

Experience of paediatric formulations in Marketing Authorisation Applications

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Overview of the presentation

- Formulation
- Measuring device
- Reconstitution – packaging / device
- Clinical trials
- Conclusion

NB:

In blue in the slides, quotations from MA dossier.

In red in the slides, comments from health authorities.

Formulation

Examples:

Oral suspension or powder for oral suspension

Poor / no development of the preservative system: (CPMP/CVMP/QWP/115/95; EP 5.1.3)

- No pharmaceutical justification of the type of preservative system chosen
- No pharmaceutical justification of the quantitative composition chosen

« (...) known to be effective over a pH range of 4 to 8, with a broad spectrum of antimicrobial activities against yeasts, moulds and bacteria. »

« The concentrations of each components used in the preservative system is based on pharmaceutical precedent. The determination of MIC is considered to be unnecessary based on nonclinical and clinical responses and compliance with Ph.Eur.5.1.3 Efficacy of Antimicrobial Preservation. »

Formulation (2)

Poor / no development of the preservative system:

→ Inappropriate justification of the quantitative composition chosen

Formulation	Nominal Preservative Concentrations (%)		Preservative Efficacy Test Result
	Methyl Parahydroxy-benzoate	Propyl Parahydroxy-benzoate	
1	0	0	Fail
2	0.050	0.008	Passed the test but product spoilage occurred
3	0.075	0.012	Pass
4	0.100	0.015	Pass

« Although Formulation 2 passed the test in terms of microbial count, it was clear from practical observation that the preservative system was unsatisfactory. Mould growth was observed floating on top of the sample that had been inoculated with *Aspergillus brasiliensis* and the sample with *Candida albicans* had become pressurised, again indicating that the organism was fermenting within the product. »

« As suggested by the CHMP, the Company now acknowledges that the recovery and enumeration of *Aspergillus brasiliensis* was not well controlled, and that the test results generated are therefore numerically unreliable. The Company has now improved the practical control of *Aspergillus* enumeration, (...). Nevertheless, the Company will continue to use the specialist contract laboratory, until the in-house generated data can be shown to be completely reliable. »

Formulation (3)

.....
Poor / no development of the preservative system:

→ Inappropriate justification of the quantitative composition chosen

Table 19 **Glass bottles, Ro 64-0796/V36-01**

Batch no. Test microorganisms	Log reduction					
	GMZ0152/01		GMZ0154/01		GMZ0159/01	
	14 d	28 d	14 d	28 d	14 d	28 d
Staphylococcus aureus ATCC 6538	5	5	5	5	5	5
Escherichia coli ATCC 8739	5	5	5	5	5	5
Pseudomonas aeruginosa ATCC 9027	4	4	4	4	4	4
Candida albicans ATCC 10231	4	5	5	5	5	5
Zygosaccharomyces rouxii NCYC 381	5	5	5	5	5	5
Aspergillus niger ATCC 16404	3	3	3	3	3	3

(...) the requirement of Ph. Eur. for this kind of oral preparation is 3 logs reduction for bacteria and 1 log reduction for fungi. Based on these results and based on the fact that proposed product is a paediatric formulations, the concentration of preservative has not been established at the lowest feasible level(...)

Formulation (4)

.....
Poor / no development of the preservative system:

→ No / inappropriate In-use study (CPMP/QWP/2934/99)

The reconstituted product can be stored in the refrigerator for 17 days. It should be shown that the fungicidal efficacy of preservative is sufficient also during storage in the refrigerator.

In-use test should also be performed on one batch chosen towards the end of its shelf-life.

“The reconstituted suspension was repeatedly inoculated immediately after reconstitution of the powder (t=0) and after 1, 3, 7, 10, 14, 28, 42 and 56 days. Prior each inoculation and 3 days after the last inoculation the number of micro-organisms was determined(...)”

for treatment: dose administered twice daily, for 5 days.

for prevention: dose administered once daily, for 5 days or once daily for 6 weeks.

Formulation (5)

No palatability study:

Case 1: «Through use in the “specials” formulation it is known to have a high degree of patient acceptability.»

«Throughout the entire period of supplying oral X suspension as a ‘Special’ (min 2500 children treated in 9 years), no adverse reports from children, parents, pharmacists or other healthcare professionals relating to acceptability/palatability have been received.»

«Brief survey of the current Top 10 customers, to obtain feedback on the ‘collective experience’ of the hospital as to the acceptability / palatability of the formulation. In the opinion of all respondents (10/10) the formulation of oral X suspension is acceptable / palatable.»

Case 2: «The artificial orange flavour 501071 AP0551 and a sweetening agent are added to Y Oral Suspension in consideration of palatability in younger children.»

Measuring device

.....

Exemple:

Oral suspension

Poor / no development of the measuring device: (Q&A EMA:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000072.jsp&mid=W00b01ac058002c2b0#section4)

Regarding the two syringes, the suitability of the graduation regarding dosing accuracy and dosing precision should be addressed from release throughout storage until the end of shelf-life of the drug product. Moreover, a sample of the two syringes should be provided.

« The volume accuracy of the oral syringes has been determined by the supplier... »

The suitability of the syringe has not been demonstrated.(...) should be performed with the actual drug product(...)

«(...) accuracy and repeatability of full syringe volume (1ml and 5ml respectively); accuracy and repeatability of delivered dose at 0.1ml increments for the 1ml syringe; accuracy and repeatability of delivered dose at 0.2ml increments for the 5ml syringe, from 1.2 to 5ml; accuracy and repeatability of delivered dose at intermediate increments, such as 1.5ml, 2.5ml, 3.5ml, and 4.5ml; precision of each syringe (5 syringes of each volume, increments of 0.3ml, 0.6ml, and 1ml and respectively 2.5ml and 5ml. »

Measuring device (2)

Risk of medication error:

Risk of medication error due to the 2 oral syringes in the same packaging;

Risk of medication error linked to the need to use 2 syringes to obtain an exact dose;

Risk of medication error related to the expression of posology in mg/BSA in the SPC and the PIL, and the syringes provided graduated in ml.

« The applicant proposes that the 1 ml and 5 ml syringes will be provided in different colours;

Is added in the PIL: *'Your pack of X contains a bottle of medicine, a cap, a bottle adaptor and two oral syringes (a purple 1 ml syringe and a white 5 ml syringe). Always use the syringes provided to take your medicine. It is important that you use the correct dosing syringe for your medicine. Your doctor or pharmacist will advise which syringe to use depending on the dose that has been prescribed. The smaller 1 ml syringe (purple), marked from 0.1 to 1 ml, is for measuring doses of less than 1 ml. You should use this one if the total amount you have to take is less than 1 ml (each graduation of 0.1 ml is 2 mg of X). The larger 5 ml syringe (white), marked 1 ml to 5 ml, is for measuring doses of more than 1 ml (each graduation of 0.2 ml is 4 mg of X). You should use this one if the total amount you have to take is more than 1 ml.'* »

Measuring device (3)

Risk of medication error:

The applicant agrees that the risk management plan will include strategy for surveillance of medication errors as a consequence of both syringe confusion and incorrect volume administration as a consequence of mg-ml misunderstanding.

Is added in the SmPC: 'It is recommended that the prescriber states the dose in both milligrams and millilitres on the prescription.'

(...) the dose may have to be adjusted during therapy. Therefore, in clinical practice it will not be possible to give a specific dose in the prescription that will label the drug container. To a layman, "mg" and "mL" are very similar words. Indicating both may increase the risk of a dosing mistake. In conclusion, the SPC should not be used to regulate how to write prescriptions.

The applicant proposes to add a dosing table in section 4.2, SmPC and 'How to take X' section in PIL (to link BSA / dose in mg / volume in mL)

25 mg/m ²			50 mg/m ²			75 mg/m ²		
BSA (m ²)	Dose (mg)	Volume (ml)	BSA (m ²)	Dose (mg)	Volume (ml)	BSA (m ²)	Dose (mg)	Volume (ml)
0.20 - 0.29	6	0.3	0.20 - 0.23	10	0.5	0.20 - 0.23	16	0.8
0.30 - 0.36	8	0.4	0.24 - 0.26	12	0.6	0.24 - 0.26	20	1.0
0.37 - 0.43	10	0.5	0.27 - 0.29	14	0.7	0.27 - 0.34	24	1.2
0.44 - 0.51	12	0.6	0.30 - 0.33	16	0.8	0.35 - 0.39	28	1.4
0.52 - 0.60	14	0.7	0.34 - 0.37	18	0.9	0.40 - 0.43	32	1.6

Reconstitution - Packaging / Device

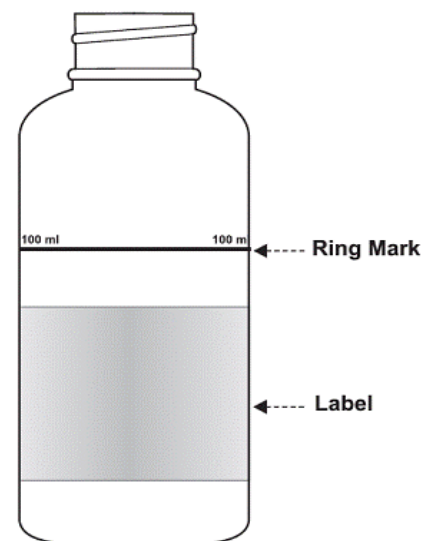
Examples:

Powder for oral suspension

Suitability / risk of medication errors / Bad exemple

«The bottle does not seem suitable for an accurate reconstitution of the suspension. The HDPE material is not translucent enough and the ring mark is hardly visible. Reconstitution errors may be expected.»

«(...)make the ring-mark slightly more prominent to further improve its visibility and additionally include embossing of “100ml” on the surface of the bottle immediately above the ring-mark. This embossing “100ml” shall appear 3 times on the bottle.»

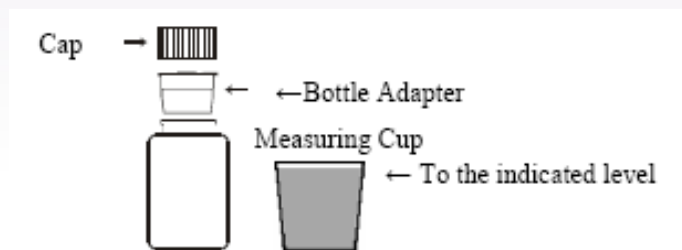


Reconstitution - Packaging / Device (2)

Suitability / risk of medication errors / Good example

«Prior to administration, Y powder for oral suspension is reconstituted in the amber glass bottle by adding the required amount of water, which is measured by means of a plastic measuring cup with a filling mark at 55 ml, followed by shaking the bottle.»

Package leaflet:



«Your pharmacist may have prepared the oral suspension for you when you collected your prescription. However, if they have not done this, then you can do it easily yourself. You only need to prepare the suspension once, at the beginning of your course. After that, all you need to do is shake the suspension well and draw up the appropriate recommended dose.

1. Tap the closed bottle gently several times to loosen the powder.
2. Measure 55 ml of water by filling the measuring cup to the indicated level (measuring cup included in the box). You should always use 55 ml of water, irrespective of the recommended dose you are taking.
3. Add all 55 ml of water into the bottle, recap the bottle and shake the closed bottle well for 15 seconds...»

Examples of clinical trials assessment

Suitability of the excipients: ethanol, complexe excipients (orasweet, oraplus ...)

Accuracy of the dose: when a tablet is crushed,...

Suitability of the preparation for administration: stability after dispersion in liquid / solid food, compatibility with nasogastric/orogastric tube ...

Conclusion

Development of paediatric formulations as appearing in Marketing Authorisation Registrations is of poor quality and far from being compliant to the draft guideline...

National specificities are strong in the assessment of paediatric formulations...

The paediatric guideline is necessary...

Close discussion is necessary with clinical assessor (palatability,...), with pre-clinical assessor (excipients) and with medication errors department (suitability of measuring device, of method of reconstitution)

Thank you for your attention

**Any
questions ?**