The application of hazard analysis and critical control points and risk management in the preparation of anti-cancer drugs

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Abstract

Objective. To apply the Hazard Analysis and Critical Control Points method to the preparation of anti-cancer drugs. To identify critical control points in our cancer chemotherapy process and to propose control measures and corrective actions to manage these processes.

Setting. The Hazard Analysis and Critical Control Points application began in January 2004 in our centralized chemotherapy compounding unit. From October 2004 to August 2005, monitoring of the process nonconformities was performed to assess the method.

Methods. According to the Hazard Analysis and Critical Control Points method, a multidisciplinary team was formed to describe and assess the cancer chemotherapy process. This team listed all of the critical points and calculated their risk indexes according to their frequency of occurrence, their severity and their detectability. The team defined monitoring, control measures and corrective actions for each identified risk. Finally, over a 10-month period, pharmacists reported each non-conformity of the process in a follow-up document.

Results. Our team described 11 steps in the cancer chemotherapy process. The team identified 39 critical control points, including 11 of higher importance with a high-risk index. Over 10 months, 16,647 preparations were performed; 1,225 non-conformities were reported during this same period.

Conclusions. The Hazard Analysis and Critical Control Points method is relevant when it is used to target a specific process such as the preparation of anti-cancer drugs. This method helped us to focus on the production steps, which can have a critical influence on product quality, and led us to improve our process.

Keywords: Hazard Analysis and Critical Control Points method, anti-cancer drugs, risk management, quality management

Introduction

Anti-cancer drugs present toxicity risks for health workers and patients [1–8]. It is recommended to centralize preparation in the pharmacy to limit the occupational exposure of health workers who come into contact with anti-cancer drugs [9–11]. At the Georges Pompidou European Hospital (HEGP, AP-HP, Paris), the production of cancer chemotherapies has been centralized in the pharmacy since 2000. Between 2000 and 2004, this production doubled, and currently tallies about 20,000 preparations per year. The preparation of anti-cancer drugs is a complex process, and many non-conformities can occur. Nevertheless, our chemotherapy compounding unit is faced with ever-growing production needs and must guarantee high product quality according to good practice guidelines [12–14]. Hazards affecting quality can be defined as biological, chemical or physical or as operations (according to the relevant legislation) that are likely to cause illness or injury to patients or health workers. Various approaches exist to identify risk issues and improve the safety of a cancer chemotherapy process, such as Failure Modes and Effects Analysis, Failure Modes, Effects and Criticality Analysis, Probabilistic Risk Assessment, Hazard and Operability studies or Hazard Analysis and Critical Control Points (HACCP). Among these approaches, we chose to apply the HACCP method to the...
preparation of anti-cancer drugs. The HACCP method is a systematic method for the identification, assessment and control of safety hazards. Historically, the HACCP program has been considered as a food safety management system, but its use has been successfully applied to medical products [15, 16]. The risk analysis, following the guidelines of the HACCP method and the monitoring of critical steps during the process, was applied to the preparation of anti-cancer drugs [17, 18]. Our analysis led us to establish a preventive monitoring system based on an effective concept for quality assurance. The experience of this HACCP application is described in this study.

**Methods**

**Setting and study period**

The study was conducted in the chemotherapy compounding unit of the pharmacy department at the Georges Pompidou European Hospital (HEGP, AP-HP, Paris). All medication orders are entered by a physician, using a computerized prescription system (CHIMIO® Computer Engineering, Paris, France, 1996–2000). Only physicians, allowed to prescribe chemotherapies, have access to the prescription system. The pharmacist checks the validity of the prescription (i.e. prescription date, compliance with the chemotherapy protocol, calculated dose, blood test results, etc.). Next, a pharmacy technician prepares the anti-cancer drug in a positive pressure isolator. An analytical control of the preparation is performed by a pharmacist prior to dispensing. Finally, preparations are delivered and dispatched to the different oncology units.

The implementation of the HACCP method began in January 2004 with the formation of the HACCP team. To assess the efficiency of the HACCP method, monitoring of non-conformities was performed from October 2004 to August 2005.

**The HACCP team**

A team was formed to define the scope of the HACCP plan. This team represented all of the relevant disciplines. It was composed of three pharmacists (head of the chemotherapy compounding unit, head of the pharmacy quality unit and head of the pharmacy department, who is also an analytical control expert), eight pharmacy technicians, three physicians (from the Hospital Chemotherapy group), a public health nurse and six experts: a microbiologist, two biomedical engineering experts, an environmental expert, two technical experts and an air conditioning expert. The head pharmacist of the chemotherapy compounding unit who has academic training (from an Engineering School) in risk management led the HACCP team.

**HACCP analysis**

First, the HACCP team drew up a full description of the product and constructed a flow diagram. It covered all steps of the cancer chemotherapy process to which the HACCP concept was applied. The HACCP team checked and evaluated the whole process according to seven principles: (i) analysis and identification of potential risks (hazard analysis); (ii) identification of critical control points; (iii) definition of limits (target levels and critical limits); (iv) in-process control (critical control points monitoring); (v) the establishment of corrective measures; (vi) the confirmation system (HACCP system verification); (v) the documentation system (procedures and records).

The application of these aspects was partly facilitated by a computerized program (HACCP Express®, Version 2000) developed by Controls, Studies and Formation for Food Quality Improvement® (CEF/AQ®, Barcelonne du Gers, France, 2000) [19]. This program helped us to summarize and analyse all the collected data. This work was performed in compliance with the ISO 9000:2000 standard.

The HACCP team listed all of the critical points that could occur at each step of the process. A hazard evaluation was conducted in which the severity of the potential hazards and the probability of their occurrence were estimated. Control measures and monitoring of the critical control points were defined, if any existed for the considered hazard. Corrective actions were planned for each critical control point. Then, the HACCP team established quality documents (procedures, operating instructions, etc.) and record-keeping files related to each critical control point.

**Critical control points’ risk index**

To assess criticality for each control point, a risk index was developed. The criticality was expressed as a risk index, which was calculated as the product of the frequency of occurrence, the severity and the detectability scores (risk index = occurrence × severity × detectability) [20, 21]. The scoring system is detailed in Table 1. The HACCP team reported each score based on published studies and the experience of experts. The risk index for each critical control point was used to rank risks by importance. If the risk index obtained was higher than 50, the critical control point was strictly monitored. If the risk index fell between 25 and 50, the critical control point was regularly monitored. If the risk index was lower than 25, the critical control point was monitored less frequently. Only critical control points with a risk index higher than 50 are treated in this article.

**Table 1** Scoring system for critical control points’ risk index in the HACCP programme

<table>
<thead>
<tr>
<th>Score</th>
<th>Easy</th>
<th>Moderate</th>
<th>Impossible</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Improbable</td>
<td>Likely</td>
<td>Frequent</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
</tbody>
</table>
Non-conformities monitoring

Each non-conformity was systematically collected during the production process. This follow-up was used to assess the HACCP program and to submit specific corrective actions for each critical control point. At the chemotherapy compounding unit, non-conformities were collected by pharmacists and pharmacy technicians and reported in a follow-up document over 10 months. Each page of this report form was divided into four parts: the name of the event reporter, a description of the non-conformity detected, the step of the process which was concerned and the corrective action undertaken. To help the reporter, a complete list of possible events (for each step of the process) was included in the document. If the event was not mentioned in the list, the reporter could explain it briefly as a free comment.

Results

Characterization of the process

According to the recommendations of the HACCP team, the whole process was characterized by 11 steps: (i) prescription; (ii) pharmacist validation; (iii) selection; (iv) decontamination; (v) material preparation; (vi) prescriber dispensing order; (vii) sterilization process; (viii) preparation; (ix) validation of the sterilization; (x) physicochemical control; (xi) delivery. The team checked on-site the relevance of the flow chart described in Fig. 1.

Description of the product

The HACCP team defined the product as an individual sterile anti-cancer drug preparation. Moreover, this medical product can be delivered in a container, syringe or an infusor. The product is cytotoxic and sterile. Consequently, precautions are required to protect pharmacy technicians during the handling and preparation process.

Critical control points analysis and corrective actions

Among the 11 steps, we identified 11 critical control points of higher importance (39 overall) with a calculated risk index above 50. The critical control points and their risk indices are detailed in Table 2. From October 2004 to August 2005, 16647 preparations were made up by the chemotherapy compounding unit for 1335 patients. During the same period, pharmacists and pharmacy technicians reported 1225 non-conformities in the follow-up document. In the present study, we described only the non-conformities of the 11 critical control points of higher importance, which represented 94% (1157 non-conformities) of the total non-conformities reported. The number of non-conformities for each critical control point is shown in Table 3.

Prescription errors. Pharmacists validated 8511 prescriptions over this period. The most frequent error was the choice of a wrong protocol by the oncologist. The monitoring of this critical point consists of checking protocol reference documents and the patient medical file. The pharmacist calls the oncologist to modify the prescription as a corrective action.

Computerized prescription system errors. To control this point, the pharmacist must calculate the dose required on his or her own and check the prescription’s consistency with the chemotherapy protocol. If a system error occurred (like a bug), only the software editor can fix the problem.

Drug storeroom temperature conditions. The temperature of the drug storeroom was measured daily. During the study period (226 days), 193 (85%) temperature reports were higher than the warning level (temperature between 15°C and 18°C or 22°C and 25°C) and 33 (25%) reached the action level (temperature up to 25°C or down 15°C).

Compounding sheet errors. A wrong batch number (drugs, containers or infusors) may be reported on the compounding sheet. This type of error was considered as a non-conformity and should be closely and systematically monitored by the pharmacy technician. Among 11866 compounding sheets considered, there were 693 non-conformities (5.84%) reported. To reduce these errors, the use of an intermediate storage system within the compounding room with a unique batch number for each product was established.
Commercial product defects. Before use, commercial products (drugs or containers) were systematically checked. For example, particles or crystals inside drug solutions (due to inappropriate storage conditions) can be identified. As a corrective action, the pharmacy technician must put the product in quarantine and inform the physicochemical control laboratory that a thorough analysis should be performed.

Microbial contamination. Microbial contamination rates were evaluated twice a month on both positive pressure isolators used. To monitor this critical point, target, warning and action levels were defined by the HACCP team using the same template as Swanson et al. [22] and Ljungqvist et al. [23]. During the study period, no microbial contamination was reported.

Analytical non-conformities. Two methods were used to qualitatively and quantitatively check anti-cancer drug products: high performance liquid chromatography and flow injection analysis [24]. In our unit, most of the products can be controlled by these methods (fluorouracil, cisplatin, oxaliplatin, carboplatin, docetaxel, paclitaxel and cyclophosphamide). A non-conformity was defined as a measured concentration outside of the $\pm 15\%$ range regarding the considered dose or a non-recognized spectrum of the controlled drug. The analytical control of the preparation started in January 2005. Among 4683 controls performed between January 2005 and August 2005, 4552 (97.2%) were within the range.

Chemical contamination. No control system has been developed to assess this critical point in the chemotherapy compounding unit.

Differences between prescription and preparation. Sometimes, preparations are not in accordance with the initial prescription. The pharmacy technician who checks the preparation before delivery can detect various errors such as the wrong intravenous bag solution or the wrong volume of the infusor. All failed products are systematically destroyed and prepared again.

Packaging non-conformities. This type of non-conformity is also detected by the pharmacy technician who checks the preparation before delivery. The most frequent abnormality is bag leakage. As a corrective action, failed products are automatically prepared again.

Discussion

A risk analysis of the anti-cancer drugs preparation process has already been conducted using different methods like Failure Modes and Effects Analysis or Failure Modes, Effects and Criticality Analysis [21]. To our knowledge, the present study is the first to apply the HACCP method to a cancer chemotherapy process. The importance of process controls has increased. This new preparation day starts the commercial product validation. Before use, commercial products (drugs or containers) were systematically checked. For example, particles or crystals inside drug solutions (due to inappropriate storage conditions) can be identified. As a corrective action, the pharmacy technician must put the product in quarantine and inform the physicochemical control laboratory that a thorough analysis should be performed.

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Table 2: Risk index of the 11 critical control points of higher importance identified by the HACCP team

<table>
<thead>
<tr>
<th>No.</th>
<th>Step</th>
<th>Critical control points</th>
<th>Detectability</th>
<th>Occurrence</th>
<th>Severity</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 and 2</td>
<td>Prescription and pharmacist validation</td>
<td>1</td>
<td>5</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Prescription errors</td>
<td>1</td>
<td>5</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>Computerized prescription system errors</td>
<td>1</td>
<td>5</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>Drug storeroom temperature conditions</td>
<td>1</td>
<td>10</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>Compounding sheet errors</td>
<td>1</td>
<td>10</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>Commercial product defects</td>
<td>5</td>
<td>1</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>Microbial contamination of the positive pressure isolator</td>
<td>5</td>
<td>10</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>Chemical contamination of the positive pressure isolator</td>
<td>10</td>
<td>1</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>8</td>
<td>Needle-stick injuries</td>
<td>1</td>
<td>5</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>Physicochemical control</td>
<td>10</td>
<td>1</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>11</td>
<td>11</td>
<td>Delivery</td>
<td>5</td>
<td>1</td>
<td>10</td>
<td>50</td>
</tr>
</tbody>
</table>

The risk index (RI) is the product of the frequency of occurrence ($O$), the severity ($S$) and the detectability ($D$) scores (RI = $O \times S \times D$).

The HACCP method in the preparation of anti-cancer drugs.
Table 3 Number of nonconformities detected for the 11 critical control points of higher importance identified by the HACCP team

<table>
<thead>
<tr>
<th>No.</th>
<th>Step</th>
<th>No. Critical control points</th>
<th>Number of non-conformities detected (n = 1157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prescription and pharmacist validation</td>
<td>1 Prescription errors</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>Selection</td>
<td>2 Computerized prescription system errors</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>Material Preparation</td>
<td>4 Drug storeroom temperature conditions</td>
<td>226</td>
</tr>
<tr>
<td>8</td>
<td>Preparation and validation of the sterilization</td>
<td>16 Compounding sheet errors</td>
<td>693</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 Microbial contamination of the positive pressure isolator</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Physicochemical control</td>
<td>26 Commercial product defects</td>
<td>17</td>
</tr>
<tr>
<td>11</td>
<td>Delivery</td>
<td>28 Chemical contamination of the positive pressure isolator</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 Needle-stick injuries</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35 Analytical nonconformities</td>
<td>131</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36 Differences between prescription and preparation</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37 Packaging nonconformities</td>
<td>8</td>
</tr>
</tbody>
</table>

Table entries for 2, 4, 16, 12, 131, 8, 8.

Delivery and is a waste of time for health workers (especially for pharmacy technicians and nurses) and patients. Finally, destroyed preparations are lost and are economically unacceptable. With the HACCP method, non-conformities are detected by in-process monitoring and are corrected with defined actions. This approach has underscored the strong points and weaknesses of our cancer chemotherapy process. Many critical control points have been highlighted thanks to the HACCP team’s efforts. The risk index calculation helped to identify the most important critical points and to establish our priorities in terms of risk management.

Nevertheless, the HACCP method did not always provide solutions to all of the issues raised, and may even hide some issues. For example, ‘microbial contamination of the compounding room’ did not obtain a high-risk index (>50), while ‘microbial contamination of the positive pressure isolator’ did. However, the microbial contamination of the compounding room should be taken into account because of its potential impact on the isolator sterility. This item is a good indicator of the area’s hygiene quality. It also gives information about hand hygiene practices of pharmacy technicians who carry out manufacturing in the positive pressure isolator. We can also consider another issue highlighted by the HACCP, such as the monitoring of the drug storeroom temperature. This monitoring showed that 85% of temperature reports were higher than the warning level. The main explanation is that most of these reports were performed during the hot season. Moreover, the temperature range defined for the warning level was inadequate and was reconsidered. The high temperature range for the warning level was modified to 24–25°C.

Among the 11 critical points of greater importance described, we did not draw up corrective actions or monitoring for some of them. Chemical contamination hazards cannot be monitored for the time being in our department. However, informing pharmacy technicians of the importance of wearing nitrile gloves at all times inside the compounding room and of the importance of changing their nitrile gloves every 30 min should represent an alternative solution to contain this hazard [25–27]. On the other hand, no corrective action appears to be adequate for needle-stick injuries. The use of needle-free medical devices could be a preventive action to protect handlers and reduce the risk of exposure to anti-cancer drugs [28]. Thereafter, this risk could be avoided definitively. To reduce prescription errors and provide for better working conditions, we decided to reorganize prescription planning in close cooperation with the oncologists [29]. As far as possible, oncologists prescribe cancer chemotherapies several days before the patient’s arrival. Depending on the anti-cancer drug’s stability, we prepared and stored the preparations until the prescriber dispensing order was received. These early prescriptions allowed us to regulate the activity and improve handling conditions. The prescription validation by the pharmacist also takes place earlier, which improves the detection of prescription errors. Finally, some corrective actions defined in our process may not be applicable for use in other hospitals. For example, the intermediate storage system in the compounding room with a unique batch number for each product implies a significant daily production and the systematic control of the products ordered.

The HACCP is a precise method that highlights issues and explains a complex process in detail. This method is helpful for focusing on the production steps, which may have a critical influence on the quality of the product. With the HACCP method, we can concentrate our limited resources on the identified critical points. Finally, the hazard analysis also provides a revision of the documented data such as standard operating procedures, production and check-up protocols.
On the other hand, the HACCP method is extremely demanding on time and human resources. This point represents the major limitation of the method. Risk indexes were obtained based on the experience of HACCP team members and hindsight of the cancer chemotherapy process. The criticality of the different points may not be relevant and can be open to discussion. Scores for the different critical control points were calculated on the basis of explicit and objective criteria insofar as possible.

In conclusion, the present study demonstrates the interest of the application of the HACCP method in the preparation of anti-cancer drugs. The efficiency of the HACCP method is relevant when this method is used to target a specific point (HACCP) history and conceptual overview. Critical points were identified and led to improvement of our process. Following the implementation of the corrective actions, a reassessment of our process is planned in view of the future certification of our unit.

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