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Use of a prospective risk analysis method to improve the safety of the cancer chemotherapy process

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Abstract

Objective. To perform a risk analysis of the cancer chemotherapy process, by comparing five different organizations. To quantitatively demonstrate the usefulness of centralization and information technologies, to identify residual risks that may be the target of additional actions.

Study design. A reengineering of the process started in 1999 and was planned to be finished in 2006. The analysis was performed after the centralization and at the beginning of information technologies integration.

Setting. Two thousand two hundred beds university hospital, with medical, surgical, haematological, gynaecological, geriatric, paediatric oncological departments. Twelve thousand cancer chemotherapies each year.

Methods. According to the failure modes, effects and criticality analysis (FMECA) method, the failure modes were defined and their criticality indexes were calculated on the basis of the likelihood of occurrence, the potential severity for the patients, and the detection probability. Criticality indexes were compared and the acceptability of residual risks was evaluated.

Results. The sum of criticality indexes of 27 identified failure modes was 3596 for the decentralized phase, 2682 for centralization, 2385 for electronic prescription, 2081 for electronic production control, and 1824 for bedside scanning (49% global reduction). The greatest improvements concerned the risk of errors in the production protocols (by a factor of 48), followed by readability problems during transmission (14) and product/dose errors during the production (8). Among the six criticality indexes remaining superior to 100 in the final process, two were judged to be acceptable, whereas further improvements were planned for the four others.

Conclusions. Centralization to the pharmacy was associated with a strong improvement but additional developments involving information technologies also contributed to a major risk reduction. A cost-effect analysis confirmed the pertinence of all developments, as the cost per gained criticality point remained stable all over the different phases.

Keywords: proactive, prospective, risk assessment, FMECA, failure mode, cost-effect analysis, cancer chemotherapy, information technologies

Antineoplastic agents are very commonly used to treat cancer and some other non-neoplastic diseases. These substances can have acute effects (irritation of skin, eyes, mucous membranes, nausea, and vomiting) in case of intoxication and can also cause chronic problems, due to their mutagenic, teratogenic, and carcinogenic effects.

Numerous cases of errors leading to inappropriate treatment, severe patient injuries or deaths are reported in the literature. Errors can occur during the three major steps of medication process—prescribing, compounding, and administration—and include under- and overdosing, schedule and timing errors, wrong drugs, infusion-rate errors, wrong administration route, omission of drugs or hydration, improper preparation of drugs, and chemotherapy given to the wrong patient [1]. The prevalence of medication errors associated with antineoplastic agents, as with other drug categories, is not precisely known, but one study, based on self-reporting, estimated a chemotherapy overdose error rate of 0.06%, with 13% of the responding centers having experienced at least one case [2]. Another study, based on direct observation, measured, in a centralized setting, overall and major preparation error rates of 0.45 and 0.19%, respectively [3].

To circumvent risks for healthcare workers and patients, several major principles are widely applied. It is recommended to centralize the preparation in the pharmacy, in class II vertical laminar airflow cabinets or isolators, to limit the number of persons handling antineoplastic agents and to better protect them [4]. Some authors have also demonstrated

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the usefulness of closed transfer systems to reduce surface contamination and recovery of antineoplastic agents in the urine [5,6]. The most frequently cited actions to minimize the risk of errors in the process are to improve the education of physicians, pharmacists, and nurses, to standardize prescriptions by creating template order sets, to increase the performance of dose-verification by multiplying independent checks, and to improve patient information [7–13]. These actions have established their interest in saving work time and reducing costs, but few studies have addressed parameters potentially influencing the safety. Information technologies can theoretically be useful to secure the whole process, but a careful evaluation of their benefits and risks is needed [14]. We have found a single published study measuring a reduction of antineoplastic prescription errors after the introduction of a computerized system [15].

Risk reduction in the cancer chemotherapy process should be a major objective for all hospitals, as the consequences can be dramatic. The best way to improve the safety is, however, difficult to predict and to evaluate, because the incident rate is low and therefore the measurement of error rate reduction is hard. A study suggested the use of a prospective risk analysis to select the most relevant actions to undertake and measured a 23% reduction in prescription errors [16]. Although this approach was interesting, the measurement of impact addressed only the prescription and was based on spontaneous incident reporting, which is not a robust method.

To analyze reliability problems, there has been a growing awareness that prospective risk analysis approaches used in several high-hazard industries need to be applied to health care. In the United States, the Joint Commission on Accreditation of Health Organizations (JCAHO) has since 1 July 2001 required each accredited hospital to conduct at least one proactive risk assessment annually [17].

Among other methods, failure modes, effects and criticality analysis (FMECA) is a well described tool that assesses systematically a process. It identifies possible or likely errors ('failure mode'), and gauges what their effect will be, even before they take place [18]. FMECA includes a quantitative evaluation of the criticality of each failure mode. The criticality indexes (or risk priority number, RPN [19]) are calculated by multiplying three components—likelihood of occurrence, severity, and detection—on the basis of known or estimated data. FMECA classifies the failure modes and determines the top critical events, which is very helpful to evaluate the acceptability of existing risks and to prioritize actions to improve the safety.

We started to apply FMECA in our hospital by reengineering the paediatric parenteral nutrition production, with a significant reduction of the criticality [20]. The method has proved to be a useful tool and we decided to apply it to other high-risk processes, like cancer chemotherapy.

About 12000 cancer chemotherapies are administered each year in our 2200 beds university hospital, in medical, surgical, haematological, gynaecological, geriatric, and paediatric departments. The production was totally centralized at the pharmacy between 1999 and 2002 and developments involving information technologies were initiated in 2002.

The objectives of this study were to perform a comparative risk analysis of five different process organizations, from decentralized to centralized production, with several levels of information technologies, to quantitatively evaluate safety improvements provided by these developments and to identify major residual risks that may be the target of additional actions.

Methods

The FMECA comparative risk analysis focused on five consecutive process organizations, reflecting the evolution over time. They are summarized in Table 1. Phase 1 was a totally decentralized and handwritten system: drugs were reconstituted by nurses in vertical laminar airflow cabinets in good manufacturing practice (GMP) unclassified rooms, with the help of predefined protocols only in some cases. Prescription protocols existed in some areas. Phase 2 was a centralized and handwritten process: all chemotherapeutic agents were produced at the pharmacy, in negative pressure isolators placed in a GMP grade C cleanroom. Prescriptions, mostly structured as protocols, were transmitted by fax and validated by pharmacists. The drugs were produced according to a pre-established protocol, completed and double-checked on the basis of prescription indications. The phase 3 implemented a computerized prescription based on predefined protocols, with an automatic calculation of production protocols, as well as direct printing of labels. The electronic tool was developed in-house by our Medical Informatic Department and was compatible with our electronic patients record. The phase 4 modified the production step, with the addition of an electronic check of product identity and weighing (CATO® program, interfaced to our prescription tool, see http://www.cato.at). In phases 1–3, the adequation of drug withdrawals was based on operator's reliability. Finally, phase 5 added an electronic control by scanning just before the administration, to verify the concordance between the drug and the patient, by the way of radiofrequency identification (RFID) tags placed on them and containing the necessary information. In phases 1–4, this control was a cognitive task carried out by nurses, with the help of a paper checklist reminding them the control points. All over the study period, physicians and nurses also significantly improved the administration of care, by developing and applying standardized operating procedures. At the time the analysis was done, in 2004, the process was running according to phase 2. Phase 3 was in an advanced state of development and phases 4 and 5 were starting.

The analysis was used to quantify the improvements consecutive to the centralization of production to the pharmacy (evolution from phases 1–2) and to evaluate what would be the impact of information technologies implementation at different levels of the process (phases 3–5). This analysis was performed according to the methodology previously described [20,21]:

Team definition

1. A team including four pharmacists (head of quality assurance, head of production, head of cytostatic reconstitution unit, and chief pharmacist) was formed for the main part of the analysis. An oncologist and a nurse specialized in oncology were associated for the

Table I Brief description of five studied phases of cancer chemotherapy process

	Decentralized (phase 1)	Centralized (phase 2)	Electronic prescribing (phase 3)	Production with CATO® (phase 4)	Bedside scanning (phase 5)
Prescription	Handwritten	Handwritten	**Electronic**	Electronic	Electronic
Transmission	Manual to the nurses	**Fax to the pharmacy**	**Electronic**	Electronic	Electronic
Validation	By the nurses	**By the pharmacist**	By the pharmacist	By the pharmacist	By the pharmacist
Production protocol	Protocols in some cases	**Calculation from a model + double-check**	**Direct electronic calculations**	Direct electronic calculations	Direct electronic calculations
Label edition	Handwritten	**Printed after transcription**	**Printed directly from prescription**	Printed directly from prescription	Printed directly from prescription
Material preparation	By nurses from prescription	**By pharmacist from protocol + double-check**	**Direct listing from prescription**	Direct listing from prescription	Direct listing from prescription
Production	By nurses in VLAC Non-GMP classified background	**In the pharmacy, isolators with GMP classified background**	In the pharmacy, isolators with GMP classified background	**Unchanged, with weighing control**	Unchanged, with weighing control
	No external control	**No external control**	No external control		
Delivery to the ward	No sending	**By hospital transport system**	By hospital transport system	By hospital transport system	By hospital transport system
Administration	Traditional controls	**Controls helped by a checklist**	Controls helped by a checklist	Controls helped by a checklist	**Electronic control**

GMP, good manufacturing practice; VLAC, vertical laminar airflow cabinet.

evaluation of prescription and administration steps, respectively.

Failure modes definition

2. The main steps of anticancer chemotherapy process, from the prescription to the administration, were defined by the team.
3. A brainstorming was organized to determine the ways the process could fail at each step. The team had to answer the following question 'What could possibly go wrong with this process step?'. The discussion was synthesized, and the failure modes were determined.

Criticality analysis

4. The likelihood of occurrence (incidence) for each failure mode was classified from 1 to 10, the severity of the potential effect for the patient from 1 to 9 and the chance to detect the failure from 1 to 9. Estimations were obtained by consensual quotations in the team for all failure modes, and also with the oncologist or the specialized nurse for the prescription and administration steps, respectively. The evaluation was carried out on the basis of explicit criteria, published elsewhere [20,21], by taking care of being as coherent as possible in the quotations of similar events.
5. The criticality index of each failure mode was calculated by multiplying the frequency, effect, and detection scores (minimum, 1; maximum, 810).
6. Results were summarized in a table comparing the criticality indexes for each mode of failure in the five process organizations.

Data analysis

7. The table of criticality indexes was analyzed by the team to compare risks associated with the five process organizations, to quantify the gained security obtained with the centralization and expected with further information technologies implementation. The sum of criticality indexes for the five processes were compared to determine the global improvement in the process security and the potential impact on patient outcome. For each mode of failure, the evolution of the criticality was discussed and the acceptability of the residual risk was evaluated . When it was not considered to be appropriate, additional improvements were planned.

Results

Failure modes definition

The process was split into nine major steps: prescription, transmission, validation, edition of the production protocol, edition of labels, material preparation, production, delivery to the ward, and administration. Twenty-seven failure modes were determined during the brainstorming.

Criticality analysis

The criticality indexes calculated from the defined frequency, severity, and detection scores for each of the failure modes are described in Table 2. The sum of criticality indexes was 3596, 2682, 2385, 2081, and 1824 for phases 1–5, respectively (Figure 1). The evolution led to criticality index reductions of –914 (–25%) from phase 1 to 2, –297 (–11%) from phase 2 to 3, –304 (–13%) from phase 3 to 4, and –257 (–12%) from phase 4 to 5. From phases 1 to 5, the total criticality diminished 1772 points (–49%) and the individual criticality indexes were reduced by a mean factor of 4.4.

For 17 out of 27 failure modes, the criticality index was smaller in the final than in the initial process, whereas the risk remained unchanged for seven and was slightly increased for two. A new mode of failure—error during the writing or validation of production protocol—appeared in phase 2. Phase 2 (centralization) contributed to reduce the criticality of 12 failure modes; the phase 3 of 5, the phase 4 of 2, and the phase 5 of 5. The criticality of seven failure modes was reduced twice during the whole process of re-engineering. The number of indexes greater than 100 diminished from 13 in the initial

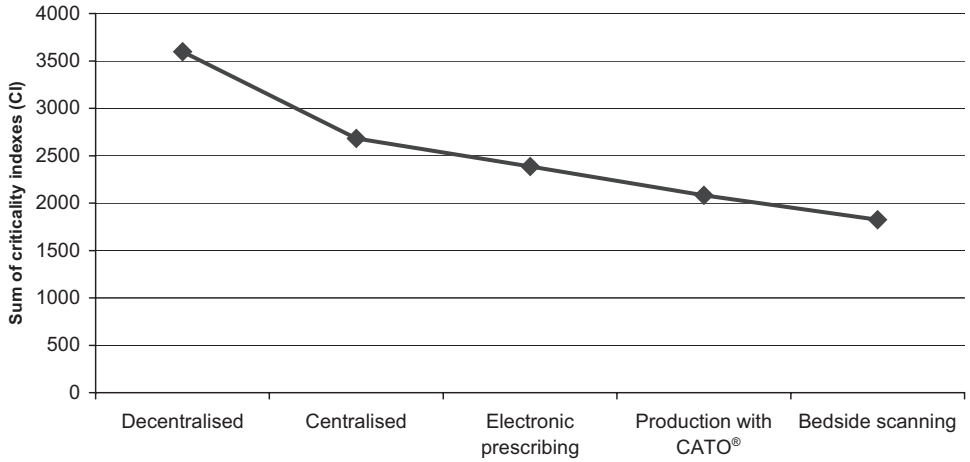

Figure 1 Evolution of the total criticality indexes (CI) in the five process organizations.

Table 2 Failure modes and comparative criticality indexes (CI) for the five process organizations

Step	Failure modes	CI				
		Decentralized	Centralized	Electronic prescribing	Production with CATO®	Bedside scanning
Prescription	Prescription protocol writing or validation error	**175**	**175**	**175**	**175**	**175**
	Choice of the wrong protocol	**147**	**147**	**147**	**147**	**147**
	Prescription error (i.e. dose, patient, route)	**135**	**135**	*54*	54	54
Transmission	Late or forgotten transmission	42	42	42	42	42
	Readability problems	98	*70*	*7*	*7*	*7*
Validation	Failure to detect prescription error	**343**	***175***	**175**	**175**	**175**
Production protocol	Production protocol writing or validation error	–	63	63	63	63
	Dosage error in production protocol	**432**	***108***	*9*	9	9
Label edition	Error in label	75	*45*	*18*	18	18
Material preparation	Error in material preparation	**135**	*81*	*54*	54	54
	Use of expired drug	27	*12*	12	12	12
	Needed product is missing	9	*6*	6	6	6
Production	Late or forgotten production	6	8	8	8	8
	Production error (product/dose)	**432**	***288***	**288**	*54*	54
	Labelling error (inversion)	**140**	***112***	**112**	*42*	42
	Microbial contamination during production	**288**	***144***	**144**	**144**	**144**
	Operator contamination	54	*18*	18	18	18
Delivery to the ward	Delivery to the wrong ward	8	24	24	24	24
Administration	Wrong patient	105	*84*	84	84	*21*
	Wrong administration route	**144**	**144**	**144**	**144**	*72*
	Wrong flow rate	**120**	**120**	**120**	**120**	*48*
	Wrong administration day/time	40	40	40	40	*20*
	Wrong conservation or drug expired	60	60	60	60	*30*
	Nurse contamination	45	45	45	45	45
	Patient contamination	32	32	32	32	32
	Microbial contamination during administration	**252**	**252**	**252**	**252**	**252**
	Extravasation	**252**	**252**	**252**	**252**	**252**
Sum		**3596**	**2682**	**2385**	**2081**	**1824**
Mean		**138**	**99**	**88**	**77**	**68**

Values in italics denote reduction of the criticality, underlined values denote increase of the criticality, and boldface values denote criticality index greater than 100.

process to 12 in phase 2, 10 in phase 3, 8 in phase 4, and 6 in final process.

The highest risks in the initial process were computed for errors (product or dose) during the production (CI = 432), errors in the production protocol (432), failure to detect a prescription error during the validation (343), and microbial contamination during production (288). In the final process, the most critical steps were risk of extravasation (252), microbial contamination during the administration (252), error during the writing/validation of prescription protocol (175) and failure to detect a prescription error during the validation (175).

The greatest risk reductions between the initial and the final processes concerned the risk of dosage errors in the production protocol (by a factor of 48), followed by readability problems during the transmission (by a factor of 14) and errors (product or dose) during the production (by a factor of 8). The two failure modes with an increased risk, as well as the new failure mode were associated with very low to low criticalities (criticality indexes = 8, 24, and 63).

Data analysis

Analyzes of the global impact concluded that each process evolution significantly increased the patient safety, by acting on complementary steps in the process. The largest gains were obtained by systematically formalizing the production protocols and by adding information technologies to reduce calculation errors and to control the production itself.

The residual risks in the final process were examined to evaluate their acceptability. Among the six criticality indexes remaining superior to 100, two of them—the microbial contamination during the production and during the administration—were judged to be acceptable, because of the classified environment used for the production and the strict procedures in place to avoid the occurrence of such an incident. At the opposite, the residual risks of the four others were judged to be unacceptable and additional safety improvements were therefore considered. To reduce the risk of error during the writing of prescription protocols, it was suggested to add a validation step by a second physician. This action will not have any impact on the likelihood of occurrence but will increase the detectability of errors. To reduce the risk of error in the choice of protocol and to improve the capacity of pharmacists to detect prescription errors, a modification of protocol organization, and classification is proposed. Finally, an interdisciplinary project was launched to reduce the frequency of extravasation and minimize their severity. The objectives were to edit institutional procedures for the administration of antineoplastic drugs and for the management of extravasations and to analyze reported incidents to start a continuous improvement process. These three additional actions should contribute to an additional reduction of the process criticality.

Discussion

The FMECA method confirmed a major safety improvement associated to the re-engineering of the anticancer chemotherapy process. A reduction of the criticality associated to most of the failure modes was observed, with a total reduction of nearly 50%. Even though such a process can obviously not avoid all errors, the risk for the patient to receive a chemotherapy with a wrong product or dosage has markedly been reduced. Furthermore, the analysis identified and classified the residual risks and thereby confronted investigators with either accepting the determined level of risk or planifying further improvements of the process. In this analysis, the most critical steps in the final process were considerably lower than in the initial process.

To centralize the production of cancer chemotherapies at the pharmacy is the most common organizational measure taken by hospitals to protect their healthcare workers from exposure. Our analysis demonstrated that the centralization also markedly improves the safety for patients, especially by increasing the detection of prescription errors (validation by a pharmacist) and by limiting production errors (production protocols). However, with this single process modification, some failure modes still have a high criticality, and this should encourage institutions to take additional measures. Our study determined a significant reduction of the global criticality by introducing electronic devices at the prescription, production, and administration steps, suggesting that these technologies could play an interesting complementary role to the centralization.

One of the major limitations of safety improvements is the cost of re-engineering. Indeed, a process modification is only worth value if the related costs are proportional to the expected improvement and when the costs are judged to be too high, the residual risks should be accepted. In our case, we roughly estimated the development costs (transformation of production unit, isolators purchase, and information technologies developments) for the four migration steps and calculated the average cost by gained point of criticality. The cost was Frs. 328/point (205 Euros/point) for the centralization, Frs. 236/point (148 Euros/point) for electronic prescribing, Frs. 164/point (103 Euros/point) for electronic guided production, and Frs. 195/point (122 Euros/point) for bedside scanning. These results, illustrated in Figure 2, confirmed the pertinence of all the developments, as the criticality/costs curve remained almost linear, even with a tendency to a reduction of the price per gained point over the evolution. Conversely, if the curve would be exponential, with a major increase of the price per gained point, one should renounce to further improvement and accept the residual risks.

The major interests of FMECA are its simplicity and the quantitative evaluation it allows by combining three complementary factors: likelihood of occurrence, severity, and detectability. It helps identifying the top critical events, which is very helpful to decide and prioritize actions to be taken. Moreover, the active discussions necessary to find consensual quotations contribute to the development of a very clear and shared vision of the process organization, taking into account all the different perspectives.

The major limitation of FMECA is an unavoidable part of subjectivity in the selection of failure modes as well as the determination of the criticality indexes. The team should be large and multidisciplinary enough to buffer this bias. In our

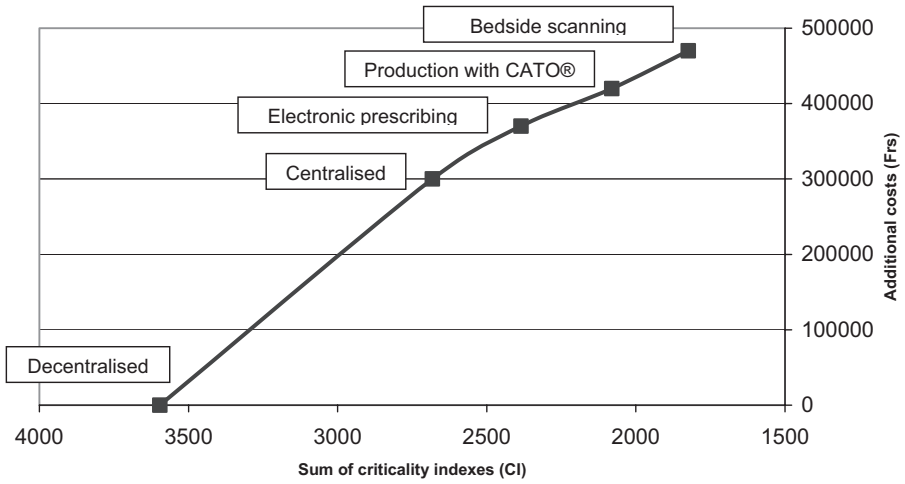

Figure 2 Additional costs related to criticality reduction in the cancer chemotherapy process.

study, we obtained consensual quotations between pharmacists, the oncologist, and the nurse, guaranteeing the best possible objectivity. Moreover, the frequency, the severity and the ability to detect a failure mode were determined on the basis of explicit criteria, which limits the variability. However, it is important to note that the main goal is to classify risk stages and to determine orders of magnitude, and therefore the method allows for some imprecision.

In conclusion, our study confirmed a major risk reduction by re-engineering our cancer chemotherapy process. Both the centralization and the implementation of information technologies had significant and complementary impacts on the global criticality, at an acceptable cost. Our work demonstrates the usefulness of risk analysis methods in health care processes and a more systematic use of these tools in the future may guide and help prioritize continuous security improvement of high-risk medical activities.

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