poster number: **GRP040**

Quality in pharmaceutical compounding for paediatric patients

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Background and Purpose

Licensed medicines for children are rare. As a result, pharmacy preparation plays a crucial role in this vulnerable patient group but its quality must be assessed carefully.
Our hospital pharmacy prepares various capsules for children by crushing and diluting licensed products. For the requested low concentrations, high and sometimes serial dilutions are necessary. We follow good pharmacy practice and use uniformity of mass as our routine quality control.

This study was conducted to assess the quality of our children capsules and therefore contribute to patient safety.
Specifically, we investigated the feasibility and quality of our dilutions and if conformity of mass is sufficient as a single routine quality control.

Material and Methods

Simulating standard concentrations, procedures and quantities, capsule samples were produced by each member of the production team.

We chose sodium chloride as the “active” compound for its accessibility, cost and detectability with one of our standard analytical methods (fig.1). Means, minimum and maximum values for chloride (in % of the labeled concentration) were identified.

The capsules were analysed for uniformity of mass (PH.EUR.6 2.9.5) and for uniformity of content (PH.EUR.6 2.9.6). Subanalysis were conducted using altered uniformity of content criteria. (fig. 2+3)

Ion chromatography for chloride with Dionex ICS90; column: IonPac® AS9-HC 4x250mm, guard: IonPac® AG9-HC 4x50mm; supressor: Dionex AMMS® III4-mm; eluent: 9mM Na_2CO_3; regenerant: 50mN H_2SO_4.

figure 1: analytical method for chloride

For capsules containing less than 300 mg (active ingredient + excipients) max. 2 capsules out of 20 with more than 10% deviation of the mean mass, not a single capsule with more than 20% deviation.

figure 2: criteria for uniformity of mass (PH.EUR.6 2.9.5)

Max. 1 capsule out of 10 is out of a 85-115% tolerance range and not a single one is out of 75-125%. If there are 2-3 capsules with more than a 15% deviation of the mean content **(CAUTION: we used labeled content for subanalysis in this study)**, further analysis of 20 capsules is allowed. Requirements are fulfilled if max. 3 capsules are out of the 85-115% range and none out of 75-125%.

figure 3: criteria for uniformity of content (PH.EUR.6 2.9.6 / **altered**)

Results

22 samples, each containing 50 capsules of either 0,1 mg or 1 mg concentration were produced by 11 members of our production team.

All samples (100%) met the PH.EUR.6 2.9.5 requirements for uniformity of mass. 4 (18%) of the samples failed the PH.EUR.6 2.9.6 criteria for uniformity of content.

The mean content of the labeled concentration was 89% (53,1-105,5%).

Subanalysis of the two different sample concentrations were carried out using altered PH.EUR.6 criteria (labeled instead of mean concentration) and are depicted in table 1 and 2.

Table 1 shows that in the 1 mg group (n=11), 3 (27%) conformed to the altered PH.EUR.6 criteria, 3 (27%) were eligible for further analysis and 5 (46%) disaccorded. The average content was 86,1% (78,1-95,3%) of the labeled concentration.

As for table 2: out of the 0,1 mg group (n=11), 2 (18%) met the altered PH.EUR.6 criteria, 2 (18%) allowed further analysis and 7 (64%) failed. The average content was 83,5% (53,1-105,5%) of the labeled concentration.

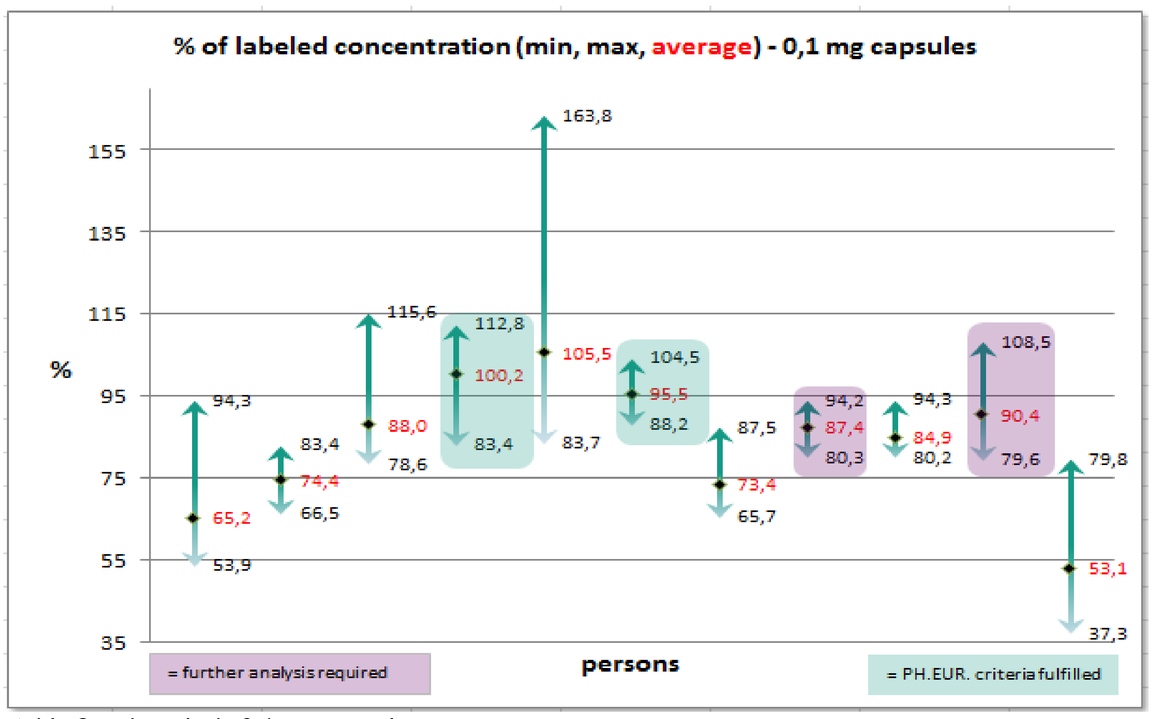

table 2: subanalysis 0,1 mg capsules

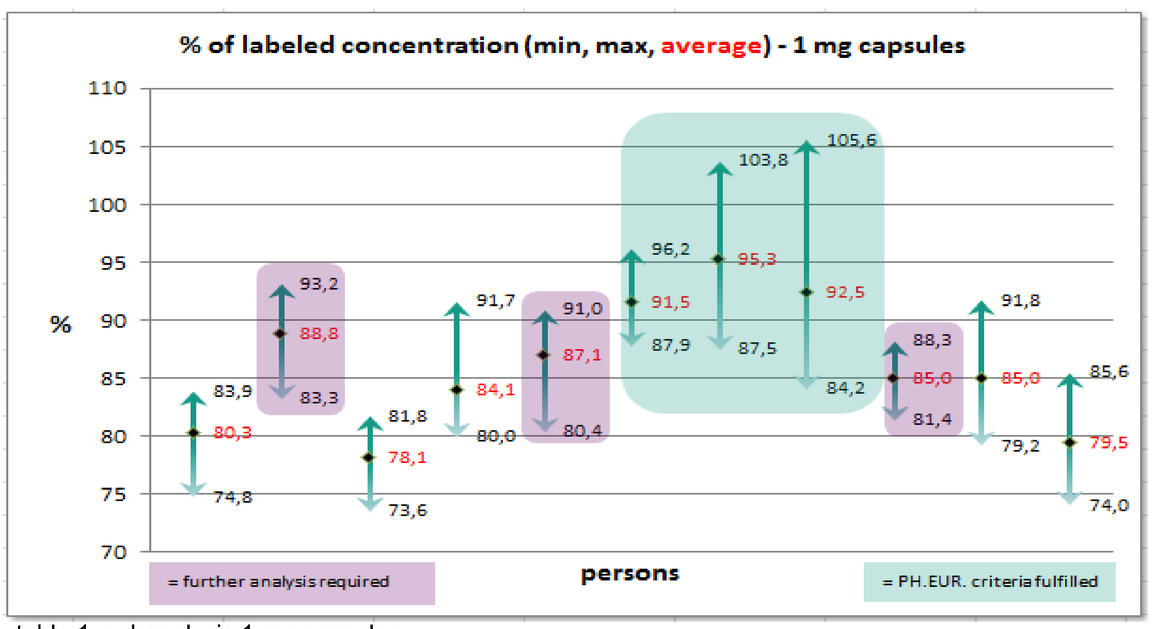

table 1: subanalysis 1 mg capsules

Conclusion and Discussion

Our study indicates that a routine check of conformity of mass is not sufficient for quality assurance of our preparations. It also showed that the dilutions don´t seem to result in acceptable concentration ranges in the capsules. This conclusion was drawn when we used labeled concentration instead of mean concentration for PH.EUR.6 testing, which in our view is more appropriate for vulnerable patient groups such as children.
A re-evaluation of the products and our production methods is planned. We will do uniformity of content testing using original extemporaneously prepared capsules instead of sodium chloride dummy capsules. A change to alternative dosage forms will also be evaluated.

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