

## The A.P.P.A.<sup>®</sup> Project: formulation, stability and quality study of a pediatric galenic preparation for the treatment of sickle cell disease at Saint Damien Hospital in Haiti



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## THE A.P.P.A.® PROJECT

- ✓ International Health Cooperation
- ✓ It is based on voluntary work
- ✓ Its aim is the realization, within the health facilities of Developing Countries, of <u>laboratories for the</u> <u>preparation of galenic medicines</u> on the basis of the local therapeutic needs.

# The medicinal products prepared must meet the requirements of:QUALITYSAFETYEFFICACY

#### The advantages are:

- Customizing the dosages and pharmaceutical forms according to the actual needs of patients
- ✓ Employing local staff, to whom a profession is taught
- Minimizing the financial commitment necessary to prepare the medicines
- ✓ Discouraging the use of counterfeit medicines



### **COUNTERFEIT MEDICINES**

"A counterfeit medicine is one which is **deliberately and fraudulently mislabeled with respect to identity and/or source**. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging" (WHO)



Douala, Cameroon

#### "IMPERFECT" COUNTERFEITS

«These products contain the right components, with an incorrect concentration and/or formulation resulting in defective quality specifications. In the vast majority of cases, they are devoid of any therapeutic efficacy»

#### "CRIMINAL" COUNTERFEITS

«They are apparently similar to the original medicinal product, but do not contain any active ingredient and can even include harmful or toxic substances. They are usually sold at high prices and for the treatment of serious pathologies. Consequences for users of criminal counterfeits can be fatal»

Di Giorgio D. Counterfeit drugs. The phenomenon and enforcement activities. Milano: Tecniche nuove; 2010.

### PHASES OF A.P.P.A.® PROJECT



Preliminary pharmaco-economic study which implies a trip on site to evaluate the local situation. Some industrial medicines should be purchased in local pharmacies and sent to the laboratory of the University of Turin to evaluate if these medicinal products, present on the local market, meet the requirement of quality.



Choice of the medicines and the related pharmaceutical forms, based on the local need.



Learning of the preparation techniques of the pharmaceutical forms by the student of pharmacy.



Internship in Italy of an operator coming from the country of destination of the Project. Purchase and delivery on site of the equipement and of the raw materials required.



Mission on site of the trained student with the purpose of setting up the laboratory and transmitting, in coordination withe the operator that was trained in Italy, to the others local operators the acquired knowledge.



Preparation of medicinal products and related quality control; moreover, routinely, some samples are sent to University of Turin, where they are tested to verify their quality.



Periodical missions of Pharmacy's students at new lab are performed each year to give a continuous supervision in the production of medicinal products and eventually to introduce new formulas according to the requests of medical doctors responsible of the health facility.

### A.P.P.A.® LABORATORIES IN THE WORLD



ANGOLA – Cubal, Nossa Senhora de Paz hospital, Compañia de Santa Teresa de Jesus.

ANGOLA – Funda, A.M.E.N. ONG health care facility.

**CAMEROUN** – Douala, La Bethanie hospital – Kribì – Saint Joseph hospital

**CAMEROUN** – Garoua, Notre Dame des Apôtres hospital, Djamboutou.

TCHAD – N'Djamena, Le Bon Samaritain hospital.

TCHAD – Biobé, Le Bon Samaritain hospital.

HAITI – Tabarre Chateaublond, N.P.H. Saint Damien paediatric hospital.

MADAGASCAR – Vohipeno, Henintsoa hospital.

MADAGASCAR – Ihosy, Eglise Catholique Apostolique Romaine medical center.

### HÔPITAL SAINT DAMIEN

- ✓ Located in Tabarre, suburb of Port-au-Prince
- ✓ Facility of excellence
- ✓ The biggest peadiatric hospital of the Caribbean
- ✓ Realized thanks to the big contribution of the Fondazione Francesca Rava – N.P.H. Italia ONLUS
- ✓ In 2015, 13300 children were visited and 3400 hospitalized



Cité Soleil



St Damien hospital

**Offered services:** 

Emergency room, surgery, laboratory of analysis, outpatients ward, cancer ward, dental clinic, recovery program for mlnourished children, vaccinations and screening ward, maternity ward, PHARMACY







The preparation of capsules



### **INTRODUCTION OF HYDROXYUREA SYRUP 100 mg/ml**

#### SICKLE CELL DISEASE (SCD)

Group of inherited red blood cell disorders. People with SCD have abnormal hemoglobin that makes the red blood cell sickle shaped and stiff

- Oxygen delivery problems
- Vascular occlusions



#### PREVALENCE

Prevalence worldwide  $\rightarrow$  1: 23 333

Prevalence among the African Americans  $\rightarrow$  1: 365

Prevalence in Haiti  $\rightarrow$  1:173

Rotz et al - Prevalence of sickle cell disease, hemoglobin S, and hemoglobin C among Haitian newborns, American Journal of Hematology, 2013



Global map of the presence or absence of the sickle cell mutation

Tewari et al -Environmental Determinants Of Severity In Sickle Cell Disease, Haematologica, September 2015



In collaboration with the *Akron Children's Hospital* of Ohio, USA, study on 50 patients:

Valutation dell'APPLICABILITY OF THE THERAPEUTICAL PROTOCOL in a DEVELOPING COUNTRY



### **INTRODUCTION OF HYDROXYUREA SYRUP 100 mg/ml**

Formulation request by the medical staff:

LIQUID PREPARATION FOR ORAL USE based on sucrose syrup (100 mg/ml) – paediatric use



100 cps
0,25 g
250,00 g
296,00 g

- 1. Preparation of an aqueous solution of hydroxyurea
- 2. Filtration
- 3. Addition of sucrose syrup

### ANALYTICAL METHOD TO PERFORM THE STABILTY TEST AND THE QUALITY CONTROL



• SIMPLE TO REPRODUCE

**IODOMETRIC TITRATION** 



- The sample is treated with NaHCO<sub>3</sub> 10% and NaH<sub>2</sub>PO<sub>4</sub> 20% solutions
- Reaction between HYDROXYUREA and 0,01 N IODINE
- The excess iodine is titrated with 0,01 N THIOSULPHATE

 $2 S_2 O_3^{2-} + I_2 \rightarrow S_4 O_6^{2-} + 2 I^{-}$ 

- Conversion factor: 1 ml of iodine 0,01 N corrisponds to 0,360 mg of hydroxyurea
- Maximum reactivity with basic pH

Alicino J.F., Assay for Hydroxyurea. Microchemical Journal.1970.15:83-87

#### **STABILITY TEST**

### **Evaluation of the expiration date**

EMA Guideline on stability testing: stability testing of existing active substances and related finished products, 2003, CPMP/QWP/122/02, rev 1 corr

STORAGE CONDITION	T (°C)	RH %	PERIOD COVERED BY DATA		
Standard (SC)	25±2	60±5	12 months. Analysis at time zero (T0), every 30 days for 3 months (SC-T1 to SC-3), after 6 months (T6), after 12 months (T12)		
Refrigerated (RC)	5±3	1	12 months. Analysis at time zero (T0), every 30 days for 3 months (RC-T1 to RC-3), after 6 months (T6), after 12 months (T12)		
Accelerated (AC)	40±2	60±5	12 months. Analysis at time zero (T0), every 30 days for 3 months (AC-T1 to AC-3), after 6 months (T6), after 12 months (T12)		

T0: time 0; T1: 30 days; T2: 60 days; T3: 90 days; T6: 180 days

T: temperature; RH: relative humidity

#### **RESULTS OF THE STABILITY TEST OF THE HYDROXYUREA SYRUP 100 mg/ml\***

Storage	Т0	T1	T2	T3	T6	T12
conditions	Δ%	Δ%	Δ%	Δ%	Δ%	Δ%
SC	-2,01%	+2,12%	+1,04%	-2,85%	-7,50%	-11,49%
RC	-	+3,96%	+0,61%	+0,57%	-4,76%	-5,42%
AC	/	+2,85%	-2,17%	-9,11%	-21,22%	-45,48%

\*The results represents the average of the analysis of 15 samples  $\Delta\%$  = percentage error compared with the expected concentration value Stability is demonstrated when: -10% <  $\Delta\%$  < +10% Stability was demonstred up to 3 months in tropical conditions

#### **QUALITY CONTROL AND QUALITY ASSURANCE**

In galenics, in accordance the European Law (Ph Eur,), "the quality as a fundamental support to the security and the efficacy" must be ensured





PHARMACEUTICAL FORMS TESTS (Ph Eur) Uniformity of content (2.9.6) Uniformity of mass (2.9.5) Disaggregation (2.9.1) Friability (2.9.7) Hardness (2.9.8) Sterility (2.6.1)

#### **INTRODUCTION OF MEDICINAL PRODUCT ON SITE**

#### AVERTISSEMENTS POUR L'EMPLOI DE L'HYDROXYUREE

PENDANT TOUTES LES OPÉRATIONES IL FAUT:

- OPÉRER SOUS LA HOTTE CHIMIQUE
- UTILISER LES GANTS, LE MASQUE ANTI POUSSIÈRE, LES LUNETTES DE PROTECTION N.B. LA MASQUE ANTI POUSSIERE EST PERSONNELLE.
  IL FAUT ÉCRIRE LE NOMBRE DE L'OPERATEUR ET LA DATE DE PREMIÈRE UTILISATION DESSUS ET LA GARDER DANS LA HOTTE.
  IL FAUT LA UTILISER PENDANT 6 MOIS AU MAXIMUM.

À LA FIN DU TRAVAIL IL FAUT:

- NETTOYER SOIGNEUSEMENT LE MATERIÈL ET LE PLAN DE TRAVAIL AVEC ALCOOL 70°
- ÉLIMINER LES DECHETS DANS UN CONTENEUR ADAPTÉ SOUS HOTTE
- SE LAVER SOIGNEUSEMENT LES MAINS

Le risques associés à l'utilisation de la substance sont les suivants - Sensibilisation respiratoire, categorie 1

Mutagénicité sur les cellules germinales, categories 1A, 1B,2

- Mutagenicite sur les cellues gerninales, calegories
- Carcinogénicité, categories, 1A, 1B, 2

Toxicité reproductive, categories 1A, 1B,2

- Toxicité spécifique pour un organe cible à la suite d'une exposition unique, categories 1,2
- Toxicité spécifique pour un organe cible à la suite d'une exposition répétée, categories 1,2
- Danger d'aspiration, categorie 1





#### PROCEDURES FOR THE PREPARATION AND THE MANIPULATION OF THE HYDROXYUREA SYRUP

Training to:

- Technical personnel of the galenic laboratory
- Technical personnel of the external pharmacy
- Nursing staff







## CONCLUSIONS



- ✓ The new formula was studied, its quality was demonstrated and its stability was tested
- ✓ The local personnel was trained to produce the medicinal product
- ✓ During 18 months about 40 liters of hydroxyurea syrup were prepared and dispensed to nearly 50 patients involved in the study
- ✓ The study is giving promising results: the treatment of sickle cell disease with hydroxyurea will improve the quality of life of many haitians



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- The NPFS Saint Damien Hospital, Haiti. In particular all the local technicians which in these years have been working in the lab







Nos petits frères et sœurs - Haiti – Hôpital Saint Damien

## FOR FURTHER INFORMATION VISIT: www.progettoappa.it WRITE AT: appa.onlus@unito.it

