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QUALITY ANALYSIS OF PRINTED PHARMACEUTICAL LEAFLET MATERIALS

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Rezumat. *Ambalajele farmaceutice, inscripționate Braille, sunt frecvent utilizate astăzi. În lucrare sunt prezentate tipurile de defecte care pot apărea la aceste ambalaje obținute prin tehnologie ofset şi indicatorii de performanță ai calității specifici organizației producătoare în care s-a realizat studiul de caz. Procesul de producție a produselor farmaceutice este guvernat de sistemul de management al calității bunelor practici de producție. Acesta este mai restrictiv comparativ cu standardul ISO 9001: 2015. Se urmăreşte calitatea de 100%, iar metodele, procedurile acordă o atenție deosebită acțiunilor preventive şi corective pentru a diminua riscul de neconformitate. În lucrare este analizată apariția defectului "prospecte tipărite pe o singură parte" cu ajutorul diagramei Ishikawa. Sunt propuse activități corective şi preventive în vederea eliminării acestui tip de defect.*

Abstract. *The pharmaceutical packaging with engraved Braille is commonly used today. The paper presents the types of defects that may occur to these packages obtained by offset technology and the performance indicators of the quality specific to the manufacturing organization where the case study was carried out. The production process of pharmaceutical products is governed by the Good Manufacturing Practice quality management system. It's more restrictive comparative with the ISO 9001:2015 standard. There is targeted the 100% quality and the procedures have a special focus on preventive and corrective actions in order to mitigate the non-conformity risk. In the paper it is analysed using the Ishikawa chart the appearance of the defect "pharmaceutical leaflets printed on one side". Corrective and preventive activities are proposed to eliminate this type of defect.*

Keywords: quality, leaflet for pharmaceutical products, offset technology, defect, Ishikawa chart

1. Introduction

The packaging market sector in Romania had a huge development, especially in the last ten years, although the consumption per capita is still on a much lower level than the recorded average in the European Union. Many factors had influenced the development of this market sector, with the buyer expectations on the first place - becoming more selective - doubled by the increase of the incomes and also by the retails' network expansion.

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The packaging has a functional role, not only an aesthetic one; it's a marketing tool and an economic factor. The original role of packaging was to protect the product. With the industrial production, development the functions of transport, storing and logistic were added to the packaging material. In average the packaging material represents a 2 - 5 % of the products' price and about 80 % of the used packaging is made out of paper and plastics.

Romania's accession to the European Union produced some modification of the packaging's profile market like mandatory quotas for recycling, environment protection, hygienically conditions of production places, and some special requirements like the Braille writing for blind people on the pharmaceutical products' packaging.

The printing houses specialized for some products invested millions of euros per year in order to win contracts for packaging materials which were produced before in a foreign country.

The ABC-IMPEX SRL, a medium size company, having local private shareholders, with headquarters in Odorheiu Secuiesc is specialized in folding cardboard box production, made of solid cardboard, and for flexible packaging materials production (printed aluminium foils, printed multi-layer foils, self-adhesive labels, all printed with flexo technology). It supplies for the pharmaceutical industry, food, cosmetics, self-care and others (Fig. 1).

Fig. 1. Pharmaceutical products.

In the 28 years of activity the company managed to impose itself on the Romanian packaging market, becoming a national leader for pharmaceutical packaging and also for other sectors, having an active number of more than 2000 different items produced.

The ABC-IMPEX SRL has a quality management system certified ISO 9001 from early 1998 by SGS UK.

2. Specific defects of packaging materials

The ABC-IMPEX SRLs' main target is to provide products in conformity with the standards and the agreed specifications, and to conform to the customer required parameters and properties.

Figure 2 shows the entire production flow of a pharmaceutical leaflet.

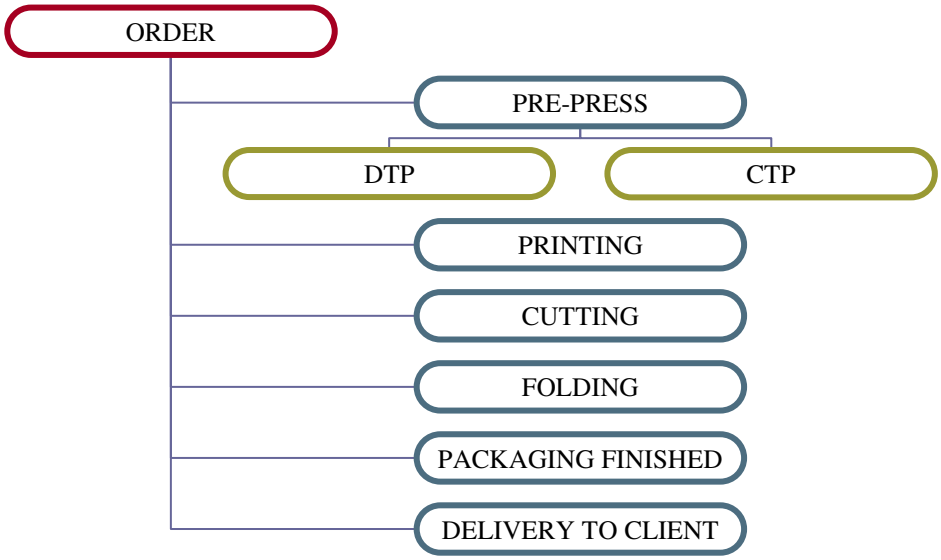


Fig. 2. Production flow of a pharmaceutical leaflet.

The conformity of the products means the absence of deviations. In the manufacturing operations the inherent action of some factors is present due to numerous unpredictable causes that cannot be completely prevented from the technological point of view.

The defects of packaging materials are classified into three distinct categories [4]:

- critical defects:
  - the critical defects are the sum of all non-conformities which makes the packaging material unusable;
  - the product category with critical defects cannot be delivered to customers;
- major defects:
  - the category of major defects is made of the totality of non-conformities which reduces the production process efficiency by extra sorting operations and influences the products' aspect;
  - the product category with major defects can be delivered to the customer with previous customer approval, and has to be clearly marked and separated from the rest of the products;

- minor defects:
  - the category of minor defects is made of the totality of non-conformities which reduces slightly the aspect of the packaging material, are visible, but do not influence the usability of the products;
  - the product category with minor defects is allowed to be delivered to customers.

2.1. Acceptable quality level

The acceptable quality level (AQL) represents the maximum number of defects per product unit which can be considered acceptable. If the identified total number of non-conformities in a certain production batch is lower or equal with the specified acceptable quality level, the batch has to be accepted.

In conformity with the SR 12898-90 standard, correspondingly for each defect category, the AQL values are the following [1]:

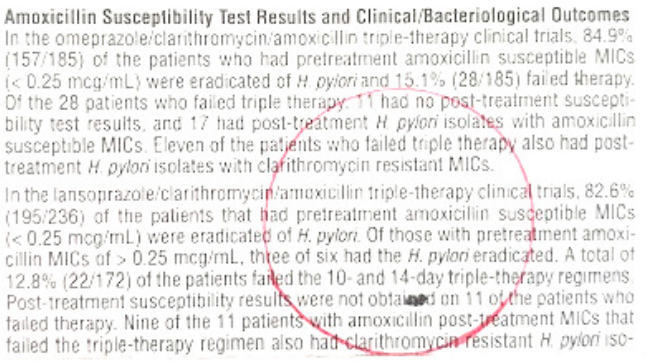
- for critical defects: AQL = 0 %;
- for major defects: AQL = 2.5 %;
- for minor defects: AQL = 6.5 %.

The existence of a AQL does not mean that a certain percentage of non-conform product units is totally accepted or wanted, it just means that a compromise between the customers' quality expectation and the quality that the technology can output [7] has to be made.

The ABC-IMPEX SRL company internal quality specifications offer a description of the quality deviations which do not characterize the whole batch of products, which does not affect the product's aspect, being acceptable.

Table 1. Defects type description

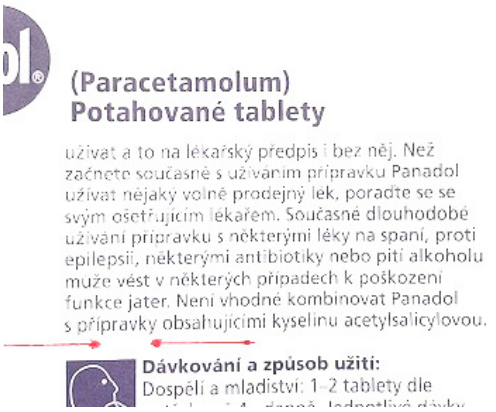
Type of defect	*Defects description*	*AQL*
Critical defect (Fig. 3)	wrong pharma-barcode, missing pharma-code, pharma-code line and gap dimensions out of specified tolerance	*
	colour does not match with master	*
Major defect (Fig. 4)	colour shade is out of tolerance	2.5
	missing 50% or more from a word or symbol in text, or from a character in a title line	2.5
Minor defect (Fig. 5)	sandpaper effect on the paper's printed or varnished surface (effect of the offset powder)	6.5
	the varnish-free areas dedicated for products marking are partially covered with coating, but there is still enough space for marking; the tolerance for the varnish-free area outline is 1 mm.	6.5



Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes
In the omeprazole/clarithromycin/amoxicillin triple-therapy clinical trials, 84.9% (157/185) of the patients who had pretreatment amoxicillin susceptible MICs (< 0.25 mcg/mL) were eradicated of *H. pylori* and 15.1% (28/185) failed therapy. Of the 28 patients who failed triple therapy, 11 had no post-treatment susceptibility test results, and 17 had post-treatment *H. pylori* isolates with amoxicillin susceptible MICs. Eleven of the patients who failed triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs.

In the lansoprazole/clarithromycin/amoxicillin triple-therapy clinical trials, 82.6% (195/236) of the patients that had pretreatment amoxicillin susceptible MICs (< 0.25 mcg/mL) were eradicated of *H. pylori*. Of those with pretreatment amoxicillin MICs of > 0.25 mcg/mL, three of six had the *H. pylori* eradicated. A total of 12.8% (22/172) of the patients failed the 10- and 14-day triple-therapy regimens. Post-treatment susceptibility results were not obtained on 11 of the patients who failed therapy. Nine of the 11 patients with amoxicillin post-treatment MICs that failed the triple-therapy regimen also had clarithromycin resistant *H. pylori* iso-

Fig. 3. Critical defect (colour spot on the text).

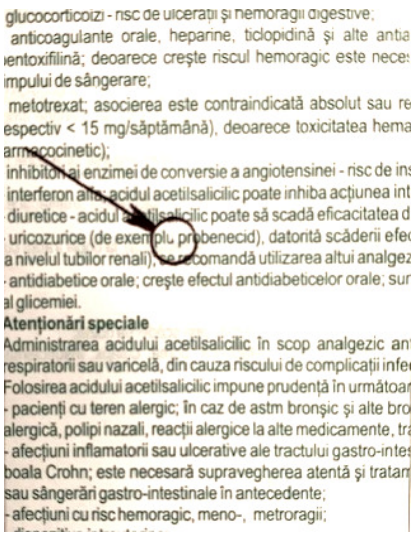


(Paracetamolum)
Potahované tablety

užívat a to na lékařský předpis i bez něj. Než začnete současně s užíváním přípravku Panadol užívat nějaký volně prodejný lék, poraďte se se svým ošetřujícím lékařem. Současné dlouhodobé užívání přípravku s některými léky na spaní, proti epilepsii, některými antibiotiky nebo pití alkoholu může vést v některých případech k poškození funkce jater. Není vhodné kombinovat Panadol s přípravky obsahujícími kyselinu acetylsalicylovou.

Dávkování a způsob užití:
Dospělí a mladiství: 1–2 tablety dle

Fig. 4. Major defect (colour spot).



glucocorticoizi - risc de ulcerații și hemoragii digestive;
anticoagulante orale, heparine, ticlopidină și alte antia
pentoxifilină; deoarece crește riscul hemoragic este nece
timpului de sângerare;
metotrexat; asocierea este contraindicată absolut sau re
respectiv < 15 mg/săptămână), deoarece toxicitatea hema
farmacocinetic);
inhibitori ai enzimei de conversie a angiotensinei - risc de ins
interferon alfa; acidul acetilsalicilic poate inhiba acțiunea int
diuretice - acidul acetilsalicilic poate să scadă eficacitatea d
uricozurice (de exemplu, probenecid), datorită scăderii efec
a nivelul tubilor renali); se recomandă utilizarea altui analgez
antidiabetice orale; crește efectul antidiabeticelor orale; sur
al glicemiei.
Atenționări speciale
Administrarea acidului acetilsalicilic în scop analgezic ant
respiratorii sau varicelă, din cauza riscului de complicații infe
Folosirea acidului acetilsalicilic impune prudență în următoar
- pacienți cu teren alergic; în caz de astm bronșic și alte bro
alergică, polipi nazali, reacții alergice la alte medicamente, tr
- afecțiuni inflamatorii sau ulcerative ale tractului gastro-intes
boala Crohn; este necesară supravegherea atentă și tratam
sau sângerări gastro-intestinale în antecedente;
- afecțiuni cu risc hemoragic, meno-, metroragii;

Fig. 5. Minor defect (partial absence of one letter).

2.2. Performance indicators of quality continuous improvement

For achieving the organization quality targets like satisfying or surpassing customer's expectations, efficient usage of resources, organization's financial performance improvement, the management collects a series of info and dates which concerns all part categories like:

- customer category and market segments served,
- the effectiveness of human resources,
- suppliers performance,
- the offered products and services quality etc.

The evaluation of the results and performances achieved within ABC-IMPEX SRL is done taking into account the concerns of parts, namely: internal and external customers, suppliers and partners. The performance indicators of the organization are grouped as follows:

- regarding the customer relationship: customer satisfaction level, number of customer complaints, number of positive customer reviews,
- regarding the quality of the offered products: the number of defects per lot, the quality level of the product determined by the set of quality characteristics,
- regarding the financial point of view: the solvency and financial liquidity assessment indicators of the organization (income level, profit rate, quality costs or, more precisely non-quality costs),
- human resources: job absenteeism, replacement rate of staff,
- for the efficiency and performance of the work system: productivity per employee, nature and frequency of improvement actions undertaken,
- regarding the overall performance of the organization: the production cycle duration, quality audits carried out.

3. Case Study: Pharmaceutical leaflets printed on one side only (missing print on the other side)

The object of the analysis
A leaflet has been identified at the packing operation, which is printed only on one side (the text is missing on the back side).

Documents and information underlying the analysis
Batch files no. 128647
Quality control records

Defect analysis
It is used the cause-effect diagram (Ishikawa chart). This chart allows highlighting and hierarchizing the causes (real and potential) of a given defect. It is also used to investigate the expected results of an action, highlighting the relationships

between the different causes of a particular phenomenon, or as a process of recording ideas [5].

For the construction of the Ishikawa chart, the following steps are followed [2]:

- defining the problem - what causes chart will be analysed (it is preferable to define in a group);
- defining the main categories of possible causes - in the field of production these usually are: working hand, methods, environment, machines, materials (ISO 9004 standard recommends delimitation of the following main categories of causes: data and information system, equipment, measuring devices, staff, environment, materials, methods);
- building the chart is done by mentioning the effect in the right box and determining the position of the main categories of causes;
- developing the chart: the causes are specified for each level of detail. In this way, the primary, secondary and minor causal elements are explicitly and rationally correlated [3].

Figure 6 shows the investigation result made on double-side leaflet printing process because of the non-conformity appearance, classified in "missing print on one side" defect category.

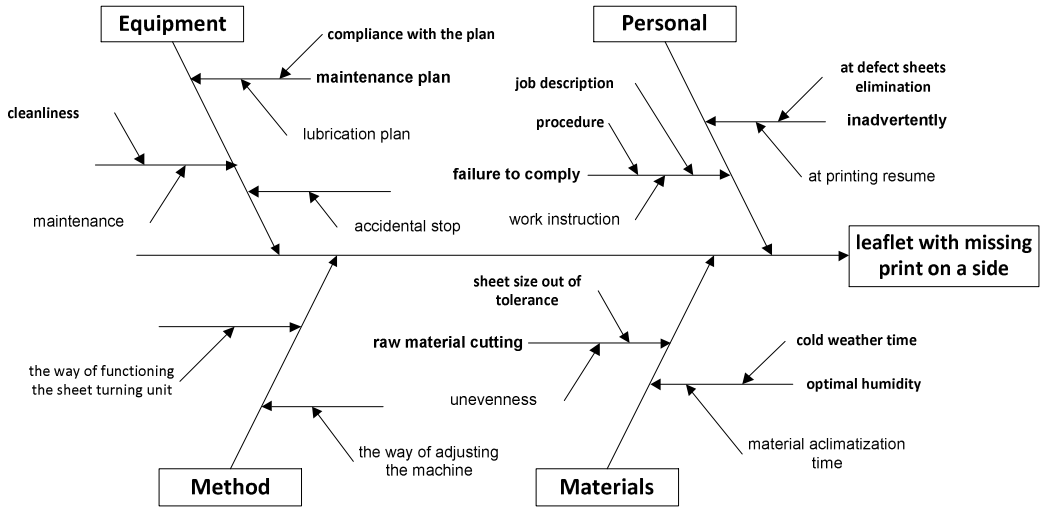


Fig. 6. Ishikawa chart for leaflet with missing print on a side.

The result of the analysis

From the analysis made, it appears that an unprinted or partially printed leaflet appears when the machine stops during the printing process due to unforeseen events (e.g. imperfect paper feeding). In such situations there is a sudden stop, and the printing units pneumatically go out of pressure.

According to the information in the batch file, the leaflets were printed on sheets with imposition of 5 pieces per sheet. There should be two situations, namely:

1) Partial printing of the face of leaflets:
   - in this case there should be from 1 to 5 leaflets with missing print on back side.
2) Leaflets that are not printed on one side:
   - in this case there should be a number of 5 leaflets.

The steps of resuming production when the printing equipment is stopped, i.e. the steps to be taken to separate and eliminate any defective products, are governed by IL 09801: "Working instruction for resuming the printing process in the event of a stop".

The fact that the missing print non-conform leaflet has reached in the workflow of packaging operation confirms that the person responsible for the printing has failed to fully comply with the requirements and obligations of the above-mentioned instruction.

Referring to the technical layout of an offset printing machine (Fig. 7), the main components of a sheet-fed offset printing machine are as follows: (1) paper feeder unit, (2) printing units and (3) sheet delivery unit. Note: the printing job that was the subject of the case study was done on a Heidelberg Speedmaster SM XL 75-4-P+L printing machine, manufactured in 2016.

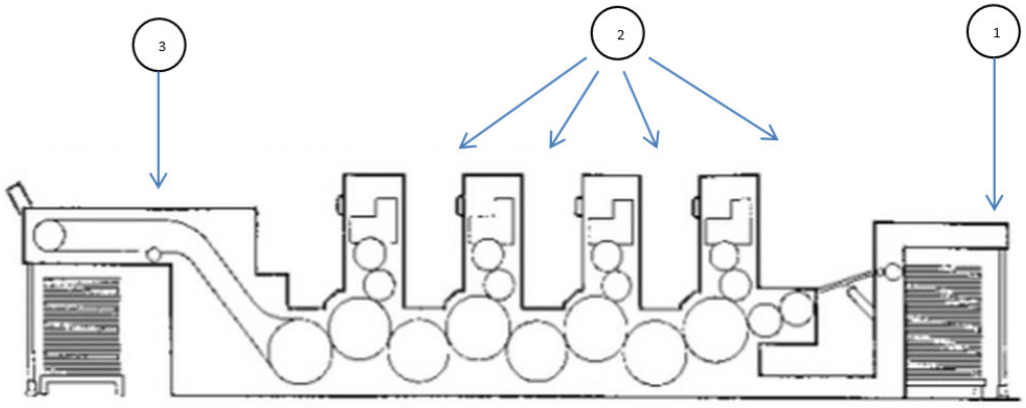


Fig. 7. Heidelberg Speedmaster SM XL 75-4-P+L printing machine.

For an accidental stop there are two scenarios:

1. The cause of machine stop is a paper feeding interruption or misaligned sheet (timing problem, front lay or side lay alignment). In this case, the sheets successfully fed into the machine will run through the machine correctly and will be correctly printed; only the feeder part of the machine will stop.

2. For an unexpected technical cause or the detection of an incorrect sheet transfer from a cylinder to another (sheet travel monitor), the machine stops abruptly, the sheets remaining stuck in the machine.

In the printing process, from the feeder part of the machine the sheets are separated one by one and are fed with an uninterrupted flow into the printing unit.

In this case from the available four printing units only two of them were used for printing, the job having one colour on the face side and one colour on the back side. The perfecting unit located in between the two activated printing units was activated for sheet turning.

In the first activated printing unit was the printing plate for the face of the leaflets and in the second activated printing unit was the plate for the back side. When the machine is running and the printing is ON, there is an uninterrupted sheet flow throughout the entire machine length.

From the feeder to the delivery unit the sheets complete consecutively the following phases:

- feeding phase (in this phase the sheets are unprinted on both sides),
- there should be activated and non-activated printing units, the non-activated units are transporting the sheets only,
- printing the face side of the leaflets (the sheets are printed on one side),
- perfecting, or sheet turning (the sheets are still printed on only one side),
- printing the back side of the leaflets (the sheets will be printed on both sides).

Totally from the feeder unit to the delivery unit there are about 10 sheets in an uninterrupted flow.

When an accidental stop is made, only the sheets before the first activated printing unit are both side unprinted, the sheets in between the two activated printing units are one side printed (the ones from the perfecting unit also) and the sheets which passed the second activated printing unit are printed on both sides.

As described above, the operator's responsibility refers to the fact that the 10 sheets in the phases mentioned above at the time of a stop must be extracted and examined and the non-conform product has to be removed.

Corrective actions taken:

1. The responsibility for removing the sheets and for checking them before resuming the printing in case of an accidental stop belongs to the printer-operator. In this respect, the process of raising the awareness of the involved people through half-yearly planned training will continue, until it ensures that the responsible person understands the consequences of such negligence.

2. A monitoring period was started in which whenever the operator will have to apply the provisions of IL 09801, the cause of machine stop was investigated and recorded as categories: raw material quality, technical issues, professional competence etc. [8].

Conclusions

The production process of pharmaceutical products is governed by the Good Manufacturing Practice quality management system. It's more restrictive comparative with the ISO 9001:2015 standard [6]. There is targeted the 100% quality and the procedures have a special focus on preventive and corrective actions in order to mitigate the non-conformity risk. In the GMP quality management system the pharma manufacturing sites must conduct direct audits at suppliers production sites in order to control in an efficient way the gap in the supply chain. The packaging manufacturer has to make their best in order to provide defect-free materials. From the printing-house side the risk of cross contamination and the missing print issues are critical defects and a need to understand the root cause of occurrence is most important.

The detail study together with the identification of all possible cause-effect relationship can lead the printer operators to mitigate the number of deviations, to increase the trust in the quality management and the customers to understand and to trust in the supplier's capability of controlling and taking corrective actions.

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