Region Hovedstadens Apotek

Product Dossier and Risk Evaluation for Extemporaneous Preparations Keeps Focus on Patients

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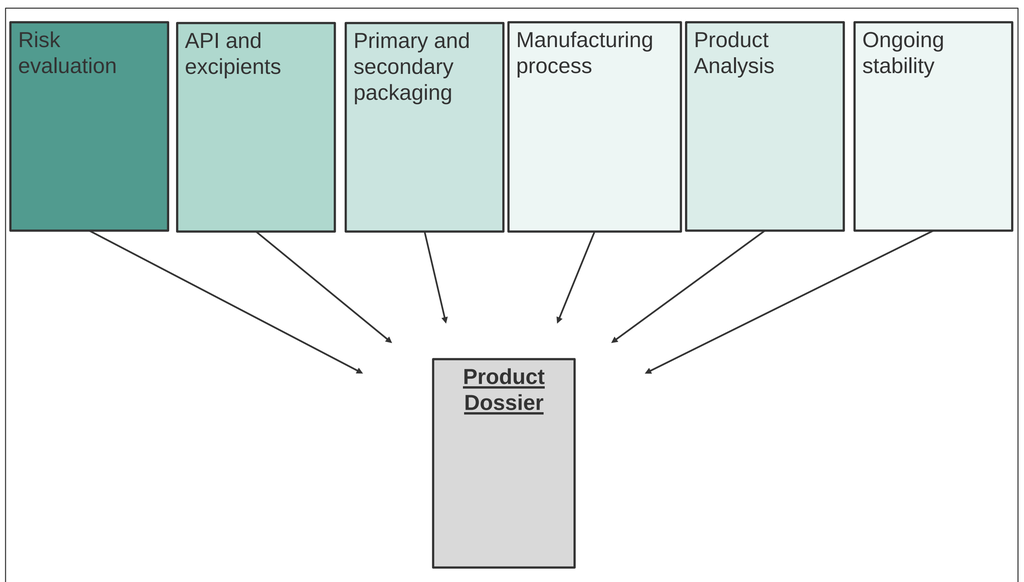
WHAT WAS DONE?

A Product Dossier for all extemporaneous preparations was established in The Capital Region Pharmacy, Denmark. It contains a risk evaluation and information about the specific value of the preparations, a demonstration that the active pharmaceutical ingredient(s), excipients and containers meet relevant requirements, an evaluation of the stability of the product, and a description of the preparation process and analysis.
All the information needed for the product dossiers were contained in various documents and needed to be collected through collaboration.



Information needed for the Product dossier.
It required the collaboration of several departments.

WHY WAS IT DONE?

On July 1st, 2016, an EU resolution caused a new national requirement to establish a product dossier for new as well as known extemporaneous preparations produced by the hospital pharmacy. We therefore had to establish product dossiers for 450 known products in our facilities.

HOW WAS IT DONE?

To approach the task, an interdisciplinary project group was formed. It consisted of members from Quality Assurance, Quality Control, Stability, The Drug Information Center and Production. A formulation for a collaborative approach was established to ensure a high and uniform quality of the product dossiers.

Senior specialists in each group collaborated on formulating and approving the first couple of Product dossiers to establish the quality level of information obtained and documented. This was approved among all the departments.
The information obtained included e.g., information and evaluation of API and excipients, ongoing stability studies, indication of the drug and alternative preparations.
Furthermore, a person from each department were selected to oversee the task and follow up to ensure the progress of the project. This included prioritizing the order of the products to be described.
See the box on the right for further description of the product dossier and an example.

WHAT HAS BEEN ACHIEVED?

Product dossiers for our products have successfully been implemented.
In some cases, the formulation regarding excipients was changed to better ensure patient safety. Based on stability data, storing of some products were changed.
Collaboration across departments has enabled us to ensure compilations of Product dossiers for our pharmaceutical stock preparations.
Completing the product dossiers on existing products has ensured a pool of knowledge about our products collected in one document and accessible to all departments in the hospital pharmacy.

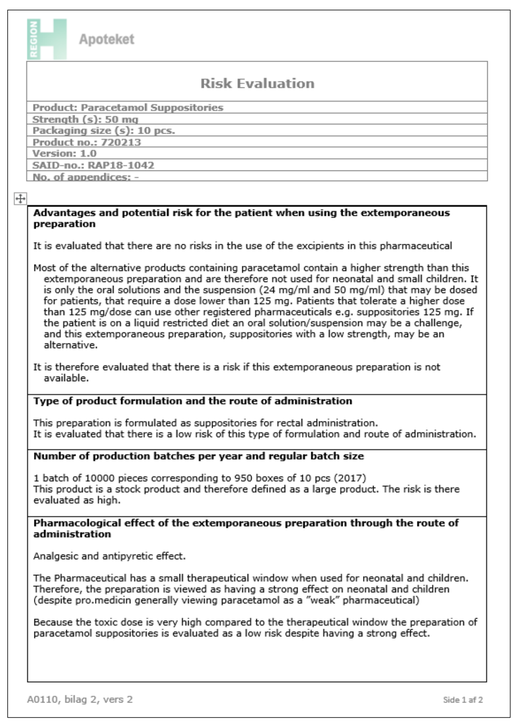
WHAT NEXT?

Through the interdisciplinary approach product dossiers ensure the focus on the quality, safety and benefits for the patients. All existing extemporaneous products will be maintained and evaluated anytime there may be a change in production.
Furthermore, the stability data will be continuously reviewed and along with the data the product dossiers and risk evaluation will be reviewed.
For all new products, a product dossier will be prepared according to the guidelines set up.
Having the information in one document ensures that all departments can quickly obtain information needed to consistently maintain and evaluate product quality and thereby the specific value of our production

PRODUCT DOSSIER

A product dossier consists of 2 documents: The Risk evaluation and the product dossier. Below is also an example of a filled-out Risk Evaluation and product dossier for the product Paracetamol suppositories 50 mg.

Risk evaluation:
The risk evaluation consists of the evaluation of advantages and potential risks for the patients using the specific product. Is this a product that is highly specialized, and would be essential in a back order, or may it be possible to substitute the product with another pharmaceutical.
The risk evaluation also evaluates how the drug is administered and the pharmacological effect, how it is manufactured (Sterile/non-sterile), how many annual bathces and batch size, as well as the therapeutic window. All this information is evaluated, and the product is given a risk level from low to high.



Apoteket

Risk Evaluation

Product: Paracetamol Suppositories
Strength (s): 50 mg
Packaging size (s): 10 pcs.
Product no.: 720213
Version: 1.0
SAID-no.: RAP18-1042
No. of appendices: -

Advantages and potential risk for the patient when using the extemporaneous preparation

It is evaluated that there are no risks in the use of the excipients in this pharmaceutical

Most of the alternative products containing paracetamol contain a higher strength than this extemporaneous preparation and are therefore not used for neonatal and small children. It is only the oral solutions and the suspension (24 mg/ml and 50 mg/ml) that may be dosed for patients, that require a dose lower than 125 mg. Patients that tolerate a higher dose than 125 mg/dose can use other registered pharmaceuticals e.g. suppositories 125 mg. If the patient is on a liquid restricted diet an oral solution/suspension may be a challenge, and this extemporaneous preparation, suppositories with a low strength, may be an alternative.

It is therefore evaluated that there is a risk if this extemporaneous preparation is not available.

Type of product formulation and the route of administration

This preparation is formulated as suppositories for rectal administration.
It is evaluated that there is a low risk of this type of formulation and route of administration.

Number of production batches per year and regular batch size

1 batch of 10000 pieces corresponding to 950 boxes of 10 pcs (2017)
This product is a stock product and therefore defined as a large product. The risk is there evaluated as high.

Pharmacological effect of the extemporaneous preparation through the route of administration

Analgesic and antipyretic effect.

The Pharmaceutical has a small therapeutical window when used for neonatal and children. Therefore, the preparation is viewed as having a strong effect on neonatal and children (despite pro.medicin generally viewing paracetamol as a "weak" pharmaceutical)

Because the toxic dose is very high compared to the therapeutical window the preparation of paracetamol suppositories is evaluated as a low risk despite having a strong effect.

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Apoteket

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Therapeutical window (dose intervals for therapeutical doses)

Using paracetamol for neonatal and children the therapeutical window is evaluated as small.

Overdose: A single dose of more than 125 mg/kg body weight for children may cause liver failure, that in the worst case may cause death.

The therapeutical window is evaluated as small, but the toxic effect is very high compared to the therapeutical window. Therefore, it is evaluated that paracetamol suppositories have a medium risk.

Type of formulation proces

Non-sterile production. Risk is low.

Conclusion

Overall, the risk of using this extemporaneous pharmaceutical for patients is evaluated as low.

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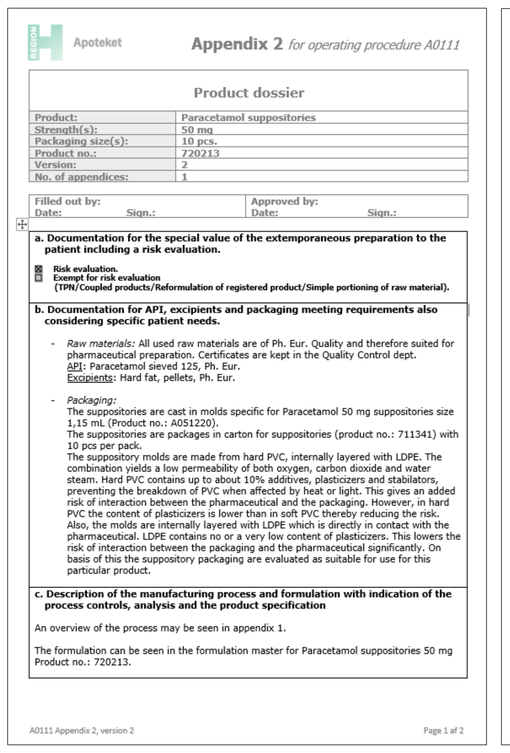
Product dossier:
Firstly it states whether a risk evaluation must be conducted. Some preparations e.g. TPN and simple reformulations of registrered pharmaceuticals are exempt.
Next, it evaluates the starting materials (API, excipients and containers) and ensure they meet the relevant requirements. Furthermore the manufacturing proces is described including process controls and the product analysis to fullfill the product specification. Furthermore the product dossier contain special information on the use of the pharmaceutical including potential special requirements e.g. storage temperatures.
Lastly the product dossier contains a short description of the stability data.



Apoteket **Appendix 2** *for operating procedure A0111*

Product dossier

Product:	Paracetamol suppositories
Strength(s):	50 mg
Packaging size(s):	10 pcs.
Product no.:	720213
Version:	2
No. of appendices:	1

Filled out by: Date: Sign.:	Approved by: Date: Sign.:

a. Documentation for the special value of the extemporaneous preparation to the patient including a risk evaluation.

☒ Risk evaluation.
☐ Exempt for risk evaluation
(TPN/Coupled products/Reformulation of registered product/Simple portioning of raw material).

b. Documentation for API, excipients and packaging meeting requirements also considering specific patient needs.

- *Raw materials:* All used raw materials are of Ph. Eur. Quality and therefore suited for pharmaceutical preparation. Certificates are kept in the Quality Control dept.
  API: Paracetamol sieved 125, Ph. Eur.
  Excipients: Hard fat, pellets, Ph. Eur.
- *Packaging:*
  The suppositories are cast in molds specific for Paracetamol 50 mg suppositories size 1,15 mL (Product no.: A051220).
  The suppositories are packages in carton for suppositories (product no.: 711341) with 10 pcs per pack.
  The suppository molds are made from hard PVC, internally layered with LDPE. The combination yields a low permeability of both oxygen, carbon dioxide and water steam. Hard PVC contains up to about 10% additives, plasticizers and stabilators, preventing the breakdown of PVC when affected by heat or light. This gives an added risk of interaction between the pharmaceutical and the packaging. However, in hard PVC the content of plasticizers is lower than in soft PVC thereby reducing the risk. Also, the molds are internally layered with LDPE which is directly in contact with the pharmaceutical. LDPE contains no or a very low content of plasticizers. This lowers the risk of interaction between the packaging and the pharmaceutical significantly. On basis of this the suppository packaging are evaluated as suitable for use for this particular product.

c. Description of the manufacturing process and formulation with indication of the process controls, analysis and the product specification

An overview of the process may be seen in appendix 1.

The formulation can be seen in the formulation master for Paracetamol suppositories 50 mg Product no.: 720213.

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Apoteket **Appendix 2** *for operating procedure A0111*

Product analysis will be conducted according to the analysis guidance LIMS analysis no.: 720213.

Bulk may be contained for one year at 2-8°C before packaging.

A visual inspection is conducted along with odor.
Analysis will be conducted according to the European pharmacopeia and includes average mass, variation in mass and dose, identification and quantification of the active pharmaceutical, and decay over time.

d. Development and background documentation for the manufacturing process.

An overview of the process may be seen in appendix 1.

Production equipment:
The temperature is gradually increased during casting to ensure the stability of the suppository temperature. The thermostat on the casting vessel is set 2 degrees below the wanted temperature according to page 4 in the formulation master. There is a stirrer in the casting vessel that will turn during the casting. This ensures a homogenous mass.

Batch size:
The batch size is 10000 pieces. The batch size has been determined based on sales, stability of the product and the capacity of the production equipment.

Sampling:
20 suppositories are sampled after a predetermined schematic divided throughout all rolls in the batch. This to ensure the process is in control throughout the entire casting.
Furthermore 10 suppositories are sampled randomly throughout the batch for the test for decay.
2 random boxes of 10 suppositories are saved as reference samples.

Argumentation for types of analysis:
Analysis follow the European pharmacopeia.
Average mass, and variation in mass and dose ensure the patients are given the correct dose.
Decay over time ensures the treatment will be effective within the wanted time frame.

e. Description of use of the pharmaceutical including relevant information for the patient and the prescribing doctor

The product is used for weak to moderate pain and will reduce fever. The product is primarily used in pediatric wards. (SAID-case no.: KFS13-2186).

On the label is printed: "To be stored in refrigerator (2°C to 8°C)" and "For insertion into the rectum"

f. Information on stability and stability documentation

The durability of the product from production is 2 years at 2°C to 8°C. the stability of the product has been confirmed through a schematic evaluation of data from continuous stability testing. Data is stored in SAU.

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ACKNOWLEDGEMENTS

We wish to conclude with a word of thanks to all colleagues in the departments for their hard work in making this a success.

https://www.ehp.eu/gpis/product-dossier-and-risk-evaluation-extemporaneous-preparations-keeps-Focus-patients