero, M. J., & Schmitt, E. (2005). Clarifying terminology for adverse drug events. *Ann Intern Med*, 142(1), 77; author reply 77-78.
- Patterson, E. S., Cook, R. I., Woods, D. D., & Render, M. L. (2004). Examining the Complexity Behind a Medication Error: Generic Pattern in Communication. *IEEE Transactions on systems, man, and cybernetics-Part A:Systems and humans*, 34(6), 749-756.
- Phillips, J., Beam, S., Brinker, A., Holquist, C., Honig, P., Lee, L. Y., et al. (2001). Retrospective analysis of mortalities associated with medication errors. *Am J Health Syst Pharm*, 58(19), 1835-1841.

- Pichon, R., Zelger, G. L., Wacker, P., Vodoz, A. L., & Humbert, J. (2002). Analysis and quantification of prescribing and transcription errors in a paediatric oncology service. *Pharm World Sci*, 24(1), 12-15.
- Reason, J. (1990). *Human Error*: Cambridge University Press.
- Reason, J. (1995). Understanding adverse events: human factors. *Qual Health Care*, 4(2), 80-89.
- Reason, J. (1997). *Managing the Risks of Organizational Accidents*: Ashgate.
- Rinke, M. L., Shore, A. D., Morlock, L., Hicks, R. W., & Miller, M. R. (2007). Characteristics of pediatric chemotherapy medication errors in a national error reporting database. *Cancer*, 110(1), 186-195.
- Robinson, D. L., Heigham, M., & Clark, J. (2006). Using Failure Mode and Effects Analysis for safe administration of chemotherapy to hospitalized children with cancer. *Jt Comm J Qual Patient Saf*, 32(3), 161-166.
- Sano, H. S., Waddell, J. A., Solimando, D. A., Jr., Doulaveris, P., & Myhand, R. (2005). Study of the effect of standardized chemotherapy order forms on prescribing errors and anti-emetic cost. *J Oncol Pharm Pract*, 11(1), 21-30.
- Scavuzzo, J., & Gamba, N. (2004). Bridging the gap: the Virtual Chemotherapy Unit. *J Pediatr Oncol Nurs*, 21(1), 27-32.
- Schulmeister, L. (1999). Chemotherapy medication errors: descriptions, severity, and contributing factors. *Oncol Nurs Forum*, 26(6), 1033-1042.
- Schulmeister, L. (2005). Ten simple strategies to prevent chemotherapy errors. *Clin J Oncol Nurs*, 9(2), 201-205.
- Schulmeister, L. (2006). Look-alike, sound-alike oncology medications. *Clin J Oncol Nurs*, 10(1), 35-41.
- Schulmeister, L. (2008). Patient misidentification in oncology care. *Clin J Oncol Nurs*, 12(3), 495-498.
- Schwappach, D. L., & Wernli, M. (2010a). Chemotherapy patients' perceptions of drug administration safety. *J Clin Oncol*, 28(17), 2896-2901.
- Schwappach, D. L., & Wernli, M. (2010b). Medication errors in chemotherapy: incidence, types and involvement of patients in prevention. A review of the literature. *Eur J Cancer Care (Engl)*, 19(3), 285-292.
- Serrano Fabia, A., Cavero Rodrigo, E., Albert Mari, A., Almenar Cubells, D., & Jimenez Torres, N. V. (2005). Pharmaceutical validation as a process of improving the quality of antineoplastic treatment. *J Oncol Pharm Pract*, 11(2), 45-50.
- Slama, C., Jerome, J., Jacquot, C., & Bonan, B. (2005). Prescription errors with cytotoxic drugs and the inadequacy of existing classifications. *Pharm World Sci*, 27(4), 339-343.



- Small, M. D., Barrett, A., & Price, G. M. (2008). The impact of computerized prescribing on error rate in a department of Oncology/Hematology. *J Oncol Pharm Pract*, 14(4), 181-187.
- Soop, M., Fryksmark, U., Koster, M., & Haglund, B. (2009). The incidence of adverse events in Swedish hospitals: a retrospective medical record review study. *Int J Qual Health Care*, 21(4), 285-291.
- Spath, P. L. (2003). Using failure mode and effects analysis to improve patient safety. *AORN J*, 78(1), 16-37; quiz 41-14.
- Swedish Association of the Pharmaceutical Industry. (2011). FASS. Retrieved April 5, 2011, from <http://www.fass.se/LIF/home/index.jsp>
- Swedish Cancer Society. (2010). Cancerfundsrapporten (Report from The Swedish Cancer Society - in Swedish).
- Swedish Transport Administration. (2011). Antalet döda i vägtrafiken det lägsta på nästan 100 år - Sverige klarar EUs halveringsmål. (The number of dead in roadtraffic the lowest in nearly 100 years - Sweden reaches EUs goal - in Swedish). Retrieved February 16, 2011, from <http://www.trafikverket.se/Pressrum/Pressmeddelanden/Pressmeddelanden/Nationell/2011-01/Antalet-doda-i-vagtrafiken-det-lagsta-pa-nastan-100-ar---Sverige-klarar-EUs-halveringsmal/>
- Svedmyr, D. (2011). Parenteral cytotoxic preparations 2008: Fyhr, A.
- Taylor-Adams, S., & Vincent, C. (2011). Systems Analysis of Clinical Incidents. The London Protocol. Retrieved May 3, 2011, from <http://www.ihl.org/NR/rdonlyres/D27F998F-402E-441E-8B42-BF68C6481451/551/041304VincentSystemsAnalysisofClinicalIncidentsPro.pdf>
- Ternov, S., & Akselsson, R. (2004). A method, DEB analysis, for proactive risk analysis applied to air traffic control. *Safety Science*, 42(7), 657-673.
- Ternov, S., & Akselsson, R. (2005). System weaknesses as contributing causes of accidents in health care. *Int J Qual Health Care*, 17(1), 5-13.
- Walsh, K. E., Dodd, K. S., Seetharaman, K., Roblin, D. W., Herrinton, L. J., Von Worley, A., et al. (2009). Medication errors among adults and children with cancer in the outpatient setting. *J Clin Oncol*, 27(6), 891-896.
- van Tilburg, C. M., Leistikow, I. P., Rademaker, C. M., Bierings, M. B., & van Dijk, A. T. (2006). Health Care Failure Mode and Effect Analysis: a useful proactive risk analysis in a pediatric oncology ward. *Qual Saf Health Care*, 15(1), 58-63.
- White, R. E., Trbovich, P. L., Easty, A. C., Savage, P., Trip, K., & Hyland, S. (2010). Checking it twice: an evaluation of checklists for detecting medication errors at the bedside using a chemotherapy model. *Qual Saf Health Care*, 19(6), 562-567.

- Vincent, C., Taylor-Adams, S., Chapman, E. J., Hewett, D., Prior, S., Strange, P., et al. (2000). How to investigate and analyse clinical incidents: clinical risk unit and association of litigation and risk management protocol. *BMJ*, 320(7237), 777-781.
- Vincent, C. A. (2004). Analysis of clinical incidents: a window on the system not a search for root causes. *Qual Saf Health Care*, 13(4), 242-243.
- Winterstein, A. G., Johns, T. E., Rosenberg, E. I., Hatton, R. C., Gonzalez-Rothi, R., & Kanjanarat, P. (2004). Nature and causes of clinically significant medication errors in a tertiary care hospital. *Am J Health Syst Pharm*, 61(18), 1908-1916.
- Voeffray, M., Pannatier, A., Stupp, R., Fucina, N., Leyvraz, S., & Wasserfallen, J.-B. (2006). Effect of computerisation on the quality and safety of chemotherapy prescription. *Quality and safety in health care*, 15(6), 418-421.
- Womer, R. B., Tracy, E., Soo-Hoo, W., Bickert, B., DiTaranto, S., & Barnsteiner, J. H. (2002). Multidisciplinary systems approach to chemotherapy safety: rebuilding processes and holding the gains. *J Clin Oncol*, 20(24), 4705-4712.
- World Health Organization, W. (2007). Information Exchange System. Alert No. 115. Retrieved March 1, 2011, from [http://www.who.int/medicines/publications/drugalerts/Alert\\_115\\_vincristine.pdf](http://www.who.int/medicines/publications/drugalerts/Alert_115_vincristine.pdf)
- Wu, A. W., Lipshutz, A. K., & Pronovost, P. J. (2008). Effectiveness and efficiency of root cause analysis in medicine. *JAMA*, 299(6), 685-687.
- Yu, K. H., Nation, R. L., & Dooley, M. J. (2005). Multiplicity of medication safety terms, definitions and functional meanings: when is enough enough? *Qual Saf Health Care*, 14(5), 358-363.
- Zernikow, B., Michel, E., Fleischhack, G., & Bode, U. (1999). Accidental iatrogenic intoxications by cytotoxic drugs: error analysis and practical preventive strategies. *Drug Saf*, 21(1), 57-74.
- Ödegård, S. (2006). *Säker Vård - patientskador, rapportering och prevention*. (Safe Health Care - patient injuries, reporting and prevention - in Swedish). Gothenburg.
- Ödegård, S. (Ed.). (2007). *I rättvisans namn. Ansvar, skuld och säkerhet i vården*. (In the name of justice. Responsibility, blame and safety in healthcare - in Swedish): Liber.





# System weaknesses in the process of treating patients with cytotoxic drugs

*Sven Ternov<sup>1</sup>*

*AnnSofie Fyhr<sup>2</sup>*

*Roland Akselsson, professor*

*Division of Ergonomics and Aerosol Technology,*

*Department of Design Sciences,*

*Faculty of Engineering, Lund University, Sweden*

*<sup>1</sup>MD. At the time of the study even investigator at the National Board of Health and Welfare*

*<sup>2</sup>M Sc (Pharmacy), Hospital Pharmacy, University Hospital, Lund*

Corresponding author: Sven Ternov, Division of Ergonomics and Aerosol Technology, , Lund University, Box 118, SE-22100 Lund, Sweden.

E-Mail: [sven.ternov@mailbox.swipnet.se](mailto:sven.ternov@mailbox.swipnet.se)

## Abstract

*Purpose:* Complex production systems as, for instance, health care, offshore industry, nuclear power industry or aviation occasionally suffer from severe system breakdowns. Lessons learnt from these accidents often lead to changes in the “system”. A more rational approach would be to identify these “system weaknesses” before accidents happen. The aim with the study was to proactively disclose system weaknesses in this process at a department of oncology.

*Methods:* A proactive risk analysis method was applied to the process “Treatment of patients with cytotoxic drugs”. The used method for proactive risk analysis, the DEB method, is described herein. The system weaknesses (i.e. latent system failures and insufficient safety barriers), which could cause these hazards, were identified during the analysis.

*Results:* The study identified a number of latent system failures in the process of “treating patients with cytotoxic drugs”, and offers suggestions to eliminate these hazards. The most dangerous errors are described, and barriers are suggested to prevent or mitigate these errors.

*Conclusion:* The studied main process, “Treatment of patients with cytotoxic drugs”, is a process which involves great risks and tiny margins for error mitigation. Overall, the safety barriers at the ward unit are weak or non-existent. With the starting point from the findings of the study, a generic checklist for hazard identification is proposed.

### *Acknowledgements*

We would like to express our thanks to Peter Andersson, Stabbarp Consulting, for joining the analysis team. We would also like to express our gratitude to the Department of Oncology, the University Hospital of Lund, for their wholehearted support for the analysis and in particular the head physician of the unit, Dr. Eva Cavallin-Ståhl, Dr. Thomas Relander, the head nurse at the ward unit, Ms. Siv Johnsson, assistant head nurse, Ms. Maj-Britt Hedenbro and nurse Ms. Jeanette Reidarstad. We would also like to thank Apoteket AB for their financial support thus enabling AnnSofie Fyhr to be one of the co-authors of this article.

## Introduction

Betsy Lehman, a 39-year-old health care reporter, died from a drug overdose during treatment of metastatic breast cancer. According to the investigational protocol, the cyclophosphamide dose was "4 g/sq m over a period of four days". This ambiguous order was misinterpreted by a number of health professionals. What should have been ordered was a daily dose of one g/sq m for four days in a row. Instead, the patient received cyclophosphamide 6,52 g/day for four consecutive days, a total of 26,08 g instead of 6,52 g. The Lehman case, and other case reports, may have been the starting points of discussions on how to prevent medication errors in cancer chemotherapy in USA (1). At the University Hospital in Lund, Sweden, a similar case occurred 1995. A 9 year old girl received four times the intended dose of melphalan and three times the intended dose of carboplatin and subsequently died from the overdose (2). The consequences of errors involving cytotoxic drugs can be devastating because these drugs typically have narrow therapeutic ranges. In addition, chemotherapy regimens have become increasingly complex, involving supportive medication and new drugs.

The risks involving chemotherapy errors in the chain from ordering the cytotoxic drugs by the physicians, to the preparation of the drugs by the pharmacists and their administration by the nurses, have attracted attention. Several articles have been written on the subject (3-6) offering various advice on how to minimise these risks.

In this study a proactive method for risk analysis will be used for identifying the risks when prescribing and administering cytotoxic drugs to patients.

Most of the preparations of the cytotoxic drugs at the Lund University Hospital, Sweden, are prepared at a centralised unit run by the hospital pharmacy. Through the system of reporting "near misses", knowledge was obtained at the pharmacy of the possibility of several kinds of errors that could occur. This information was subsequently used for preventive measure purposes. One such preventive measure was to improve the risk awareness among physicians, pharmacists and nurses.

Complex production systems as, for instance, those used in health care, the offshore industry, the nuclear power industry and aviation occasionally suffer from severe system breakdowns

resulting in losses of lives and material. Lessons learnt from such events often lead to changes in the “system” such as changes in equipment and working procedures so as to eliminate the hazards that led to the system breakdown (7). The tragedy is that sometimes people have to die before the necessity for these changes is identified. A more rational approach would be to identify these “system weaknesses” before accidents happen.

System weaknesses consist of latent system failures and insufficient safety barriers (8, 9).

- Latent system failures can be, for instance, insufficient maintenance of equipment, inappropriate or outdated equipment, insufficient introduction of new staff and inappropriate adaptation of working tasks to human cognitive ability.
- Safety barriers are different kinds of hindrances, built into the system. Their purpose is to detect and identify operator errors before they influence the system or, and even better, to prevent the operator from acting in an erroneous way (10, 11)

Safety barriers can be administrative, e.g. the check of the medication by the nurse prior to administering it to the patient, or technical, e.g. the use of incompatible fittings for different kinds of anaesthetic gases. Barriers can be weak/relative or strong/absolute, depending on their ability to detect and identify disturbances/erroneous acts. Administrative barriers are often weaker than technical barriers (10, 11).

In a process model view on accidents, these seldom occur because of a single wrong action or single disturbance (7, 12). Normally, complex systems have sufficient defence barriers to make this very unlikely. Instead, accidents are believed to evolve over time where multiple disturbances interact to the point where the defence mechanisms of the system are insufficient to counteract the negative impact on the system of the disturbances. The system gradually loses control and a system breakdown is imminent.



In this study, we define “system breakdown”, or an unwanted event, as one or more of the following:

- administering the wrong drug
- the correct drug but in the wrong dosage
- the correct drug in the correct dosage but in the wrong infusion fluid or volume
- the correct drug in the correct dosage but given too many or too few times
- drug given to the wrong patient
- drug given with wrong infusion time
- the correct drug administered via an incorrect route

The aim of this study is to identify system weaknesses in the processes of prescribing and administering cytotoxic drugs by applying a method for proactive risk analysis to this process. Based on the findings from the study, we propose a generic check list for minimizing the risks with cytotoxic drugs, which might prove to be of benefit to other departments of oncology.

## Description of the method “DEB analysis”

The DEB analysis is a prospective risk assessment method based on a systemic accident model (8,9) As it is described in length elsewhere (13) this chapter will only give a brief overview of the method.

In a systemic accident model preconditions for errors/unsafe acts, committed by the operators in the sharp end of the system, will arise from failures higher up in the system, the blunt end. The blunt end may typically consist of line management and corporate management. Failures in the blunt end may result in latent conditions, or latent failures. Further, blunt end failures may result in lack of adequate safe guards, safety barriers, in the system, making the system less error tolerant.

The scope for the DEB analysis is to disclose latent failures and insufficient safety barriers, in this study labelled “system weaknesses”.

The method DEB analysis (Disturbance Effect Barrier) is developed from a method used by the nuclear power industry to retrospectively analyse accidents and incidents (13). In Sweden, this retrospective method is called MTO-analysis (Man-Technique-Organisation) (10, 14). It has also been used for studying incidents in health care (11). The DEB analysis, however, is *proactive*, i.e. no accident/incident involved. The idea is to be a step ahead of a potential incident/accident. The DEB analysis has been validated for processes in air traffic control (13).

The method is operator-centred. It starts with a task analysis, i.e. a detailed mapping of the sequence of operator activities (“who is doing what?”) for carrying out the designated work task in the chosen (sub-) process. A key tool in the analysis is the asking of “what happens if...” questions within operator activities (13). The management system of the organisation is an important focus for the DEB analysis. Issues such as the appropriateness of procedures and their implementation, the clarity of roles and responsibility for the staff and the management engagement, will be assessed during the analysis.

In certain respects the method has similarities with the HAZOP method (15), in its use of guide words when asking the “what happens, if...” questions (see below). Another similarity is the dependency on a reference group consisting of operators. A major difference is that the issue for HAZOP is to identify risks concerning the design of technical equipment. The DEB analysis is used for identifying “design errors” in the human-system interface. In another article (13) the similarities and differences between DEB analysis, Failure Mode and Effect Analysis (FMEA) and Action Error Analysis are discussed.

The DEB analysis uses knowledge from the domain of cognitive psychology in assessing the possibility for human error, such as models concerning limitations of human information processing and models for human problem solving strategies (8, 9, 16, 17). It therefore could be said that the DEB analysis integrates an operator centred approach with system analysis. It integrates the concept of accident process theory (12), system failure model (8), auditing of management systems (18) and information processing models from cognitive psychology: (8).

## **Steps of the analysis**

### *1. Process description*

A precondition for the analysis is access to a fairly detailed process description. If the process is comprehensive, its description should be broken down to manageable sub-processes. If this is not already done, this is where the analysis starts.

### *2. Choose sub-processes*

After this, some or all sub-processes will be chosen for analysis. The choice should preferably be made in cooperation with the organisation concerned, using criteria such as risks for system failure and frequency of process disturbances.

### *3. Task analysis*

After having chosen a (sub-) process to analyse, the first step is to make a detailed *task analysis*, i.e. to describe the operator actions during the different working task sequences. It is important to capture the problem solving process for the operator, i.e. to describe which problems should be solved and which information the operator needs for that purpose. This is later needed for the disturbance analysis (see below).

### *4. Management system audit*

In this step, part of the management (quality-) system will be examined for consequence and consistency. For the sequences in the task analysis, we will look into the procedures (written or non-written) guiding the operator during the sequences, and examine whether the procedure is consequently implemented.

### *5. Disturbance analysis*

The next step is to perform a *disturbance analysis*. For each action sequence the question is asked: What would happen if the operator does too little, too much, too late, does nothing, or does it incorrectly? When asking these questions, the analysis of the operator's problem solving, as described in the task analysis, should be used. Disturbances may typically occur if the necessary information for problem solving is not available in a clear and unambiguous way, or if the operator is prevented from focusing on the task due to interruptions and competing tasks. As a result, a number of rather theoretical hypotheses concerning process disturbances are generated.

### *6. Validation of hypotheses on disturbances*

The hypotheses are validated by interviewing the operators and, if applicable, by analysing incident/accident reports.

### *7. Effects on the system*

For the validated hypotheses on disturbances, the operators are asked: Which effects on the system performance might these disturbances have? Thus disturbances not able to influence the system in a harmful way are sorted out. The remaining disturbances are analysed according to the next step.

### *8. Identification of system weaknesses*

In this step the following questions are addressed:

Are latent system failures identifiable as contributing causes for these disturbances?

Do safety barriers exist in the system, which prevent harmful system influence due to these disturbances? If not, how can such barriers be designed?

A flow chart, "DEB-diagram", is the working tool for the DEB. In this, the action sequences are plotted against a time axis. The results of the different steps in the analysis, described above, are written in columns under the action sequence, which has been analysed.

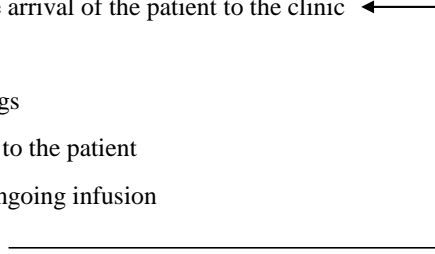
## Material and Methods

The process chosen to analyse was the treatment of patients with cytotoxic drugs at the hospital pharmacy and at an oncological ward unit at the Department of Oncology, University Hospital, Lund, Sweden.

A brief description of the process involved is as follows.

The process starts with the planning of the treatment by the doctor. A clinical evaluation of the patient is made often combined with blood tests.. The cytotoxic drugs are then prescribed by the doctor. The chemotherapy protocols are described in a manual giving detail on the drugs to be used, the dosage per square meter and the duration of the treatment. Calculation of the dosage to the actual body surface area of the patient also has to be carried out. The prescription is ordered on the cytotoxic treatment card (CTC) and delivered to the pharmacy preparation unit. The pharmacist checks the prescription, prepares the batch documentation and prints the labels for the preparations. He/she also collects the drugs, infusion bags and infusion sets to be used. Another pharmacist prepares the solutions. The preparations are then delivered to the ward together with the CTC and are given to the patient by the nurse at the oncological ward unit. The nurse follows up on the patient during the treatment. After the treatment, the patient is seen by a doctor, and discharged. When it is time for the next treatment the entire process starts all over again, i.e. an iterative process, see below.

The process was broken down into the following sub-processes:

- Decision on the treatment of a patient with a certain chemotherapy protocol
  - Planning of the treatment on the arrival of the patient to the clinic ←
  - Prescription of the treatment
  - Preparation of the cytotoxic drugs
  - Administration of the treatment to the patient
  - Monitoring the patient during ongoing infusion
  - Planning for the next treatment
- 

The sub-process of preparation of the cytotoxic drugs was, for various reasons, excluded from the DEB analysis (this analysis was completed at a later stage, though not included in this

article). All of the other sub-processes were analysed with the DEB analysis. However, the subprocess of preparation was assessed, not with the DEB analysis, but by means of scrutinizing the error reports from the pharmacy.

Please note that the first sub-process concerning the decision on the treatment of a patient with a certain chemotherapy protocol is not included in the iterative process. This action takes place once, after the diagnosis has been established, and possibly again when the choice of chemotherapy protocol has to be adjusted, but is not part of the iterative process here described, per se.

The team of analysts consisted of a pharmacist from the hospital pharmacy, responsible for the preparation of cytotoxic infusions at the department of oncology, a safety engineer from the nuclear power industry in Sweden and a licensed doctor with more than ten years of experience within risk management analysis in health care.

The hospital pharmacy took the initiative for this analysis. The management of the department of oncology expressed interest in joining, and an agreement was made. A reference group consisting of a doctor and a nurse from the ward unit was established. Steps one to four in the analysis (see section “Description of the method”) were accomplished mainly with the help of this reference group. During steps five to seven, interviews were conducted with three doctors and five nurses from the ward unit, and three pharmacists, concerning errors in the indata from the ward unit, for the preparation of the cytotoxic infusions. Furthermore, the management of the department of oncology was also interviewed. In addition, on site observations were conducted at the ward unit. For the barrier analysis in step eight, input from the incident reporting system from the pharmacy was used for discussion purposes with the reference group.

The gathering of data took place in the spring 1998.

## Results of the DEB analysis

### **Overview**

Table 1 shows the possible disturbances in the different sub processes, identified with the DEB analysis. Furthermore, the table shows the system effect of the disturbances and latent system failures that might contribute to the disturbances. Also the barrier functions are commented upon in the table, concerning mitigation from the effect of disturbances.



Sub process	Task	Disturbance	Effect	Latent system failures (see table 2)	Barriers (see table 3)
Decision on treatment	Doctor identifies actual protocol in manual	The doctor uses an outdated version of the protocol	Wrong cytotoxic drug is prescribed, or the right drug in the wrong dosage	1	Web-based updating
Planning for treatment	Clinical evaluation of the patient: Fit for planned protocol?	Misjudgement of the patient's condition	Protocol is not adjusted, too high dose is prescribed	4	Barrier # 1
Planning for treatment	Prescription of blood tests	Wrong blood tests are prescribed	Protocol is not adjusted	1, 4	Barrier # 3
Planning for treatment	Evaluation of laboratory tests	Misjudgement of laboratory tests, or missing tests not detected.	Protocol is not adjusted, too high dose is prescribed	3, 5, 6	May be detected by the nurse Barrier # 2, 4
Prescription	The doctor calculates body area	The doctor calculates the area wrongly	The dosage is not correct	2, 7	May be detected by the pharmacy Barrier # 5
Prescription	The doctor calculates 24 h dose	The doctor misunderstands the guidelines in the manual	The dosage may be doubled or tripled.	2, 7	May be detected by the pharmacy Barrier # 5
Prescription	The doctor transfers the prescription from the manual to the CTC	Error in transferring	The wrong drug, or the right drug in the wrong dosage, is written on the CTC	2, 7, 8	Double checked by the pharmacy, i.e. strong barrier Barrier # 5
Prescription	The nurse brings the CTC to the manufacturing unit	The nurse takes the CTC from another patient	The wrong infusion is prepared	9	May be detected by the nurse
Administering of the treatment	The nurse checks the labels of the cytotoxic preparation against the CTC	The nurse misses the control	The wrong drug, or the right drug in the wrong dosage, is administered to the patient	3, 8	Barrier # 6
Administering of the treatment	The nurse prepares the infusion pump	The nurse makes an error in preparing the pump	The patient is given the drug too slowly or too fast	10	Barrier # 6
Follow up of ongoing treatment	The nurse observes the patient during ongoing infusion	The nurse fails to observe the patient	Errors in prescribing or manufacturing may be detected too late	11	Barrier # 6
Planning for next treatment	New blood tests are prescribed	The blood tests are not prescribed, or the wrong tests are prescribed, or the results never arrive	The regime is not adjusted properly	3, 4, 6	Nurse may detect Barrier # 3

Table 1 shows the identified disturbances and their system effect, correlated to work tasks in the sub-processes, and the corresponding latent system failures (see table 2). Also the suggested barrier functions are shown (numbers refer to table 3)

In table 2, the corresponding latent system failures are shown, i.e. contributory causes for the disturbances mentioned above, identified in the DEB analysis. Figure 1 shows, in a simplified manner, where the latent system failures are present in the process.

No.	Latent system failure	Explanation
1	The procedures for updating the manual for chemotherapy protocols are unsafe	The document control system does not ensure that all manuals are correctly updated.
2	The procedures for cooperation between department of oncology and pharmacy are implicit and not clear.	The department expects the pharmacy to check the CTC for correctness concerning regime and dosage. The pharmacy only does this if work pressure permits.
3	Responsibility and authority for the nurses are not defined.	The nurses act as barriers against the doctor's errors (see table 1), thereby taking upon themselves undue responsibilities.
4	Necessary competence for doctors is not properly defined	This will increase the risk of making a wrong clinical evaluation.
5	The procedures for responsibility concerning evaluation of the results of blood tests are unsafe	A doctor is supposed to do this, but often forgets. A nurse will then do it. If this nurse lacks experience, as can be the case during vacations, a misjudgement might be made.
6	The procedures for tracing the results of blood tests are inappropriate	No log is kept to ensure that ordered blood tests have arrived in due time, i.e. there is no closed feedback loop.
7	The procedures for transfer of information from manual for chemotherapy protocols to CTC is inappropriate	Humans are not good at transferring information. It is very easy to make errors.
8	The procedures for filling in the CTC are unsafe	Often the handwriting is illegible. Different doctors also use different systems for filling in the CTC. Subsequently the CTC is difficult to use for the nurse for the last check before administering the preparations to the patient.
9	The procedures for marking the CTC with proper patient ID are unsafe	A CTC from the wrong patient can be given to the manufacturing unit.
10	The technical equipment (infusion pumps) are of different brands at different ward units at the department of oncology	Personnel from different units work together during weekends.
11	The procedure for monitoring the patient during treatment is unsafe	The final possibility of detecting errors in prescription and/or preparation is to discover an abnormal reaction to the infusion.

Table 2. Identified latent system failures that might cause the disturbances mentioned in table 1, together with a brief explanation. For more extensive discussion, see the section "Discussion". See also figure 1 that shows where in the process the latent system failures are present.

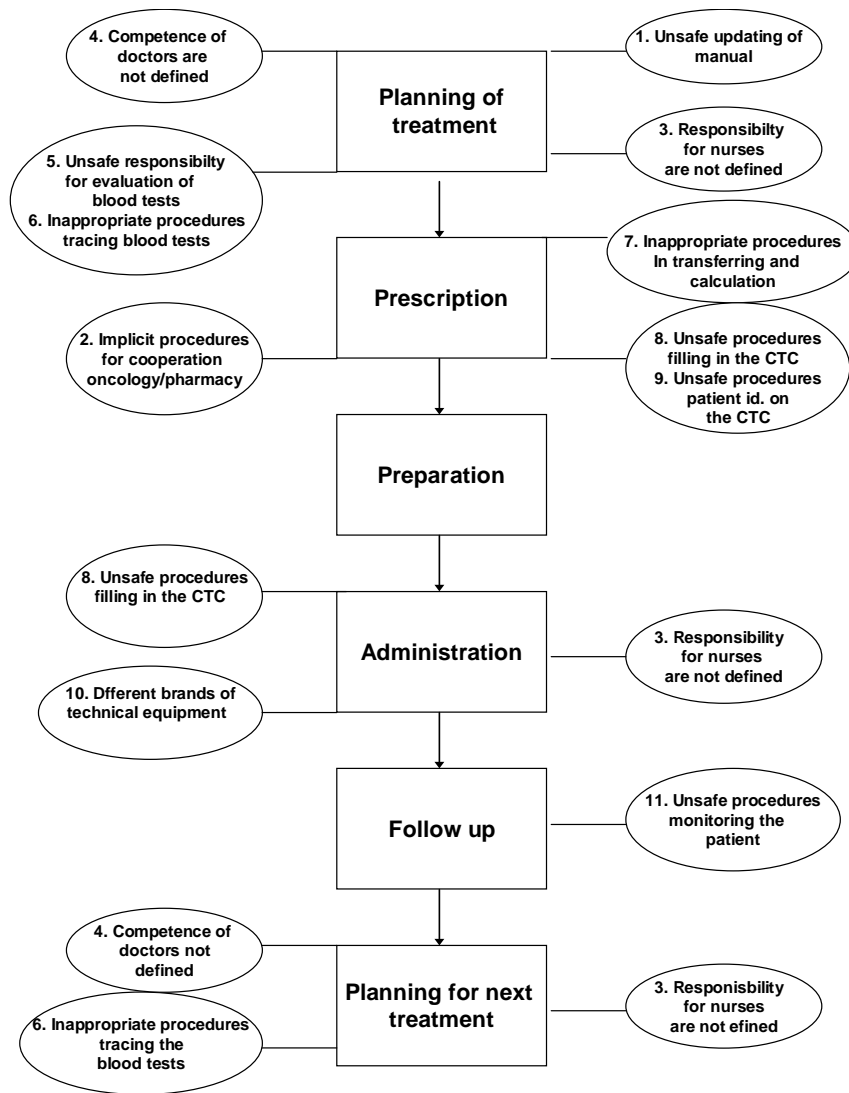


Figure 1. Latent system failures in the process "Treatment of patients with cytotoxic drugs". The numbering in the elipses refers to the numbering in table 2, where a brief explanation is given.

## **A. Latent system failures**

Below, the identified latent system failures are described, including the suggestions made to the oncological department and the pharmacy in order to reduce risks (see also table 2 in the Results section)

### *1. The procedures for transfer of information from the manual for chemotherapy protocols to CTC (Cytotoxic Treatment Card) are inappropriate*

Quite a huge amount of information has to be manually transferred from the manual to the CTC. Due to limited cognitive resources, the human operator is not very good at this. Errors in transferring data are common: drugs are mixed up, dosage in  $\text{mg}/\text{m}^2$  are wrong, necessary lab tests are missed, dosage intervals are incorrect, body surface area is wrongly calculated etc. If this information in the manual was stored in a database and electronically transferred to the CTC, this hazard might substantially be reduced.

### *2. The procedures for updating the manual for chemotherapy protocols are unsafe*

At three different tasks, the information from the manual has to be correct so as not to endanger the patient: 1. at prescription, 2. at preparation, and 3. in connection with administering. Updating of the manual, for all users, might be facilitated using an IT-solution.

### *3. The procedures for cooperation between the pharmacy and the department of oncology are implicit and not clear.*

For maintaining a high level of safety, it is of the greatest importance that all prescriptions are clear and unambiguous. The procedures for handling unclear prescriptions are ill-defined. According to standard procedures, the pharmacy has to call the doctor responsible in order to verify any unclear prescription. However, according to the interviews conducted with the pharmacists, the doctor is quite often unavailable, and if so, the pharmacist may, quite often, receive a rude answer in return. The effect of this is that the pharmacist becomes reluctant to verify the prescription and starts using guesswork instead, thus introducing a substantial risk in the system.

The pharmacist checks the prescription for errors, such as body surface area, calculation from dose per square meter to dose for the actual body surface area, and number of days for the treatment. This check, however, is not formally regulated in the contract between the

pharmacy and the ward unit. It is only done if time is available for the pharmacist, and if it is remembered. Unfortunately however, doctors rely on this being done, thus increasing the risk for harm to the patient.

*4. The technical equipment (infusion pumps) consists of different brands at different ward units at the department of oncology*

Personnel from different units work together e.g. during weekends. It is suggested that only one brand of infusion pumps are used.

*5. The procedures for evaluating the results of blood tests are unsafe*

Aberrant laboratory results, as for instance a decreasing number of white blood cells, should be discovered immediately in order to adjust the regime. The responsible doctor is supposed to check incoming laboratory results on a daily basis but this is not done consequently.

Therefore, nurses and secretaries take this duty upon themselves, thus acknowledging a work task and a responsibility that is not formally theirs. This can constitute a hazard.

*6. The procedures of filling in the CTC are unsafe*

The procedures of filling in the CTC are partly obscure and existing procedures are implemented inconsequently. This sometimes makes the CTC difficult to read. The often illegible handwriting of doctors may also be added to this problem. The consequence of this is that the barrier function of the CTC can become compromised, both for the preparation unit and during the nurse's task of administering the drug to the patient. The focus of attention for the staff will be on interpretation of what actually is written on the CTC and not on detecting errors such as a wrongly calculated daily dose.

*7. The procedures for tracing the results of blood tests are inappropriate*

Blood tests are normally carried out at the local hospital of the patient, and faxed to the department of oncology. There is, however, no procedure for checking orders for blood tests against incoming results. In the worst case, the consequence could be that prescription for a new treatment is carried out disregarding vital test results. A suggestion might be to develop a warning system for missing test results.

*8. The procedures for marking the CTC with proper patient identity are unsafe*

Some of the sheets in the CTC are not marked with the name and personal ID number of the patient concerned. When copying these sheets confusion could be created as to the identity of the patient.

*9. Responsibility and authority for the nurses are not defined.*

According to the task description for the nurses, they merely have to carry out the prescribed treatment. However, the nurses also check the doctors' prescription and the doctors' evaluation of blood tests, and, at times, they detect quite a few errors. Thus, the nurses act as barriers against errors made by the doctors (see table 1), thereby taking upon themselves undue responsibilities. Obviously, double checks are necessary, but should be carried out by the doctors themselves. This latent system failure should even be looked upon in context with the latent system failures # 10 (competence of doctors) and # 5 (evaluating blood tests).

*10. Necessary competence for the doctors is not properly defined*

The responsible doctor carries out a complicated and cognitive demanding work task, in an area with very low tolerance for error (errors in oncology tend to be irreversible, i.e. a very limited window for error recovery). Furthermore, this system has quite weak barriers against mistakes. Errors in judgement are very dependant on the experience and competence of the doctor concerned. Therefore, it is a hazard that the definition of competence for doctors, prescribing treatment for cancer patients, is inadequate.

*11. The procedure for monitoring the patient during treatment is unsafe*

The last possibility of detecting errors in prescription and/or preparation is the discovery of an abnormal reaction to the treatment. This is typically carried out by the nurses. There is no documented procedure for this monitoring of the patient. Thus, the risk is that such monitoring is not carried out consequently, and therefore missing adverse reactions to the treatment.

## **B. Safety barriers**

When conducting the barrier analysis, material was used from the incident reporting system of the pharmacy. This material showed that a complex pattern of barriers against errors existed in some sub-processes, with the potential of detecting errors in previous sub-processes. For example, concerning errors in the sub-processes of planning and prescription of treatment, the sub-process of preparation would have barriers implemented against these errors, and for errors in the sub- process of preparation, the sub-process of administering would have barriers for these errors.

In order to get an overview of this rather complex system of barriers, a so-called tracking diagram was designed. A simplified version of this, showing the principles used, is shown in figure 2.

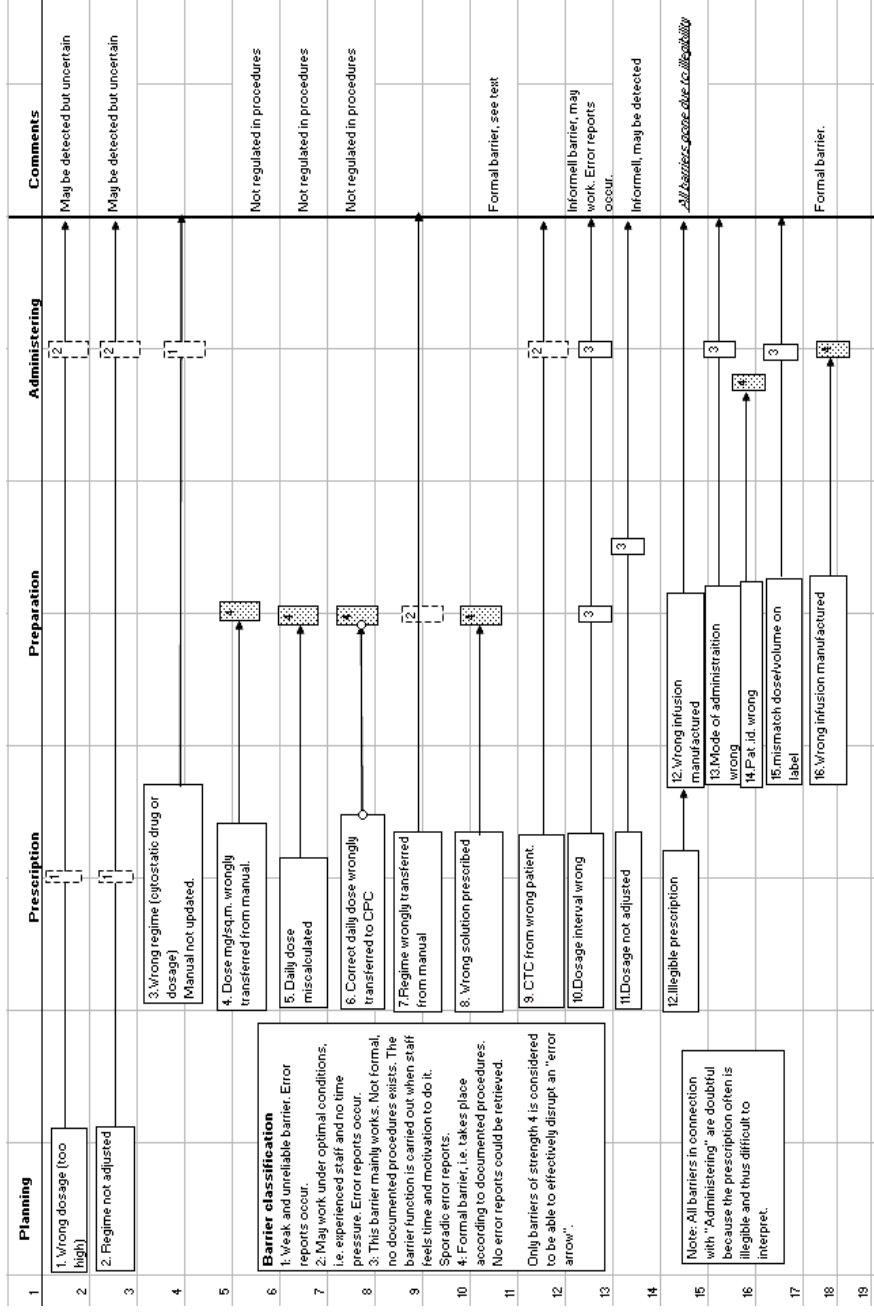
The diagram shows that disturbances during planning of the treatment (and partly during prescription) are the most dangerous since there are only weak barriers to counteract the effect of the disturbances. The grading of the barrier function from 1-4 is based on the information from the incident reporting system. The incident report analysis indicates where the errors were detected.

Many disturbances during prescription will be discovered at the preparation unit (pharmacy). Disturbances arising at the preparation unit may be discovered during the process of administering. The barriers in this sub-process are, however, to a high degree, not formal (as discussed under Results, latent system failures, #3).

The barrier functions in the sub process of administering the cytotoxic drugs, which may counteract the effect of errors in planning, prescription and preparation, are very dependent on the nurse having a readable cytotoxic treatment card (CTC) (see further under Results, latent system failures, #6 and #8).

Below are the errors listed, which, according to the analysis depicted in the tracking diagram, created the greatest probability for causing harm to the patient. (Suggested barrier functions are discussed in the section “Discussion”).

Figure 2. Tracking diagram for disturbances in relation to barriers.





The diagram shows that disturbances during planning of the treatment (and partly during prescription) are the most dangerous since there are only weak barriers to counteract the effect of the disturbances. The grading of the barrier function from 1-4 is based on the information from the incident reporting system. The incident report analysis indicates where the errors were detected.

Many disturbances during prescription will be discovered at the preparation unit (pharmacy). Disturbances arising at the preparation unit may be discovered during the process of administering. The barriers in this sub-process are, however, to a high degree, not formal (as discussed under Results, latent system failures, #3).

The barrier functions in the sub process of administering the cytotoxic drugs, which may counteract the effect of errors in planning, prescription and preparation, are very dependent on the nurse having a readable cytotoxic treatment card (CTC) (see further under Results, latent system failures, #6 and #8).

Below are the errors listed, which, according to the analysis depicted in the tracking diagram, created the greatest probability for causing harm to the patient. (Suggested barrier functions are discussed in the section “Discussion”).

- 1. Clinical misjudgement of the patient before prescription*
- 2. Misjudgement of laboratory results before prescription*
- 3. Necessary blood tests are not taken*
- 4. Blood test results do not arrive, or arrive too late, to the clinic*
- 5. Errors in prescriptions and errors in filling in the CTC*

6. *Wrong infusion is administered to the patient (wrong drug, wrong amount, or wrong infusion rate)*

These errors, together with suggested barriers (further discussed in the section “Discussion”) are listed in table 3. Figure 3 shows, in a simplified manner, where in the process the most dangerous errors can be found.

No.	Description	Suggested barriers
1	Clinical misjudgement of the patient before prescription	Double check by another doctor Computerisation
2	Misjudgement of laboratory results	Double check by another doctor Computerisation
3	Necessary blood tests are not taken	Computerisation
4	Blood test results do not arrive, or arrive too late, to the clinic, and are thus forgotten	Computerised supervision function concerning ordered and received blood tests
5	Errors in prescription and errors in filling in the CTC	Computerisation
6	Wrong infusion is administered to the patient (wrong drug, wrong amount, wrong infusion rate)	Scheduled monitoring of patients with ongoing infusion.

Table 3. The table shows the errors which might create the greatest probability for causing harm to the patient, and recommended barriers, as a result of the DEB analysis. The barriers suggested are discussed in the section “Discussion”. See also figure 3 that shows where in the process these errors can be found.

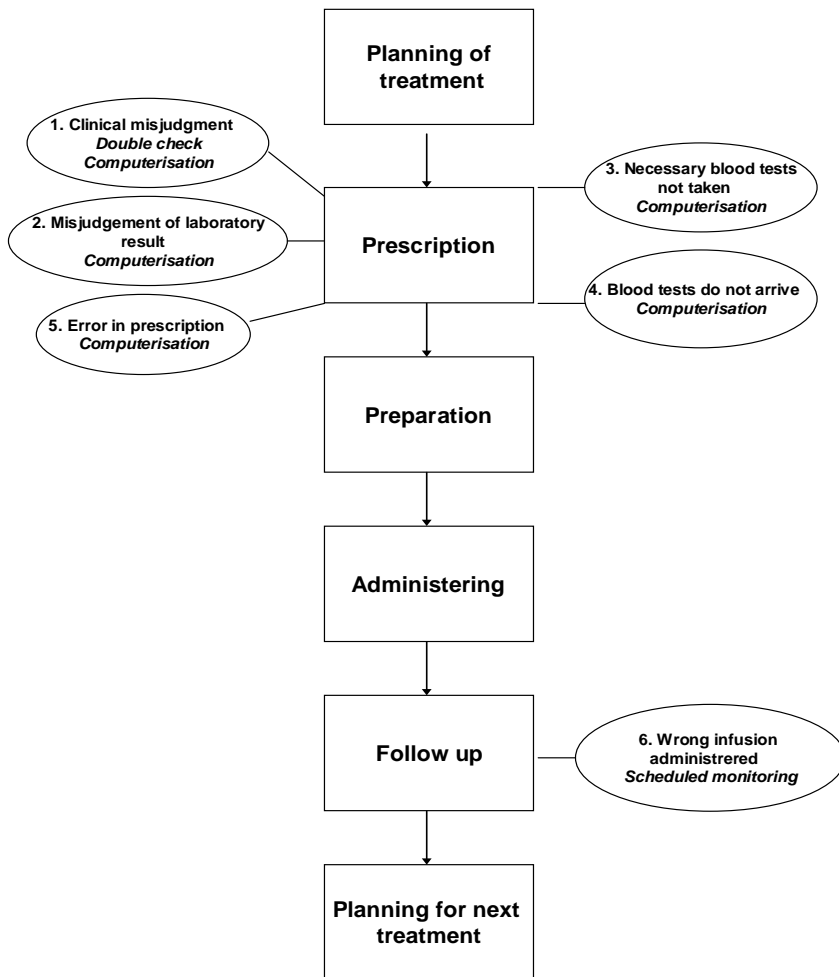


Figure 3. The errors with the highest probability of creating harm to the patient, and recommended barrier. The numbering in the eclipses refer to the numbering in table 3. The suggested barriers are shown in italics.

## Discussion

The discussion covers the following topics:

- Errors/Safety barriers
- Validity of the results
- Suggestion for a generic check list
- Risk reduction by using computerisation

### **Errors/safety barriers**

The analysis of safety barriers was carried out together with the reference group. The reference group agreed to the following critical errors, and to the potential mitigation of these:

#### *1. Clinical misjudgement of the patient before prescription*

The term “clinical misjudgement” includes misjudgement of blood test. This mistake can, with a degree of luck, be detected by the pharmacy (who has access to the results of the blood tests), or by the ward nurse, but this barrier is rather weak and informal. A double check by a second physician might reduce this hazard.

#### *2. Misjudgement of laboratory results before prescription*

A better stringency of procedures concerning the physician’s obligation to check incoming post for blood tests would prove helpful. A double checking procedure carried out by a second physician might also increase safety. Finally, computerisation may accomplish a blockage of the prescription if the proper blood tests are not acknowledged by the physician, or if the results are outside established reference values.

#### *3. Necessary blood tests are not taken*

Computerisation can be used to block the prescription if the results from necessary blood tests are not available.

#### *4. Blood test results do not arrive, or arrive too late, to the clinic.*

A computerised tracking function, with appropriate alert functions, could keep track of which blood tests have been ordered from the patient’s home laboratory, which blood tests have been

taken and mailed to the department of oncology, and which results have been received. The system should alert the staff at the department of oncology in the event of a mismatch between ordered and received blood tests.

#### *5. Errors in prescriptions and errors in filling in the CTC*

Most of these errors might be prevented by computerisation, such as errors in transferring information, and errors in calculation.

#### *6. Wrong treatment is administered to the patient (wrong drug, wrong amount, or wrong infusion rate)*

This hazard implies that all the previous barriers have been bypassed. However, a possibility for error mitigation might still exist if the patient clinically reacts adversely to the error during the ongoing infusion. This, however, will assume that firmly established routines exist for monitoring the patient during the infusion.

#### *7. The last barrier – the patient*

If the patients are given adequate information as to the chemotherapy they are to receive, they can act as the last barrier (6).

### **Validity of the results**

The quality of the results from the DEB analysis seems to be very dependant on the composition and understanding of the reference operator team used for validation (steps # 6, see “Description of method”). Also, for the interviews with miscellaneous staff, it is crucial that they understand the purpose of the study. Concerning some of the staff interviews, a tendency was noted that the doctors (not the nurses) would “defend” the system, i.e. try to make it appear safer than it was, instead of volunteering into a discussion of possible hazards. This was probably due to their level of understanding the purpose of the analysis.

How can we be sure that all essential errors, and concomitant system weaknesses, are covered in this analysis? The answer is that we can not. However, the reference group agreed to the task analysis, and played their brain storming role well. Thus, we believe that the probability that we missed essential error opportunities, and thus latent system failures, is minor.

## Generic check list

Could the results from this analysis be generalised to another department of oncology, and the results used at another place? Quite a few of the identified latent system failures seem to be rather generic, such as the transferral procedure of information, track keeping of blood test results, role identification for different actors, and the important question concerning necessary staff competence for different tasks (6, 22). We therefore believe that the results from this analysis might be used by other departments as a kind of checklist for opportunities to avoid errors, on the precondition that these departments employ similar processes for “treatment of patients with cytotoxic drugs” as the one studied.

Such a generic checklist is presented in table 4. The items in the checklist (first column) correspond with table 2, Latent system failures. The second column in table 4, “check questions”, contains the identified latent system failures from table 2, transformed into questions. Finally, the column “notes” elaborates on the checklist items, using information from the study. The aim with this column is to make it easier for the reader/user to understand the background for the checklist questions. Please observe that this checklist includes the six sub-processes investigated, but not the sub-process of preparation (refer to the chapter on Material and Methods).

Item	Check questions	Notes
1. Updating of manual for chemotherapy protocols	Do you have a proper document control system in place so as to ensure correct updating of all the protocols (both at the ward unit, and at the pharmacy)?	A safer way of ensuring updating would be to have a web-based manual.
2. Cooperation between oncological department and pharmacy	Do you have written and implemented procedures concerning the cooperation between oncological department - pharmacy?	In this study the department assumed that the pharmacy (preparation unit) would check the correctness of the CTC. They did, but only occasionally.
3. Responsibility nurses vs. doctors	Are you sure that what the nurses should do, and what the doctors should do is unambiguous? Do you have written and implemented procedures for this?	In this study the nurses sometimes acted as barriers against the doctor’s prescription errors, thereby taking upon themselves undue responsibilities. Also, as mentioned above, they carried out duties assigned to the doctors by checking incoming results of blood tests.
4. Competency for doctors	Have you clearly defined the necessary level of competence for doctors during the different tasks in the process of treating patients with cytotoxic drugs?	For instance, how have you defined the level of competency for the doctor who will make the clinical evaluation of the patient before next treatment? Same question for the doctor who will transfer the protocol from the manual to the CTC?

5. Evaluation of blood tests	Who is responsible for evaluation of incoming blood tests? The doctors, presumably. But do they do it?	In this study a doctor is supposed to do this, but often “forgets”. A nurse will then do it. If this nurse lacks experience, as can be the case during vacations, a <b>misjudgement might occur</b> .
6. Blood tests, traceability	Which procedures do you have for keeping track of ordered blood tests? Can you trace if an ordered blood test never gets carried out, or if the answer gets lost in the mail system?	You need a closed feedback loop for this to ensure safety. Otherwise you risk continuing with a dosage, which should have been adjusted.
7. Transferral of information	How are your procedures for transferring information from the chemotherapy protocol to the CTC?	Humans are not good at transferring information. It is very easy to make errors. Do you have any barriers in place for detecting errors during this task? Have you identified the proper level of competency for the doctor carrying out this task? Can she/he do it in an undisturbed environment? Is sufficient time allocated for this task?
8. Filling in of the CTC	Do you have written and implemented procedures for this task?	Different doctors tend to use different systems for filling in the CTC. Often the handwriting is illegible. This increases the risk of errors in preparation, and makes the CTC difficult to use for the nurse during the last check before administering the drugs to the patient The department might use regular audits on this, checking a number of filled in CTC's for appropriateness.
9. Proper patient ID on the CTC?	How do you ensure that all pages in the CTC belong to the right patient? Is it possible that you can give a CTC to the pharmacy preparation unit with wrong patient ID?	
10. Equipment	Are your infusion pumps at the department of one brand and model only? Do you have proper procedures for training the staff in using this equipment? Do you keep a training log?	Different brands and models can constitute a hazard especially, as seen in this study, when staff from different ward units and used to different brands of infusion pumps, substitute for each other during holidays and weekends.
11. Monitoring of patient	Do you have procedures for observing and documenting the patient's reactions during ongoing infusion?	Careful monitoring of adverse reactions during the treatment may be the last possibility to detect errors earlier in the process. This is mainly a concern for the nurses who ought to be trained for looking for such reactions, according to a strict schedule for observation. Furthermore, they should be encouraged to do it, and have easy access to doctors for discussing any aberrations.

Table 4. Generic checklist for identifying hazards in the process of treating patients with cytotoxic drugs. (Note: Hazards in preparing the cytotoxic drugs at the preparation unit at the pharmacy is excluded).For barrier analysis, the tracking diagram, figure 3 can be used, as well as table 2, for inspiration.

Would another team of investigators obtain the same results? If the investigators were properly trained in the method, had sufficient domain knowledge, performed a thorough task analysis, and had an adequate staff reference group, we believe that they would arrive at more or less the same results as those in this analysis.

We found that the process examined contained many dangerous errors and that the suggested barriers often are computerisation. In a management case study, failure mode and effect analysis (FMEA) was used to examine all the processes involved in chemotherapy ordering and administration (20). Critical failures and root causes were identified by a multidisciplinary team. As a result, a Web-based system with diagnosis-specific standing orders integrating laboratory data with nursing documentation system was developed. The system is reported to be uniform and safe for ordering of chemotherapeutic and adjuvant agents. In another study (21) a computerised provider order entry (CPOE) was developed guided by multidisciplinary FMEA. As a result of this, a reduction of ordering errors, such as improper dosing, incorrect dosing calculations, missing cumulative dose calculations and incomplete nursing checklists, in pediatric chemotherapy has been reported.

### **Computerization**

Experiences from more than seven years with computer software for pharmacy oncology services are reported (19). The system has safeguards throughout the order-entry and preparation process and gives the pharmacist a possibility to review the patients' previous therapy including body surface area and treatment protocol. It has proven an invaluable tool for detecting prescribing errors and preventing preparation and administration errors, and, according to the authors, no significant errors have occurred since the computer program was implemented

We suggest a computerisation that involves all the studied sub-processes for treatment with cytotoxic drugs, , including control of the blood testing, the preparation by the pharmacists and the administration by the nurses. Even the electronic updating of the cytotoxic treatment manual should be computerised. The database in this program should contain "patient profiles", being able to compare former treatments with the current prescription, and being able to pose check questions in the event of discrepancies being detected. We would, however, like to add a warning that although computerised procedures might solve some problems, they have a tendency to introduce quite new hazards. Before such a step is



undertaken, a new DEB analysis ought therefore to be carried out, assessing the new computerised procedures

To summarise the requirements for computerisation:

- The program should have access to a database concerning the manual for chemotherapy protocols.
- The updating procedures for the manual should be simple and transparent.
- The program should be able to generate a CTC when a regime is decided upon, including the length and weight of the patient, and the date for the start of treatment.
- The program should be able to calculate the proper doses during the treatment period.
- The program should be able to check maximum and accumulated doses, and alert those concerned should these be exceeded.
- Alerted dosages must be acknowledged before the CTC can be printed out.
- Necessary blood tests according to the manual must be present and acknowledged by the physician before the print out of the CTC is possible.
- The program should supply the pharmacy with necessary documentation and labels for marking the prepared infusions and injections.

We find that the studied main process, “Treatment of patients with cytotoxic drugs”, is a process that involves great risks and tiny margins for error mitigation.

Overall, the barriers are weak or non-existent at the ward unit. This is clearly seen in the tracking diagram, figure 2, where far too many errors are able to defy detection before the effect of the error hits the patient. Thus there is good potential for improving the process of treating patients with cytotoxic drugs.

## References

1. Cohen MR, Anderson RW, Attilio RM et al. Preventing medication errors in cancer chemotherapy. *Am J Health-Syst Pharm*. 1996; 53:737-46.
2. The National Board of Health and Welfare, Sweden. Incident report according to the mandatory reporting act, number 41-146/96 (in Swedish).
3. Cousins DH, Upton DR, Cohen MR. Reducing the risks of chemotherapy errors. *The Hospital Pharmacists*. 1995; 2:117-20.
4. Attilio RM. Caring enough to Understand: The Road to Oncology Medication Error Prevention. *Hospital Pharmacy*. 1996; 31:17-26.
5. Goldspiel BR, DeChristoforo R, Daniels CE. A continuous-improvement approach for reducing the number of chemotherapy-related medication errors. *Am J Health-Syst Pharm*. 2000; 57: S4-S9.
6. Fernandez CV. Can we prevent cytotoxic disasters? *Br J of Haematology*. 2000; 108:464-9.
7. Cook RI, Woods DD. Operating at the sharp end: The complexity of human error. In: Bogner MS, (Ed.). *Human error in medicine*. New Jersey, Lawrence Erlbaum Associates; 1994.
8. Reason J. *Human Error*. Cambridge, Cambridge University Press; 1990.
9. Reason J. *Managing the risks of organizational accidents*. Vermont, Ashgate; 1997.
10. Ternov, S. The human side of medical mistakes. In: Spath P (Ed.) *Error reduction in Health Care*. Jossey-Bass, New York; 2000.
11. Ternov S, Akselsson R. System weaknesses as contributing causes for accidents in health care. *International journal for quality in health care*. 2005; 17:5-13.
12. Kjellén U. The deviation concept in occupational accident control - I. *Accident analysis and prevention*. 1984; 16(4):289-306.
13. Ternov S, Akselsson R. A method, DEB analysis, for proactive risk analysis applied to air traffic control. *Safety Science*. 2004; 42:657-73.
14. INPO (Institute of Nuclear Power Operations). *Human Performance Enhancement System, program description*. INPO document INPO 90-005, Atlanta; 1990.
15. Kletz T. *HAZOP and HAZAN – Identifying and assessing process industry hazards*. Rugby, Institution of Chemical Engineers; 1999.
16. Rasmussen J. Human errors. A taxonomy for describing human malfunction in industrial installations. *Journal of Occupational Accidents*. 1982; 4:311-33.
17. Roske-Hofstrand R, Murphy E. Human information processing in air traffic control. In: Smolensky MW, Stein ES (Eds.) *Human factors in air traffic control*. San Diego, California, Academic Press; 1998.
18. ISO 9000 International standards for quality management, Stockholm, SIS förlag; 1996.
19. Berard CM, Mahoney CD, Welch DW et al. Computer software for pharmacy oncology services. *Am J Health-Syst Pharm* 1996; 53:752-6.
20. Kozakiewicz JM, Benis LJ, Fisher SM et al. Safe chemotherapy administration: Using failure mode and effect analysis in computerized prescriber order entry. *Am J Health-Syst Pharm*. 2005; 62:1813-6.

21. Kim RG, Allen RC, Arcedi Rjet et al. Error Reduction in Pediatric Chemotherapy. *Arch Pediatr Adolesc Med.* 2006; 160:495-8.
22. Branowicki P, O'Neill J, Dwyer JL et al. Improving Complex Medication Systems An Interdisciplinary Approach, *J Nurs Adm.* 2003; 33(4):199-200.



## Paper II



## **Characteristics of Medication Errors with Parenteral Cytotoxic Drugs**

*AnnSofie Fyhr<sup>1</sup>, MSc (Pharm),  
Division of Ergonomics and Aerosol Technology,  
Lund University, Sweden*

*Roland Akselsson, Professor,  
Division of Ergonomics and Aerosol Technology,  
Lund University, Sweden*

*<sup>1</sup>At the time of the study, supervisor of the pharmacy oncology preparation service,  
Hospital Pharmacy, University Hospital, Lund, Sweden*

Corresponding author: AnnSofie Fyhr,  
Division of Ergonomics and Aerosol Technology, Lund University,  
P.O. Box 118, SE-221 00 Lund, Sweden  
E-mail: [annsofie.fyhr@design.lth.se](mailto:annsofie.fyhr@design.lth.se)  
Phone: +46 46 222 05 17; Mobile: +46 702 169 329  
Fax: +46 46 222 44 31

## ABSTRACT

**Objective.** To identify the characteristics of medication errors involving parenteral cytotoxic drugs in Sweden.

**Design.** Retrospective study. Medication error reported involving a cytotoxic drug, administered parenterally at hospital. The reports were retrieved from the national error reporting systems and were analysed using qualitative content analysis for their characteristics.

**Setting.** National healthcare system.

**Participants.** Cases reported from 1996 to 2008. A total of 60 case reports met the inclusion criteria and were reviewed.

**Interventions.** None.

**Main Outcome Measures.** Cytotoxic drugs involved, type of error, where the error occurred, error detection mechanism, and consequences for the patient.

**Results.** The most commonly involved cytotoxic drugs were fluorouracil, carboplatin, cytarabine, and doxorubicin. The platinum containing drugs often caused serious consequences for the patients. The most common error type were too high doses (45%) followed by wrong drug (30%). Twenty-five of the medication errors (42%) occurred when doctors were prescribing or transcribing. All of the preparations were delivered to the patient causing temporary or life-threatening harm. In nearly 50%, these errors were discovered due to adverse reactions from the patient. Another twenty-five of the medication errors (42%) started with preparation at the pharmacies. The remaining ten medication errors (16%) were due to errors during preparation by nurses (5/60) and administration by nurses to the wrong patient (5/60). The errors were discovered by healthcare professionals and by patients or relatives.

**Conclusion.** It is of utmost importance to minimise the potential for errors in the prescribing stage. The identification of drugs and patients should also be improved.

**Keywords:** medication errors, cytotoxic drugs, chemotherapy



## Introduction

Errors involving cytotoxic drugs are not rare [1] and have the potential of being fatal [2] and should therefore be prevented. A review of the literature on medication errors (MEs) in chemotherapy, their incidences and characteristics, has recently been presented by Schwappach and Wernli [3].

Parenteral cytotoxic drug treatments are administered on an inpatient or outpatient basis. A team consisting of doctors, pharmacists and nurses is responsible for the prescription, preparation, administration, and monitoring of the treatment. About 50 different cytotoxic drugs, including monoclonal antibodies, are used for parenteral administration in Sweden today. These drugs are administered in a wide variety of cancer therapies, both for curative and palliative care, and they are used in the treatment of small children up to elderly people. They can be used as a single drug or in combinations in complex regimes over several consecutive days repeated after 2 to 3 weeks. For most of the drugs, the dose is based on body surface area or other patient-specific factors (e.g. weight, renal function). Most cytotoxic drugs have a narrow therapeutic index. At the same time, for some of these drugs, such as cytarabine, and methotrexate, dosages vary widely depending on the condition being treated, how the drug is used, and the use of supportive therapy. Cytotoxic drugs, given parenterally and orally, are classified as “high-alert medications” according to the Institute for Safe Medication Practice (ISMP) [4].

In Sweden approximately 350,000 parenteral cytotoxic preparations are prepared annually (2008). Most of them, 330,000, are prepared by hospital pharmacists (legislation requires that pharmacists have at least a bachelor’s degree for preparation of cytotoxic drugs), and the rest by nurses in the unit [5]. At the time of the study hospital pharmacies were run by a governmental company, Apoteket AB, and thus by an external partner to healthcare.

Healthcare providers in Sweden are legally obliged to report serious injuries and risks of injuries to the National Board of Health and Welfare (NBHW), pursuant to lex Maria [6]. All hospitals and pharmacies have local incident reporting systems, most of them now computerised. The incidents reported by hospital staff are assessed by a person appointed by the management. If the incident is judged to be serious, it is sent to the medical director of the hospital who is responsible for the final decision to report or not according to lex Maria. For the pharmacies the final decision has been centralised to the quality department. In 2008 a total of 1,102 incidents were reported according to lex Maria [7]. About 250 (23%) of these involved a medication [8]. Reports according to lex Maria were, after investigation, reported to a national risk database, administered by the NBHW. Complaints filed to the Medical Responsibility Board (HSAN) were also reported to the national risk database [9]. The HSAN was a national authority that assessed medical negligence. Complaints could be filed from a patient, a close relative or the NBHW. The role of HSAN to judge medical negligence ended in 2010 and the role of NBHW has changed.

The purpose of reporting incidents is to learn in order to make improvements. Reporting systems often fail to fulfil their intended role because they are underused [1]. Information on reported MEs should be shared with other institutions, so that many can learn from the errors of a few. It could thus be of value to present the experiences from Sweden and 13 years of case reports to the national regulators on MEs with parenteral cytotoxic drugs. The errors were analysed in detail in order to gain as much knowledge as possible from them. The definition of an ME used is the one proposed by Ferner and Aronson of the UK: “A

medication error is a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient” [10].

The aim of this study was to identify the characteristics of the medication errors involving parenteral cytotoxic drugs in Sweden in order to answer the following questions: Which drugs were involved? What types of errors were made? Where in the medication use process did the errors take place? How were these errors discovered? What were the consequences for the patients?

## Materials and methods

Cases reported to the national error reporting systems have been used for a retrospective qualitative analysis. The inclusion criteria for this study are: A medication error reported according to the lex Maria Act or to the Medical Responsibility Board (HSAN) between 1996 and 2008 involving a cytotoxic drug (ATC classification L01) and administered parenterally at a hospital. Problems with blood tests or other necessary tests during the treatment period are included if they result in the wrong treatment. Misdiagnoses, subcutaneous drug extravasation of the infusion, or problems with peripheral or central venous line during administration are excluded. Several reports on the same case were counted as one ME.

The material consists of ME reports obtained in the following ways:

- Reports retrieved from the national risk database from 1996 to mid 2006. A total of 101 reports were found; of these 44 met the inclusion criteria. Most of the reports excluded involved oral cytotoxic drugs.
- Reports retrieved from the NBHW database as the result of a search for reports involving the word “cytostatika” for 2006-2008. A total of 12 reports were found; of these eight met the inclusion criteria.
- Eight reports were found using other sources: in a report retrieved from the national risk database (1), a colleague informed from another hospital pharmacy (4), the incident occurred at the university hospital where one of the authors worked (3).

The MEs were reported from the whole country and according to the content in Figure 1.

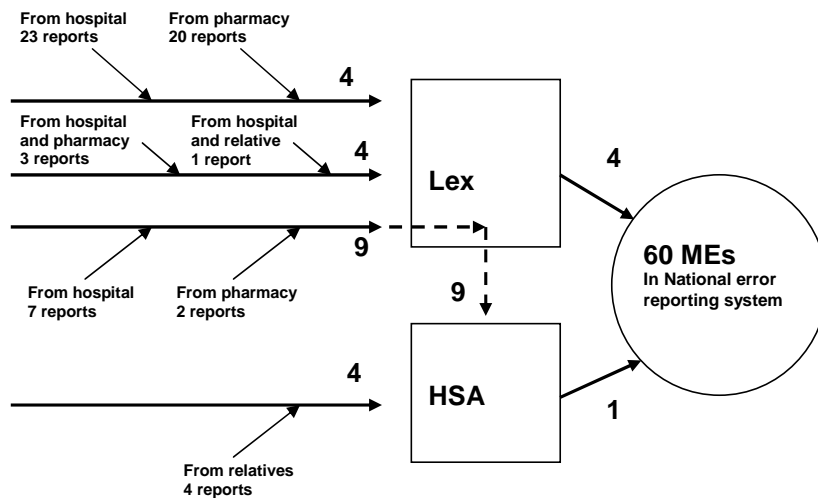


Figure 1. Origin of reports. A total of 56 reports were filed according to lex Maria. Nine of these were reported to HSAN from NBHW, together with four reports from relatives a total of 13 were investigated by HSAN.

A total of 60 MEs meeting the inclusion criteria were found. The case reports were read and tables were compiled based on:

- Cytotoxic drugs involved.
- Type of error: wrong dose (too high, too low), wrong drug, wrong patient, wrong ambulatory pump, other.
- Where the error occurred in the medication use process (i.e. in prescribing and transcribing, preparation or administration).
- The error detection mechanisms (i.e. how and by whom the error was discovered).
- The consequences for the patient according to the NCC MERP Index for Categorising Medication Errors [11] of the National Coordinating Council for Medication Error Reporting and Prevention, USA. This index was used for classification of the severity of the outcome: Category B-D *Error, No harm*; Category E-H *Error, Harm*, and Category I *Error, Death* (i.e. an error occurred that may have contributed to or resulted in the patient's death). Category A is *No Error* and thus was not included.

In 50 (83%) of the MEs the patient was an adult, and in 10 (17%) of the events a child.

## Results

Table 1 gives examples of some typical MEs. A brief compilation of all 60 MEs can be found in [12].

ID No	Report	Drug	Where	What happened/Discovered/Consequences
#6	Lex Maria	Cisplatin should have been cyclophosphamide	University hospital	Patient received another patient's drug, 30 mg of cisplatin instead of cyclophosphamide. <i>Nurse discovered during further preparation and informed the doctor.</i> The patient had to stay at hospital for 1 night. The treatment was delayed for 1 week. No permanent harm.
#16	Lex Maria	Doxorubicin	Pharmacy	Pump run at too high a speed during preparation; home pump delivered drug during 1 instead of 48 hours. <i>Discovered by patient/nurse when the infusion was so quick.</i> Extra treatment prescribed. Probably no harm.
#18	Lex Maria HSAN	Vincristine	University hospital	Dose that was 10 times higher than prescribed. A dose of 2.0 mg became 20 mg when prepared by a nurse. <i>Discovered the same afternoon during nursing rounds; her colleagues reacted.</i> Serious neurological harm; treated in respirator for a period. The patient died after 7 months.
#19	Lex Maria HSAN	Cisplatin	Pharmacy	Double dose prepared. Prescription "Cisplatin 0.5 mg, 190 mg, 380 mL to be diluted in 2x1000 mL NaCl 9 mg/mL" was interpreted as a dose of 380 mg. <i>The first pharmacist pondered the dose in the evening, contacted the hospital and the error was discovered.</i> Patient became deaf.
#40	HSAN	Etoposide	University hospital	Total dose for the course became dose per day, 330 mg, 3 times per day for 3 days, should have been 110 mg, 3 times per day for 3 days. <i>Nurse suspected that the dose was too high and treatment was not given on day 3.</i> Patient suffered from anaemia and was hospitalised for two weeks.
#53	Lex Maria	Carboplatin	County hospital	Prescription for five days should have been only for one day. Due to hearing disturbances from cisplatin, there was a switch to carboplatin. Dose 800 mg per day. <i>Discovered when the patient came back with adverse reactions, hospitalised for a week.</i> Probably no long-term harm.

Table 1. Examples of medication errors reported according to lex Maria and/or HSAN.

The most commonly involved cytotoxic drugs were fluorouracil, followed by carboplatin, cytarabine, and doxorubicin (Table 2). In five of the cases two drugs were involved in the error. Fluorouracil was used in ambulatory pumps and in three of the errors the wrong pumps were used in preparation. This resulted in the dose being delivered too fast. Doses that were too high were prescribed and there were mix-ups with other drugs during preparation. Two of the errors involving carboplatin occurred when it replaced cisplatin due to the latter's adverse effects on the kidneys and hearing. Carboplatin should then have been given for only one day but was mistakenly given for three or five days, which is the normal length of the treatment for cisplatin. One child and two adult patients received overdoses of carboplatin due to a misinterpretation of the Calvert formula on two different occasions. There was also a mix-up during preparation by the nurse resulting in the use of carboplatin instead of cisplatin. Total dose for a treatment period was misinterpreted as dose per day leading to overdoses of carboplatin and melphalan. For cytarabine four of the errors were too high doses, including two cases with tenfold errors, both of which occurred during preparation at the pharmacy.

Four of the errors involving doxorubicin were too high doses, a mix-up with epirubicin and the use of the wrong ambulatory pump.

<b>Drug</b>	<b>Number of medication errors</b> (incl. when used in combinations of drugs)	<b>Category of medication error*</b>
Fluorouracil	9	death (1); harm (3); no harm (5)
Carboplatin	6 (7)	death (1); harm**) (5); no harm (1)
Cytarabine	6 (7)	harm (2); no harm (4)
Doxorubicin	4 (7)	no harm (4)
Vincristine	4 (6)	harm (3); no harm (1)
Cisplatin	4	death (1); harm (2); no harm (1)
Etoposide	4	death (1); harm (2); no harm (1)
Cyclophosphamide	2 (3)	no harm (2)
Melphalan	2 (3)	death (1); harm (1)
Methotrexate	2	harm (1); no harm (1)
Others	12	harm (4); no harm (8)
Doxorubicin and vincristine	2	harm (1); no harm (1)
Carboplatin and melphalan	1	death (1)
Daunorubicin and cytarabine	1	no harm (1)
Doxorubicin and cyclophosphamide	1	harm (1)
<b>Total</b>	<b>60</b>	<b>death (6); harm (25); no harm (30)</b>

\*) Note that Category I *Error, Death* is an error that may have contributed to or resulted in the patient's death.

\*\*) One ME involved two patients.

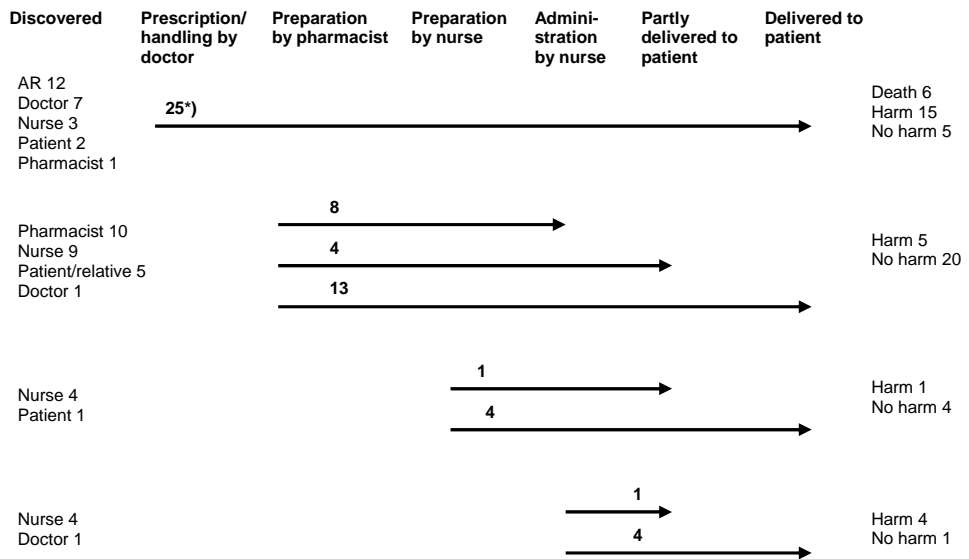
Table 2. Cytotoxic drugs involved in the medication errors and consequences for the patients.

Each of the MEs was classified into one of six categories (Table 3). Doses that were too high originating from prescribing and transcribing or preparation were the largest category. Tenfold errors were made by doctors (cyclophosphamide), pharmacists (cytarabine, twice), and nurses (vincristine). In two of the MEs, including the tenfold error with cyclophosphamide, the error occurred during transcription from the doctors' prescriptions to the orders to the pharmacy. These have to be signed by the doctor making him/her responsible for the error. The wrong drug being used during preparation, both by pharmacists and nurses, or prescription was the second largest category. Examples of mix-ups between drugs were vincristine-vinblastine, docetaxel-paclitaxel, and cytarabine-ifosfamide. Totally, there were 18 cases where drugs were mixed up. The wrong ambulatory pump was used during preparation by pharmacists in four cases, typically resulting in too quick a rate of infusion. In five of the MEs the drug was administered to the wrong patient.

<b>Error</b>	<b>Prescribing and transcribing by doctors</b>	<b>Preparation by pharmacist</b>	<b>Preparation by nurse</b>	<b>Administration by nurses</b>
Wrong dose: too high	18	7	2	
ong drug	3	13	2	
Wrong patient				5
Wrong ambulatory pump		4		
Wrong dose: too low or not specified	1	1		
Other	3		1	
Totally	25	25	5	5

Table 3. Error type and where in the medication use process the error occurred.

Twenty-five of the MEs (42%) occurred when doctors were prescribing or transcribing an order to the pharmacy. Twenty-five of the MEs (42%) occurred within the pharmacies, and the remaining 10 MEs (16%) occurred when the nurses prepared (5 MEs) or administered the drug to the wrong patient (5 MEs), see Figure 2. When the ME started at the prescribing stage, all of the cytotoxic preparations were delivered to the patient. The mistakes were revealed by an adverse reaction in the patient or found later by a professional or the patient. There were cases where the first dose in a treatment regimen was given and then the error was discovered. The doctor was informed and further treatment could be corrected or adjusted and necessary supportive care given.



\*) One ME involved 2 patients.

Figure 2. Start and fate of the investigated medication errors. It shows if the drugs were delivered to the patient or if the error was intercepted. The left column lists who discovered the ME or if it was discovered due to an adverse reaction (AR). The right column lists the consequences for the patients.

If the ME started at the pharmacy, nurses stopped delivery of the infusion to the patient in eight of the cases. In Sweden nurses have to check the labelling from the pharmacy to see if it corresponds to the prescription written by the doctor. Five of the intercepted MEs were discovered this way. The others were discovered due to precipitations in one case, and to the wrong colour of the infusion in two cases (should have been yellow for methotrexate and red for doxorubicin). A pharmacist intercepted the on-going treatment in four cases, and in 13 cases the drug was delivered to the patient. When the erroneous preparations were prepared by a nurse, all but one were delivered to the patient. It was the same for administration of a preparation to the wrong patient: all but one were delivered.

The consequences for the patients were especially severe when the doctor made an error in prescribing and transcribing. Six of these MEs were judged as Category I, *Error, Death*, 15 as Category E-H, *Error, Harm*, and five as Category B-D, *Error, No harm*. When the ME started during preparation it led to *Harm* in five and *No harm* in 20 of the cases; 12 of them were intercepted.



## Discussion

The most severe MEs in this study occurred during prescribing and transcribing by doctors. All six errors classified as *Error, Death* and 15 of the 25 errors classified as *Error, Harm* started at this stage. We are convinced that almost all MEs belonging to *Error, Death* were reported to the databases used in this study. Based on this we can state that most severe MEs in Sweden start with errors in prescribing and transcribing by doctors. Similar results were found in a study by Gandhi et al. [13]. In other studies the stage responsible for most of the errors [14-15] or the most fatal outcome was administration [16]. The difference in results may be due to different material, to different definitions in the studies or to national/cultural differences.

It is interesting to note that of the 14 errors intercepted in total in our investigation, none started in the prescribing and transcribing stage. In a study from the USA data from the U.S. Pharmacopeia Medication Errors Reporting Program was reviewed [17]. The authors found that in some of the cases (5/40) nurses and pharmacists intercepted the wrong medication which was ordered. Most certainly there are also such interceptions in Sweden, but for some reasons they are not reported according to lex Maria while some other interceptions of errors starting at other stages are. This points at a weakness in the national database (lex Maria). The databases run by individual hospitals are hopefully better for learning from intercepted errors.

Nurses sometimes acted as barriers against errors occurring during preparation by pharmacists. Ways to improve the nurses' role as a barrier against errors ought to include thorough checking that the label and prescription correspond together with ample training and good experience. When nurses prepared or administered the drug to the patient, the error was seldom detected. In one of the cases the patient detected an error before the drug was administered. If patients are properly informed of the treatment, they can be involved in detection and prevention of errors as proposed in [3]. Interestingly, in some cases both pharmacists and nurses realised their mistakes themselves the same day or within 24 hours. This may be due to the practical handling of drug vials, syringes, infusions or patients. When they realised their mistakes they acted promptly to stop the infusion if it was possible and informed the doctor.

In several cases the drugs containing platinum caused serious consequences for the patients leading to death, hearing loss or depressed immune system and infection. Serious consequences with platinum containing drugs are also described in [2,16-17]. The same types of errors with the drugs found in this study have previously been presented in single case studies. This strengthens that we can learn from them and the precautions we can take in our organisations. In the single case studies, it was a misinterpretation of the Calvert formula that resulted in an overdose of carboplatin in two children [18]. One case report describes a prescribing and administration error of cisplatin [19] and another report describes a cisplatin preparation error [20].

In this study the most common error types were wrong dose and wrong drug. This is similar to other studies, such as [2,14,17]. Only a few errors with too low dose ( $\leq 2$  compared to 18 with too high doses) were reported in this study indicating underreporting. Too low dose can lead to therapeutic failure with serious consequences and should be reported and learnt from. Some of the causes for errors with too high doses or the wrong drug are well described. Tenfold or decimal point errors are a well recognised risk to patients, existing in the prescribing, preparation, and administration steps of the medication use system [21]. Look-alike and sound-alike drugs in oncology may cause or contribute to potentially harmful

medication errors and there have been attempts to identify the drugs at risk [22-23]. The problems with patient misidentification in oncology care have also been reported [24].

The pharmacies reported MEs where the error meant a risk for the patients; the drug was not fully delivered to the patient in nearly half of the MEs. The healthcare facilities reported only a few MEs where the administration was intercepted. This could be explained, for example, by differences in the judgement processes (lex Maria or not), by differences in organisations, size of organisations or culture. It may also be because pharmacies belong to another organisation and prefer to receive an independent judgement from the authorities.

In ten (17%) of the cases the patient was a child. Compared to the number of children receiving cancer treatment every year this may be seen as high. There are several possible explanations: the great variation in size among children, dosing both according to body surface and per kg, and different methods for the calculation of body surface increasing the possibilities for errors. The treatment itself can be very complex and involve a risk to the patient. Another explanation may be that the parents closely follow the treatment and notice any problem, leading to more reports.

There are circumstances that have to be considered when interpreting this study. Cases from 1996 to 2008 were analyzed and during this time there were several changes, such as in treatment protocols, drugs available, and in the work for improvements of patient safety. Furthermore, our data was limited to the content of the written reports from the NBHW or HSAN. The reports vary in quality and amount of information provided due to different authors and changes over the years. In the last years of the investigation period, the healthcare facility or pharmacy had made a root cause analysis before sending the report to NBHW, thus giving more comprehensive information. The data collected were limited to the content and ease of data extraction from the national risk database. Reporting to that risk database ended in mid 2006 making it difficult to find all relevant reports after that. In addition, due to one of the author's contacts with colleagues at pharmacies and with university hospital staff, there probably is an overrepresentation of MEs from these two venues. Another concern is underreporting. Thus, the number of MEs in the study period was probably not reflective of a true incidence rate. This may be supported by the fact that 4 of the 60 reports were filed by relatives of the patient and not by the healthcare facility. It is also supported, as already mentioned, by the fact that we had no MEs initiated at the prescribing and transcribing stage that were intercepted. More reports and reports of good quality offer better opportunities for analysis and suggestions for improvements.

In this study we describe the characteristics of the MEs. Most of these error types identified have been described previously in the literature, which means that studies like this can be used as a source of information for improved patient safety. It is of utmost importance to minimise the potential for errors in the prescribing stage. This could be done using CPOE not only for prescribing but also for the whole medication use process. One example of development and implementation of CPOE is presented by Greenberg et al [25]. The identification of drugs and patients should also be improved (e.g. by bar coding). The use of bar-coding and telepharmacy during preparation has been presented by O'Neale et al [26]. These technologies provide a means to improve the accuracy of preparations by decreasing the likelihood of using incorrect products or quantities of drug.

The next step will be to examine why these errors occurred. We plan to investigate the same material for system failures and missing barriers or barriers that did not capture the errors:

Are there any common patterns? What other lessons can be learnt from these MEs and what countermeasures need to be taken?

### **Acknowledgements**

We would like to thank the Swedish National Board of Health and Welfare together with the Swedish Medical Responsibility Board for their kind assistance in the data retrieval.

## References

1. Erdlenbruch B, Lakomek M, Bjerre LM. Editorial: chemotherapy errors in oncology. *Med Pediatr Oncol* 2002; 38: 353-6.
2. Phillips J, Beam S, Brinker A *et al*. Retrospective analysis of mortalities associated with medication errors. *Am J Health Syst Pharm* 2001; 58: 1835-41.
3. Schwappach DLB, Wernli M. Medication errors in chemotherapy: incidence, types and involvement of patients in prevention. A review of the literature. *Eur J Cancer Care (Engl)* 2010; 19: 285-92.
4. Institute for Safe Medication Practice (ISMP) High Alert Medication List: <http://www.ismp.org/Tools/highalertmedications.pdf> Accessed [2010 Dec 03].
5. Svedmyr D, Apoteket Farmaci AB, personal communication 2011 February 10.
6. The National Board of Health and Welfare, Lex Maria: <http://www.socialstyrelsen.se/lexmaria> Accessed [2010 Nov 8].
7. The National Board of Health and Welfare, Lex Maria, Statistics: <http://www.socialstyrelsen.se/statistik/statistikefteramne/lexmaria> Accessed [2010 Nov 29].
8. Fryksmark U, The National Board of Health and Welfare, personal communication 2011 February 10.
9. Medical Responsibility Board (HSAN): <http://www.hsan.se/eng/fel.asp> Accessed [2010 Dec 6].
10. Ferner RE, Aronson JK. Clarification of terminology in medication errors: definitions and classification. *Drug Saf* 2006; 29: 1011-22.
11. National Coordinating Council for Medication Error Reporting and Prevention, Types of Medication Errors: <http://www.nccmerp.org/pdf/indexBW2001-06-12.pdf> Accessed [2010 Nov 3].
12. Lund University, publications: <http://lup.lub.lu.se/luur/download?func=downloadFile&recordOid=1786272&fileOid=1786278> Accessed [2011 Feb 24].
13. Gandhi TK, Bartel SB, Shulman LN *et al*. Medication safety in the ambulatory chemotherapy setting. *Cancer* 2005; 104: 2477-83.
14. Rinke ML, Shore AD, Morlock L *et al*. Characteristics of pediatric chemotherapy medication errors in a national error reporting database. *Cancer* 2007;110: 186-95.
15. Walsh KE, Dodd KS, Seetharaman K *et al*. Medication errors among adults and children with cancer in the outpatient setting. *J Clin Oncol* 2009; 27: 891-6.

16. Zernikow B, Michel E, Fleischhack G *et al.* Accidental iatrogenic intoxications by cytotoxic drugs: Error analysis and practical preventive strategies. *Drug Safety* 1999; 21: 57-74.
17. Mehta P, Beltz S, Cousins D. A review of the national chemotherapy errors database and recommendations for safe administration. *Int J Pediatr Hematol Oncol* 1998; 5: 463-73.
18. Liem RI, Higman MA, Chen AR *et al.* Misinterpretation of a Calvert-derived formula leading to carboplatin overdose in two children. *J Pediatr Hematol Oncol* 2003; 25: 818-21.
19. Pourrat X, Antier D, Crenn I *et al.* A prescription and administration error of cisplatin: a case report. *Pharm World Sci* 2004; 26: 64-5.
20. Vila-Torres E, Albert-Mari A, Almenar-Cubells D *et al.* Cisplatin preparation error; patient management and morbidity. *J Oncol Pharm Pract* 2009; 15: 249-53.
21. Lesar TS. Tenfold medication dose prescribing errors. *Ann Pharmacother* 2002; 36: 1833-9.
22. Schulmeister L. Look-alike, sound-alike oncology medications. *Clin J Oncol Nurs* 2006; 10: 35-41.
23. Kovacic L, Chambers C. Look-alike, sound-alike drugs in oncology. *J Oncol Pharm Pract* 2010; 0: 1-15.
24. Schulmeister L. Patient misidentification in oncology care. *Clin J Oncol Nurs* 2008; 12: 495-8.
25. Greenberg A, Kramer S, Welch V *et al.* Cancer Care Ontario's computerized physician order entry system: a province wide patient safety innovation. *Healthc Q* 2006; 9 Spec No: 108-13.
26. O'Neal BC, Worden JC, Coudry RJ. Telepharmacy and bar-code technology in an i.v. chemotherapy admixture area. *Am J Health Syst Pharm* 2009; 66: 1211-7.



