A.P.P.A.® Project: study of pediatric formulations for using in developing Countries

POLITECNICO DI TORINO

UNIVERSITÀ DEGLI STUDI DI TORINO

CUCS TORINO 2013

Immaginare culture della cooperazione:
le Università in rete per le nuove sfide dello sviluppo

III Congresso scientifico CUCS
Torino, 19-21 Settembre 2013

A.P.P.A.® Project: study of pediatric formulations for using in developing Countries

Francesca Baratta[1,2], Francesca Tarditi[1] and Paola Brusa[1,2]

[1] Aid Progress Pharmacist Agreement® onlus, via P. Giuria 9, 10125 Torino, Italy

[2] Department of Scienza e Tecnologia del Farmaco, University of Turin, via P. Giuria 9, 10125 Torino, Italy

Abstract

The *A.P.P.A.*® Project [1] is the result of the cooperation between the Pharmacy Faculty (TO) and local Pharmacists and it is in agreement with the International Health Cooperation principles. The Project is structured in six phases, through which it is possible to obtain an effective and functional **galenic lab in hospitals located in developing Countries** (DC). Due to the different socio-economic conditions each lab is a reality different from the others, always without forgetting the goal of opening labs that produce quality medicinal products. For each lab a specific handbook has been studied: each of them reflects the different local needs. For this reason, in the last two labs carried out in Angola and Haiti, it was necessary to introduce several formulations for pediatric use. For each preparation specific tests were performed to verify the stability under different environmental conditions, in accordance with the European Medicines Agency (EMA) guidelines [2].

Achieved Results

The **galenic medicines** studied until now for **pediatric use** have been prepared in different pharmaceutical forms:

✓**Solutions**: captopril, furosemide
✓**Suspension**: amoxicillin, carbocysteine, chloramphenicol, erythromycin, magnesium and aluminum hydroxide, metronidazole, vitamin B complex
✓**Syrups**: ascorbic acid, carbocysteine, ibuprofen, iron sulphate, paracetamol, potassium canrenoate, propranolol, quinine, ranitidine, salbutamol, vitamin B6
✓**Drops**: nifedipine, quinine, ranitidine, salbutamol, vitamin B6
✓**Suppositories**: paracetamol

For each preparation specific tests were performed to verify the **quality** and also the **stability** under different environmental conditions, in accordance with the **EMA guidelines** . Up today, all formulations have proved to be stable in "Refrigerated" conditions (T=5±3 °C) and "Standard" conditions (T=40±2 °C, UR 60±5%) for **12 months**, in "Accelerated" conditions (T=25±2 °C, UR 60±5%) for **3 months**.

Objectives

✓To realize **pediatric formulation** according to the needs of different hospitals
✓ To verify the **quality** [3-4] and also the **stability** [2] of the medicinal products under different environmental conditions

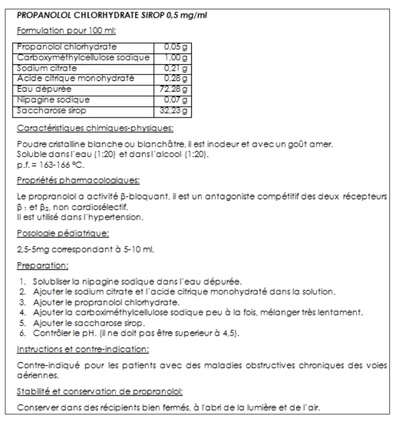
The study of pediatric formulation is very important considering that the **availability** of preparations designed for children is **limited**. Furthermore should not be underestimated the extremely high incidence of **counterfeit medicines** in DC [5].
For pediatric use **suppository** and **liquid preparations for oral use** should be preferred; in particular liquid preparations allow a simple modulation of the amount in function of the weight of several children afferent to the hospital.

The main goal of the stability study is that the preparations could therefore be **preserved in complete safety at homes even if these houses, as often happens in DC, are not equipped with air conditioners or refrigerators**.

"Pharmacien de la route"

Methodological approach

✓In agreement whit local medical doctors the **drugs** for the pediatric therapy are **chosen** and then **formulated** [6]: liquid oral formulations are preferred and appropriate excipients are selected.
✓For each formulation a **specific card** (written in local language) has been prepared. The card shows the procedure of preparation and the characteristics of each component present in the formulation.
✓Each preparation have been tested to check its **quality** and its **stability** under different environmental conditions in accordance with the EMA guidelines.



PROPANOLOL CHLORHYDRATE SIROP 0,5 mg/ml

Formulation pour 100 ml:

Propanolol chlorhydrate	0,05 g
Carboxymethylcellulose sodique	1,00 g
Sodium citrate	0,21 g
Acide citrique monohydraté	0,28 g
Eau dépurée	72,28 g
Nipagine sodique	0,07 g
Saccharose sirop	32,23 g

Caractéristiques chimiques-physiques:

Poudre cristalline blanche ou blanchâtre, il est inodeur et avec un goût amer.
Soluble dans l'eau (1:20) et dans l'alcool (1:20).
p.f. = 163-166 °C.

Propriétés pharmacologiques:

Le propranolol a activité β-bloquant, il est un antagoniste compétitif des deux récepteurs β_1 et β_2 non cardioséléctif.
Il est utilisé dans l'hypertension.

Posologie pédiatrique:

2,5-5mg correspondant à 5-10 ml.

Preparation:

1. Solubiliser la nipagine sodique dans l'eau dépurée.
2. Ajouter le sodium citrate et l'acide citrique monohydraté dans la solution.
3. Ajouter le propranolol chlorhydrate.
4. Ajouter la carboximéthylcellulose sodique peu à la fois, mélanger très lentament.
5. Ajouter le saccharose sirop.
6. Contrôler le pH. (Il ne doit pas être supérieur à 4,5).

Instructions et contre-indication:

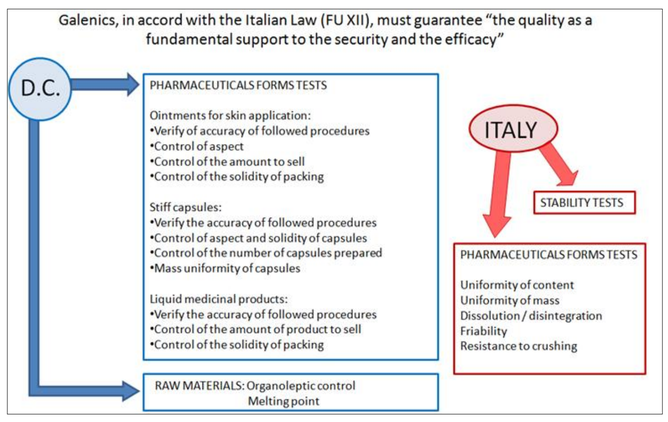
Contre-indiqué pour les patients avec des maladies obstructives chroniques des voies aériennes.

Stabilité et conservation de propranolol:

Conserver dans des récipients bien fermés, à l'abri de la lumière et de l'air.

Card for the preparation of the Propranolol syrup

Operator of the *A.P.P.A.*® lab of Haiti



Quality control and quality assurance

Considering the environmental conditions present in DC where the galenic products will be use and in order to investigate the stability of these medicinal products, *A.P.P.A.*®
performed a survey of the stability of various galenic dosage forms using different environmental conditions in accordance with the EMA guidelines. We endeavoured to gather information on stability of galenics at extreme environmental conditions (high temperatures and relative humidity) that might prove useful in those Countries (*e.g.*, African ones) where the tropical climate is a serious threat for the quality of drugs. Stability results of samples stored in "accelerated" (T=40±2°C, RH=50±5%) conditions supplied precious information on the expected stability of galenics in tropical Countries where extreme environmental conditions are often a limiting factor for correct storage of drugs.

TEST CONDITIONS				
STORAGE CONDITION	**T (°C)**	**RH**	**PERIOD COVERED BY DATA**	**ANALYTICAL METHOD**
Standard	25±2	50±5%	analysis at time zero (T0) and every 30 days (from TS-1 to TS-n)	UV-VIS spectrophotometric assay
Refrigerator	5±3	-	analysis at time zero (T0) and every 30 days (from TS-1 to TS-n)	UV-VIS spectrophotometric assay
Accelerated	40±2	50±5%	3 months, analysis at time zero (T0) and every 30 days (from TA-1 through TA-3)	UV-VIS spectrophotometric assay

Conclusion

✓ About **30 galenic medicinal products** for pediatric use have been studied and then formulated.
✓ For all formulations **quality** and **stability** have been demonstrated in accordance with EMA guidelines.
✓ The studied pediatric formulations are currently in use in the *A.P.P.A.*® laboratories of **Haiti** and **Angola**.

1] Aid Progress Pharmacist Agreement *(A.P.P.A.*®) no-profit organization web-site. Available from: www.progettoappa.it.
[2] Guideline on stability testing: stability testing of existing active substances and related finished products, 2003, CPMP/QWP/122/02, rev 1 corr
[3] European Pharmacopoeia, 7th edition, legally valid from 01/01/2011. Supplement 7.8, legally valid from 01/07/2013 until 31/12/2013. Available from: www.edqm.eu.
[4] Ministry of Health. Good Manufacturing Practices for galenic medicinal products in pharmacy, Official Pharmacopoeia of the Italian Republic XII edition [Italian]. Roma: Polygraphic Institute of the State; 2008.
[5] Baratta F., Germano A., Brusa P. Diffusion of counterfeit drugs in developing countries and stability of galenics stored for months under different conditions of temperature and relative humidity. CMJ. 2012; 53: 173-184.
[6] Brusa P., Germano A. Technological and management procedures for Galenic Laboratory in Pharmacy. Torino; 2007, accredited by FOFI on 16/06/2008, www.fofi.it. [Italian]