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Research paper

Application of an acceptance sampling plan for post-production quality control of chemotherapeutic batches in an hospital pharmacy

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Abstract

Background: About 26,000 chemotherapeutic batches were produced in 2003 in the Institute Gustave Roussy and 83% were qualitatively and quantitatively assessed in post-production controls via an analytical platform. The rate of non-conformity (outside the specification limits of the target concentration ±10%) decreased from 8.9% to 2.2% between years 2001 and 2003. A cost- and time-saving acceptance sampling plan was applied to assay fewer batches whilst maintaining an accurate estimate of the quality level.

Methods: The opportunity to apply a single sampling plan by attributes with an acceptance quality level of 2.2% was evaluated. A prognostic study using a logistic regression model was performed for some drugs to identify risk factors associated with the non-conformity rate of preparations.

Results: Out of 26 drugs, 17 have not been sampled, since they were prepared less than 400 times per year. For six drugs, a reduction of about 50% in the number of assays was estimated. Three drugs were "at risk" of being non-conform: for these drugs, all batches were analysed.

Conclusions: The sampling plan allowed a reduction of almost 8000 analyses with respect to the number of batches analysed for 6 drugs. For the 3 drugs with the higher risk to be non-conform, associated risk factors were identified to set up corrective actions.

Keywords: Chemotherapy; Quality assurance; Sampling plan; Post-production controls; High performance thin-layer chromatography (HPTLC); Cancer

1. Introduction

The Institute Gustave Roussy (IGR) is the largest French cancer research and cancer treatment establishment. In this respect, over 30,000 chemotherapeutic batches are prepared each year. The prescription of anticancer drugs is computerized and batch production is centralized as recommended by good manufacturing practices in an isolator located in the Department of Clinical Pharmacy (DCP), to guarantee safe drug distribution [1,2]. However, failures may occur in the production process resulting in qualitative or quantitative defects. The pharmacist is responsible for the procurement, distribution, surveillance and control of all drugs used within the health system [3], and for compounding and dispensing sterile products of high quality [4,5].

Over the past six years, a global quality assurance program has been designed to enhance safety during the prescription, handling and administration of antineoplastic agents. The tracking of therapeutic objects was made possible by respecting standard operating procedures (SOPs) for manufacturing. The IGR chemotherapy manufacturing unit was submitted to the ISO 9001:2000 Certification Board and gained its certification in July 2002. This quality

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assurance program is based on written policies and procedures, specific facilities and equipment. It permits to produce quality indicators allowing to manage the personnel education, training and evaluation.

Alongside upstream quality assurance measures, the final product must be inspected. To this end, the pharmacist must check that the product was accurately compounded using the correct ingredients, the specific amounts of each ingredient and an appropriate reservoir [6]. Different methods are proposed to control preparations in chemotherapy manufacturing units [7]. Simple weighing controls are not applicable in a production unit because of the variability of preparation types in terms of drugs, dosages, volumes and their various formulations (each preparation is adapted to a particular patient). This method lacks specificity as it does not allow the identification of the drug contained in the batch. The production of two batches under similar conditions (one for therapeutic use and a second one for control) is not viable during routine practice due to the expensive costs of cytotoxic drugs. In-process double controls (visual control during preparation) are widely used, but appear to be very expensive in terms of human resources (two people for one batch). Finally, the application of quality control for drug preparations remains rare in hospital pharmacies: in 2002, a study showed that only 4.7% of American pharmacies compounding cytotoxic preparations carried out such controls which are required to be compliant with 2000 ASHP Quality Assurance for Pharmacy-Prepared of Sterile Products guidelines [8]. Various techniques are used such as microbial controls, chromatographic or refractometric assays or spectroscopic methods. Structural and quantitative information may be obtained by techniques that assess the elastic-scattering properties, such as Near-infrared (NIR) spectroscopy. NIR is based on the calculation of net analyte signal (NAS) models [9,10], and is being used for qualitative and quantitative assays, such as the determination of homogeneous mixing [11], or to control the uniformity of tablets [12]. This method shows obvious advantages based on the rapidity of the analyses and their non-destructive character, but is not so straightforward to set up. To our knowledge, this method is limited to solid dosage forms.

In our hospital production process, a therapeutic object is prepared in solution (bags or syringes) and the dose is adapted to the body surface area or body-weight of each individual patient. As the concentration is variable according to the preparations, we cannot calculate such statistical control bounds for target concentration values that need to be fixed in advance.

In 1998, the Quality Assurance and Pharmacotechnical–Pharmacochemical Functional Unit (FU) of DCP was equipped with an analytical platform using both HPTLC (high performance thin-layer chromatography) and HPLC (high performance liquid chromatography), designed to work in tandem with the Production FU. Initially designed for industrial purposes, the HPTLC system allows the control of post-production quality control of preparations. The techniques and the analytical platform are described in a previously published work [13]. The measurement of these quality indicators was included in a routine follow-up to improve quality management, process training and the recruitment of pharmaceutical technicians [13]. The platform has reached much experience: 21,550 batches derived from 40 cytotoxic drugs have been assessed and the total rate of non-conformity decreased from 8.9% in 2001 to 2.2% in the first semester of 2003. However, health care quality surveillance requires significant resource investment. For health service institutions, in the context of decreased funding, the aim is to minimize financial burden by maintaining a high level of quality for healthcare services and patient satisfaction.

The aim of this study was to determine if it was necessary to assay all therapeutic batches produced, or to calculate an individual control rate for each cytotoxic drug, according to various parameters (like number of batches or drug stability). The possibility of reducing the number of controls was evaluated through the application of an acceptance sampling plan, able to provide accurate quality level estimates. Such a reduction would be both time- and cost-saving. To our knowledge, this was the first time that such an approach was applied in an hospital manufacturing unit.

2. Materials and methods

2.1. Materials

Post-production controls permit the determination of identity, purity and concentration of active substances in batch samples, by HPTLC or HPLC methods [13].

A retrospective analysis was performed using data accumulated over five semesters (between January 2001 and June 2003). The actual individual characteristics of each preparation were known i.e. dose, volume, concentration and the container (syringe or batch). Thus, a preparation is considered as non-conform if it contains the wrong drug, or when its measured concentration is outside the specification limits defined as the target concentration $\pm 10\%$ for two consecutive assays. If it was not technically possible to perform a second assay after an initial non-conform assay and as the real status of non-verified samples (NV) was not known, the preparations corresponding to these samples were considered as non-conform. This total amount of non-conform samples (NCT) was the sum of the amount of non-conform (NC) and non-verified samples (NV).

All preparations produced for each drug during one semester were labelled as the ''lot of preparation''. For each preparation lot, the number of samples produced n and the total number of defective cases d were known.

2.2. Principle of an acceptance sampling plan

The sampling plan was popularized by Dodge and Romig and applied by the US military to test ammunition

batches during World War II. The military had to determine which bullets to accept and which ones to reject, but could not test every bullet as no bullets would be left to ship. Nevertheless, and for obvious reasons, they had to be confident that accepted bullets would not fail. Acceptance sampling, which is a compromise between no inspection at all and 100% inspection, was the solution consisting in testing a few representative bullets from the batches. The latest revision of this plan is the MIL-STD-105-E plan dating from 1989 [14–17].

An acceptance sampling plan is a proven method for accepting or rejecting a batch by inspecting a random sample of units, based on previously established quality levels. The sampling plan technique operates on the basis of probability calculations. The plan is generally denoted (n, c): for a sample size n, the lot of preparation is not accepted if there are more than c defectives. Graphically, it involves using the Operating Characteristic (OC) curve, which plots the probability of accepting the batch (Y-axis) versus the batch fraction or percent defectives (X-axis) and counting the number of defectives (Fig. 1).

It was necessary to determine two statistical risks corresponding to the levels of quality routinely accepted and rejected by the plan. First, the acceptance quality level (AQL) is a percent defective that is the base-line requirement for the quality of the producer's product. The pharmacist would like to design a sampling plan such that there would be a high probability of accepting a batch that has a defective level less than or equal to the AQL. In first semester 2003, the average conformity rate of the overall production was equal to 97.8%, which remained constant during two semesters. This conformity rate was the best quality level observed during the 5 semesters considered in this study. We decided therefore to introduce a quality control strategy using a target value of 2.2% non-conformity, representing the maximum defective percentage that we would accept on average. Thus, in the acceptance sampling plan the average quality level (AQL) was fixed to 2.2%, based on the historical records. Graphically, as shown in Fig. 1, the AQL can be determined using the OC curve by finding the quality level on the X-axis corresponding to a probability acceptance for a good batch of 0.98 (0.978%, calculated as 1-AQL). Because the batch attribution (conform or non-conform) is based on sample results, there is a possibility of making an incorrect attribution. The type I error, called alpha (α), is the probability that a batch with an acceptable quality is rejected. The producer (the pharmacist in our case) suffers when this occurs because a batch whose quality is acceptable may be rejected.

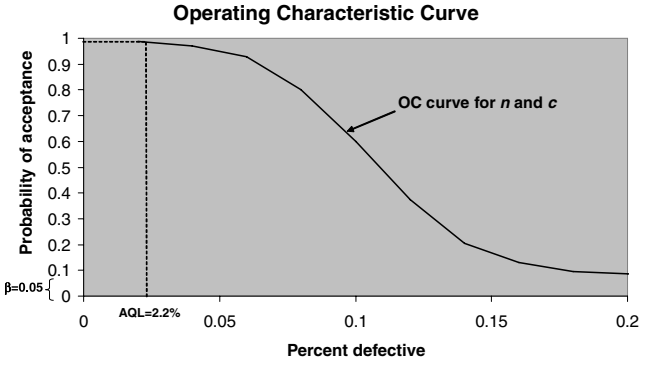

Fig. 1. Typical operating characteristics (OC) curve.

The second statistical risk, the lot tolerance percent defective (LTPD), is a designated level that would be unacceptable to the "consumer": the LTPD was set in order to have a sampling plan with a low probability of accepting a batch with a defect level as high as the LTPD. The LTPD was fixed at 0.05. On the OC curve, it is equal to the quality level on the X-axis corresponding to the probability of accepting a non-conform batch. It is associated with the consumer's risk, denoted by beta (type II error), which represents the probability that a batch is accepted with an unacceptable quality level. For obvious reasons, the consumer suffers when this occurs because a lot with unacceptable quality would be accepted. In our case, the LTPD represents the patient's risk i.e. the risk we are willing to take of accepting a batch whose concentration is outside specifications, with respect to the patient.

The type-I and -II errors were fixed at 5%.

2.3. Acceptance sampling plan application

The statistical analysis considered preparations batches, composed from all preparations produced during one semester for each drug. A single acceptance sampling by attributes consists of counting the total number of non-conform units (d) in the batch of size (n). If d was not greater than c (the acceptable number of defectives defined by the plan), the batch was classified as "acceptable" and otherwise the whole batch was marked as an "unacceptable lot".

So, for each drug, the level of acceptable batches ranged from 0 (all batches produced over the 5 semesters were unacceptable) to 5 (all batch were acceptable over the same period).

2.4. Identification of risk factors associated with the risk of being non-conform

A prognostic study using individual characteristics of each batch was performed to identify risk factors associated with the risk to be non-conform, i.e. to determine whether the preparations' parameters (dosage, concentration and packaging) influence the probability of a batch non-conformity. For each drug, the total production of one semester was ordered from the minimum to the maximum of the variable studied and divided into 4 equal categories corresponding to quartiles (0–25%, 25–50%, 50–75% and 75–100%). Odds ratios (OR) were calculated (interpreted as relative risk when the non-conformity rate is low) to determine if the non-conformity risk for each

quartile was the same as the non-conformity risk in the 4th quartile, the reference's one.

If the OR was higher than 1, the probability of non-conformity in the quartile considered was higher than in the reference quartile. The OR was statistically significant when the 95% confidence interval did not include 1. It was concluded that the characteristic of this variable (concentration, dosage...) was associated with a higher risk of non-conformity.

3. Results

In 2003, 25,968 batches were produced and sampled. The analytical platform was able to qualitative and quantitative assess analyses for 26 of the 40 cytotoxic drugs commonly used (22 by HPTLC and 4 by HPLC) [13], representing 83% of the total production.

Since 2001, the total rate of non-conformity (NCT) decreased from 8.9% to 2.2% in the last semester of 2003. This rate can be divided as follows: outside concentration specification limits (non-conform; NC = 1.9%) and not assessable for other reasons such as physicochemical instability (e.g. methotrexate, cytarabin and etoposide), or small sample sizes (non-verified; NV = 0.3%). The outside specification limits rates (NC) included both manufacturing errors and a poor homogenisation of the manufactured batches before sampling.

The acceptance sampling plan allowed drugs to be divided into 3 groups (Table 1):

Group 1: no drugs were sampled for preparations of less than 200 batches produced by semester. As the population was small, it was preferable to assay all batches, rather than to proceed by sampling. In 2003, this represented 17 drugs out of 26 and 17% of total batch production.

Group 2: Drugs for which an acceptance sampling plan was applied. For six drugs, all batches have been classified as conform for at least 4 out of 5 semesters. For each drug, the observed quality was very good with only a very small fraction of defectives and an AQL of less than 2.2%. The acceptance sampling plan was then applied as follows:

- for each drug, the number of assays n performed in the last studied semester was considered,
- n was decreased by simulation in steps of 500, or less, to calculate the sampling plan parameters: total number of controls to test, keeping the AQL at the targeted value (2.2%) and an LTPD inferior to 5%. The sample size n was decreased in small steps until LTPD was close to 5%.

All simulations are given in Table 2. An example is provided for fluorouracil: among the 2484 preparations of this drug manufactured in the first semester of 2003, 29 were non-conform, corresponding to an "observed" AQL of 1.1%. Simulations indicated that the number n of batches needed to be controlled could be decreased, when AQL was kept below 2.2% and LTPD below 5%. For this drug,

Table 2
Determination of sample size by application of acceptance sampling plan for the 6 drugs concerned during the 1st semester 2003

	n	c	AQL	LTPD
Fluorouracil				
Observed	2484	67	2.22	3.16
Proposed sampling plan	2000	55	2.22	3.28
	1500	43	2.25	3.50
	1000	30	2.25	3.81
	500	16	2.17	4.46
Ifosfamide				
Observed	852	24	2.04	3.69
Proposed sampling plan	700	20	2.02	3.84
	500	15	2.02	4.23
	400	12	1.93	4.41
	300	10	2.07	5.09
Cisplatin				
Observed	1155	31	2.02	3.40
Proposed sampling plan	1000	27	1.99	3.48
	500	15	2.01	4.23
	300	10	2.06	5.09
Epirubicin				
Observed	336	6	0.98	3.11
Proposed sampling plan	180	4	1.10	4.39
Doxorubicin				
Observed	657	19	2.03	3.92
Proposed sampling plan	600	18	2.08	4.10
	500	15	2.02	4.23
	400	13	2.13	4.70
	350	11	1.99	4.70
Cyclophosphamide				
Observed	564	17	2.07	4.16
Proposed sampling plan	500	15	2.02	4.23
	400	13	2.12	4.70
	350	11	1.99	4.70
	300	10	2.07	5.09

Table 1
Classification of the drugs into the 3 groups

Category of drugs	Drugs concerned
Group 1 (17 drugs) <400 preparations a year	Irinotecan, oxaliplatin, gemcitabine, daunorubincin, idarubicin, fludarabine, melphalan, mitoxantrone, vindesine, vinorelbine, vinblastine, vincristine, dacarbazine, thiothepa, carboplatin, paclitaxel, docetaxel,
Group 2 (6 drugs) Acceptance sampling plan	Fluorouracil, ifosfamide, cisplatin, epirubicin, doxorubicin, cyclophosphamide
Group 3 (3 drugs) At risk to be outside the specification	Methotrexate, etoposide, cytarabine

the number of required assays was $n = 500$ and $c = 16$ non-conform batches, corresponding to an AQL and a LTPD, respectively, at 2.17 and 4.46. This sampling corresponds to 80% reduction in analyses of manufactured batches (i.e. from 2484 to 500 analyses).

Significant reductions were possible in the amounts of batches to be analysed through the application of the sampling plan: ifosfamide batches analysis was reduced by 65%, epirubicin, doxorubicin and cyclophosphamide by 47%, cisplatin by 74% and fluorouracil by 80%. For the first semester of 2003, the plan permitted the avoidance of 4118 controls (16% of the total number of controls).

Group 3: Drugs at risk of being outside specifications: this group included drugs for which batches would have been rejected over at least 2 semesters (AQL > 2.2%). In 2003, this concerned three drugs (methotrexate, cytarabin, etoposide) corresponding to 22% of the entire production. For these drugs, all batches should be controlled in preference to applying the sampling plan.

Potential handling problems were identified to improve the quality process. During the first semester of 2003, cytarabin and methotrexate were the two drugs with the highest rate of non-conformity, with NCT of 3.2 and 9.0, respectively. The logistic regression results concerning the effect of individual characteristics of the preparations are shown in Tables 3–5. It can be seen that preparations with low dosages were at high risk of being non-conform (Table 3): the risk of being non-conform associated to the first quartile preparations (with the lowest dosage of methotrexate) was 10 times higher and statistically different from the other ones compared to the latest quartile. The results relative to cytarabin indicated the same tendency, but were not statistically significant.

Table 3
Influence of the dosage on the risk to be non-conform

	1st quartile	2nd quartile	3rd quartile	4th quartile
Methotrexate	OR = 10.0* IC = [2.1;47.8]	OR = 1.7 IC = [0.8;4.1]	OR = 2.1 IC = [0.8;5.1]	OR = 1
Cytarabin	OR = 2.5 IC = [0.9;6.9]	OR = 1.8 IC = [0.6;5.4]	OR = 0.5 IC = [0.2;1.9]	OR = 1

* $p < 0.05$.

Table 4
Influence of the concentration on the risk to be non-conform

	1st quartile	2nd quartile	3rd quartile	4th quartile
Methotrexate	OR = 1.7 IC = [0.9;3.5]	OR = 0.3* IC = [0.1;0.9]	OR = 0.3* IC = [0.01;0.8]	OR = 1
Cytarabin	OR = 1.7 IC = [0.7;4.3]	OR = 1.0 IC = [0.4;2.7]	OR = 0.4 IC = [0.1;1.4]	OR = 1

* $p < 0.05$.

Table 5
Influence of packaging on the risk to be non-conform for the methotrexate

	Intrathecal	Syringe (2–20 mL)	Syringe (21–60 mL)	Infusion bag
Packaging	OR = 1.7 IC = [0.7;4.2]	OR = 1.0 IC = [0.5;2.3]	OR = 3.6* IC = [1.7;7.9]	OR = 1

* $p < 0.05$.

Preparations with low concentrations were also at risk of being non-conform (Table 4). Otherwise, the results showed that preparations with "medium" concentrations seemed less at risk of being non-conform than the fourth quartile: for methotrexate, second and the third quartile preparations were 3 times less a risk of being non-conform than those of the fourth quartile.

To evaluate the effect of the container closure system of the preparation, we divided a batch of methotrexate into 4 classes: intrathecal syringes (<2 mL), small volume syringes (2–20 mL), high volume syringes (21–60 mL) and infusion bags. The reference group was the infusion bags for which the risk of being non-conform was fixed at 1. For intrathecal syringes the risk of being non-conform was 1.7 times more important than the one for infusion bags but was not significantly different (Table 5). For 21–60 mL syringes, the risk was calculated at 3.6 which was significantly different from the infusion bags' risk. On account of the poor physico-chemical stability of etoposide, it was difficult to perform a second assay, when the first one had failed. The higher rate of NCT for this drug is explained by a high rate of non-verified samples (NV), due to precipitation phenomena.

Corrective actions were set up to improve the manufacturing process and decrease the total amount of non-conformity. A freeze-dried methotrexate was used which required to be diluted into a syringe causing difficulties to homogenise, risks of handling and non-conformities. At present, the manufacturing process of intrathecal syringes for methotrexate and cytarabin has been modified using a ready-to-use solution instead of the lyophilised form which had to be diluted. Moreover, for the paclitaxel batches, the shake mode was modified. For etoposide, the final concentrations were focused on a narrower concentration range in accordance with physico-chemical stability data to reduce drug precipitation.

4. Discussion

A better understanding of post-production control data was gained through the application of the statistical analysis approach herein described. During the first three years, a maximum of post-production controls were assessed. A vast amount of data (about 50,000 assays) was available after five semesters of routine practice. Analysis of these data allowed the precise measurement of a base-line quality level. This study permitted the identification of preparations "at risk of being non-conform", for which systematic controls will occur. Significantly, it was possible to apply a sampling acceptance plan for 6 drugs to reduce sampling controls. The proposed plan, based on the MIL-STD-105E single sampling plan, provides an objective and efficient system in accordance with international standards.

The experience gained during this study, together with the results obtained, and helped the pharmacist to critically evaluate the causes of batches failure. Logistic regression results showed that packaging in syringes was mainly responsible for poor results. Syringe packaging represents one-third of the entire production batches for the drugs administered in this study. Poor results may be explained by insufficient homogenisation during the production of preparations. Critical analysis has led to the implementation of measures (e.g. better homogenisation, personnel training with particular follow-up) designed to amend processes and to improve quality levels.

The AQL was attributed after three years of experience. This fixed value of 2.2% represented the non-conformity target, based on our historical records. In future, this AQL value needs of course to be re-estimated after improvement of the observed non-conformity rates. In this case, the new value of AQL will integrate the improvement of the manufacturing process. The sampling plan will be evaluated continuously. Anyway, we cannot fix an AQL value above 5% due to obvious statistical and pharmaceutical reasons.

The assessment of LTPD was difficult to estimate and was then conducted arbitrarily. The LTPD was fixed at 5%, but this value is debatable because it represented patient risk: this is the risk someone is willing to take of accepting a batch whose concentration is outside specifications. For future research, a question may be asked as to whether the same risk should be taken for all cytotoxic drugs. It would be preferable to select risks as a function of drug toxicity. Moreover, to our knowledge no guidelines or other published data are available on the application of an acceptance sampling plan on a manufacturing process of chemotherapeutic batches in an hospital pharmacy. Comparisons could not be made with other situations where the application of batches sampling is used (i.e. vaccination [18], audit of medical-claim payment [19], contamination of food [20]).

For drugs in the first group (Table 1) with batches productions inferior to 200 per semester, a batch sampling might not detect small changes in ongoing surveillances. Therefore, it was decided to continue sampling of the entire production. To this end, the technicians and the pharmacist have to pay attention to drug non-conformity rates included in the plan. On the other hand, it will be possible to add drugs to the plan, if the number of preparations increases.

The originality of this study should be underlined. First, this originality comes from the number and the diversity of qualitative and quantitative assays carried out. After 4 years, routine assays of manufactured batches have reached considerable maturity: 28 cytotoxic drugs were controlled, resulting in 23,000 assays in 2004. Post-production quality controls of chemotherapy preparations are not common practice in hospital pharmacy. This can be explained by the fact that such controls are recommended, but not compulsory. Some hospital pharmacies develop quality control programs with HPLC assays, but these controls are generally limited to the most frequently administered cytotoxic drugs. To our knowledge, except our previously published work [9], no published data were found using HPTLC techniques in hospital pharmacy. These new approaches are more developed in industrial environment. The originality of this work is also explained by the statistical techniques used, which are largely unfamiliar to health professionals outside of clinical trials. This work was possible due to the collaboration of Pharmacists from the Department of Clinical Pharmacy and statisticians from the Public Health Department of IGR.

5. Conclusion

On the basis of the data herein presented, the application of an acceptance sampling plan should be strongly considered. The use of an acceptance sampling plan is noteworthy. For an annual production of 26,000 batches, about 8000 controls could have been avoided through the application of this plan. As the routine cost of analysis is estimated at 1.50 €/batch, the plan may allow a significant costs reduction of 12,000 € per year for the hospital.

The statistical analysis described allowed the identification of 6 drugs with a risk of being non-conform and the set up of corrective actions to improve the overall rate of non-conformity. Moreover, it permits to control a more important production flow, assaying a constant number of batches with the same production's quality level estimates.

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