A.P.P.A.® Project: an example of international health cooperation

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A.P.P.A.® PROJECT: AN EXAMPLE OF INTERNATIONAL HEALTH COOPERATION

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ABSTRACT
The *A.P.P.A.*® Project is the main activity of *Aid Progress Pharmacist Agreement* no profit association; the Project, started in 2005, is the result of the cooperation between the Pharmacy Faculty (TO) and local Pharmacists. The Project is in agreement with the International Health Cooperation principles and it complies both with Italian and guest Countries laws.
Objectives:

- realizing galenic lab in hospitals located in developing Countries (DC) with the aim of preparing medicinal products which comply with adequate quality requirements, first of all to fight the widespread phenomenon of counterfeit in DC;
- customizing the dosages and pharmaceutical forms according to the actual needs of patients;
- employing local staff, teaching them a "new job" in order to open suitable school;
- minimizing the financial commitment necessary to prepare these medicines.

The Project is structured in six phases, through which it is possible to obtain an effective and functional lab: from a preliminary study of local needs up to a constantly and accurate control of the prepared galenics by analysis in the laboratories of University of Turin.
The pharmaceutical forms proposed are liquid, capsules, ointments and suppositories.
The most important results showed that several Projects are going on:

- *Centre Médico-Chirurgical Maternité la Bethanie*, Douala, Cameroon
- Hospital *Notre Dame des Apòtres*, Garoua, Cameroon
- Healt Center *Le Bon Samaritain*, N'djamena, Tchad
- Hospital *Heintsoa*, Vohipeno, Madagascar
- Dispensario Diocesano, Ihosy, Madagascar
- Hospital *Nossa Senhora da Paz*, Cubal, Angola
- A.M.E.N. Onlus center, Funda, Angola
- Hospital *Saint Damien*, Tabarre, Haiti

Each lab so far has reached a different state of evolution. All of them are growing day by day, helped by the constant support of all team *A.P.P.A.*®, whose purpose is the one of making them indipendent from both knowledges in handling galenics and economy in order to buy new raw materials using the gain of medicines sale.

COUNTERFEITS

Nowadays one of the worst plagues of Developing Countries (DC) is represented by the phenomenon of counterfeits. Custom procedures are less stringent, authorities controls are less effective so counterfeit medicines could be easily distributed in the market of these Countries with a substantial loss of public confidence in the healthcare system.

The principal target of counterfeits are life-saving drugs and it increases the risk of resulting deaths, but not only because sometimes it can give rise to events of catastrophic proportions like in Niger in 1995 where about 60.000 people had been injected with a counterfeit meningitis vaccine, or in Haiti in 1996 where a diethylene glycol contamination of pediatric syrup killed more than 80 children [1, 2].

In all DCs anti-retroviral drugs, antimalarics and antibiotics are principally affected, sometimes with staggering percentages: for instance an international study published in 2004 has shown that more than 53% of artesunate tablets sold in south-east Asia did not contain any active ingredient at all, with imaginable consequences on the fight against malaria in those Countries [1, 3].

In order to verify and better understand we have investigated the extent of the phenomenon of pharmaceutical counterfeits in some DC including the Countries where *A.P.P.A.*® is working [4]. With our research we investigated the quality of medicines purchased *in loco* from pharmacies and from unofficial street-pharmacists (figure 1). Samples collected in the different DC were analysed in the laboratories of the Department of Scienza e Tecnologia del Farmaco, University of Turin (Italy).

Fig. 1: Cameroun, street pharmacist.

Results and discussion

The study we conduced confirmed that counterfeits medicines are one of the most problematic issues in DC and we found that the absence of controls and the inadequate pharmacovigilance system causes difficulties both in revealing and monitoring the phenomenon and its effects among the population.

Based on our results it was possible to determinate that 50% of tested items were substandard drugs and 2% were counterfeits without the presence of declared API: they could be defined criminal false, a dosage form in which the active pharmaceutical ingredient is completely absent or present in an amount absolutely non effective.

The results also show that Indian drugs are often substandard: 30 out of 61 Indian samples (i.e., 41,7%) showed OOS (Out Of Specification) [5].

These outcomes we found are in accordance with international data retrievable in literature [6-9] and confirmed that the main target of counterfeiters is represented by expensive life-saving drugs (table 1) and this trend is likely to be maintained also in the future [10-14]; this research showed that it is rather common to find counterfeits in Developing Countries, even in astonishing percentages (figure 2).

Reported results and discussed topics point emphasize and increase the relevance of *A.P.P.A.*® Project in Developing Countries.

	No. (%) of samples	
Therapeutic classes	**available for analysis**	**counterfeit**
Antibiotics	76 (34.4)	30 (29.7)
Anti-inflammatories	44 (19.9)	22 (21.8)
Antipyretics	24 (10.9)	9 (8.9)
Antimalarics	17 (7.7)	6 (5.9)
Antimycotics	13 (5.9)	9 (8.9)
Antihypertensives	8 (3.6)	1 (1.0)
Antianemics	5 (2.3)	4 (4.0)
Spasmolytics	5 (2.3)	2 (2.0)
Diuretics	5 (2.3)	1 (1.0)
Antiacids	5 (2.3)	2 (2.0)
Bronchodilators	4 (1.8)	5 (5.0)
Others	15 (6.8)	10 (9.9)

Tab. 1: Therapeutic classes of the total and counterfeit samples [5].

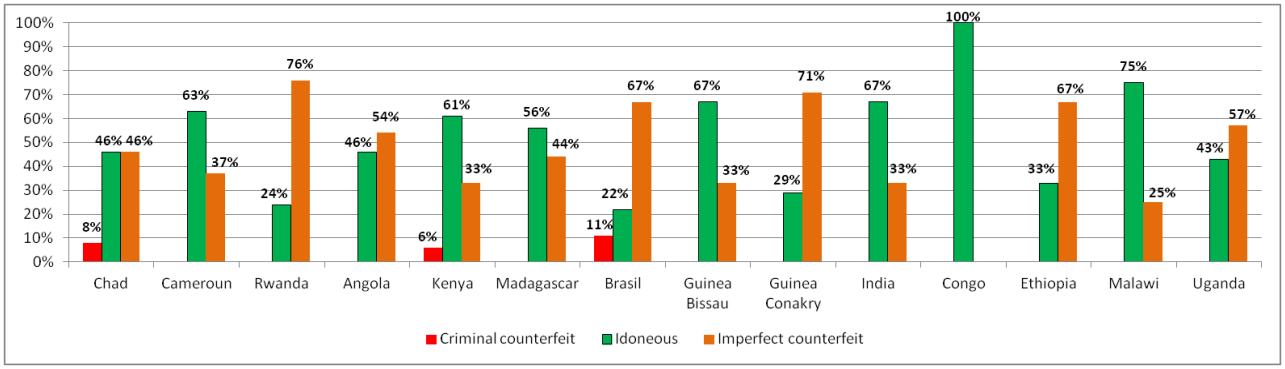

Fig 2: presence of counterfeit drugs by Country. Red bars – criminal counterfeit; green bars – idoneous; orange bars – imperfect counterfeit [5].

A.P.P.A.® PROJECT

A.P.P.A.® [4] is a no profit association based on voluntary work without any profit proposing; its main aim is *A.P.P.A.*® Project, which argues on the realization of galenic laboratories in Developing Countries around the globe in accordance with the guidelines of International Health Cooperation.

The creators of the Project teach through the Pharmacy's students to local staff how to prepare galenic medicines with a high level of quality and consequently security and efficacy. *A.P.P.A.*® Project is built on a close collaboration with the academic world, represented by University of Turin, Faculty of Pharmacy, and with Community Pharmacy.

The main objectives of the Project are:

- realizing galenic laboratories in Developing Countries with the aim of preparing medicinal products which comply with adequate quality requirements, first of all to fight the widespread phenomenon of counterfeit in DC;
- customizing the dosages and pharmaceutical forms according to the actual needs of patients;
- employing local staff, teaching them a new "job" in order to open suitable school;
- minimizing the financial commitment necessary to prepare these medicines.

Many are the main reasons to propose galenics: the first one is that the production system is low cost and the operative procedures are simple; the second one, most interesting and important in our opinion, is the possibility to prepare medicinal products with dosage and pharmaceutical forms according to the customer demand and, of course, to medical prescriptions, last but not least, this Project allows to reduce the use of counterfeit medicines in structures where the galenic lab is located.

When a new galenic laboratory is required we usually conduce a preliminary study that implies for an our staff member a trip on site to value the local situation and recipient areas [step 0 of *A.P.P.A.*® Project]. In this step a precise protocol is used to guarantee all preliminary needed information. Furthermore some medicines should be purchased in local pharmacies and sent to the laboratory of the University of Turin, which will provide for the qualitative and quantitative analyses; the results allow to value if these medicinal products, present on the local market, respect the declared characteristics or are counterfeit.

The Project complies both with Italian and guest Countries laws, always saving the quality of medicinal products. The pharmaceutical forms proposed are liquid preparations, capsules, ointments and suppositories.

This feasibility study is essential to evaluate the actual possibility of opening a new *A.P.P.A.*® lab. Only if we find the real need for the galenic laboratory required, as suggested by International Health Cooperation objectives, we can carry out with the following six phases of *A.P.P.A.*® Project:

1. The first one implies the choice of the place where the galenic lab could be realized. The medical doctor responsible of medical center will put in evidence local pathologies, then will be projected the correct pharmaceutical forms.
2. The second one implies a stage at galenic *A.P.P.A.*® laboratory at the University of Turin (Italy), for students of Pharmacy Faculty -during their experimental thesis-; the stage allows learning necessary to prepare the programmed medicinal products.
3. The third one provides staying in Italy of a person of local staff with the aim of learning the procedures of galenic preparations (about one month work) under Pharmacy's students supervision. During this period we send the material for galenic lab to the hospital (figure 3).

Fig. 3: Italy, Romel Cajuste during his stage at *A.P.P.A.*® laboratory.

4. The fourth one concern in a training period (about sixty days) in the hospital, during which the technician, who has been in Italy to learn galenic methods and procedures, will be coordinate in his work by the Pharmacy's students on site (figure 4, 5).

Fig. 4: Angola, Funda, A.M.E.N. Medical Center.

Fig. 5: Cameroun, Garoua, "Notre Dame des Apòtres″ Hospital.

5. The fifth one concerns in quality control of medicinal products routinely prepared in new galenic lab; moreover some samples of these will be sent to University of Turin, where their quality will be tested.
6. The last one concerns in periodical stages (at least forty days) for students -during their experimental thesis-. These stages will be performed each year both to permit a continuous supervision of medicinal products prepared in the lab and to study new formulations according to the request of the medical doctor responsible of the medical center which might change by the time.

Often many points must be examined and modified considering the reality and requirements of demanding structure, but without losing quality of galenics.
The Project considers a budget which includes equipment but not furniture or raw materials that strictly depends on the therapeutic requirements of the different places. The funds necessary to the whole creation of a lab are raised through the collaboration of groups involved in International Cooperation. It is indispensable to guarantee a good activity of the galenic laboratory for the hospital to reinvest the earning obtained by dispensing of medicines prepared in the conduct of the laboratory. In this way the laboratory will be self-financed and there will be a continuous production. About the raw materials, the hospital can buy them in Italy or other Countries respecting quality and title of the raw materials to be used.

Results and discussion

Several Projects are going on, at different state of progress:

Cameroun - Hospital La Bethanie, Bonaberi-Douala; GinTeam ONLUS; St. Joseph Congregation Hospital, Kribi - Phase 6 of *A.P.P.A.*® Project

Cameroun - Hospital "Notre Dame des Apòtres", Djamboutou-Garoua; Fondazione CUMSE Onlus - Phase 6 of *A.P.P.A.*® Project

Chad - Health Center "Le Bon Samaritain", Walia-N'Djamena; association tchadienne «Communauté pour le Progrès» (ATCP) ONG; Acra ONG - Phase 6 of *A.P.P.A.*® Project
Madagascar - Hospital "Henintsoa", Vohipeno; Anemon ONLUS - Phase 6 of *A.P.P.A.*® Project
Madagascar - Health Center, Eglise Catholique Apostolique Romaine, Ihosy; Anemon ONLUS; Lions Club Torino San Carlo - Phase 6 of *A.P.P.A.*® Project
Angola - Hospital "Nossa Senhora da Paz", Compañia de Santa Teresa de Jesus, Cubal; Dani Instruments S.p.A; Comunità di S. Egidio – ACAP (O.N.L.U.S.) - Phase 6 of *A.P.P.A.*® Project
Angola - Health Center A.M.E.N. ONG, Bairro CowBoy, Funda; Dani Instruments S.p.A; AMEN onlus – Italia - Phase 5 of *A.P.P.A.*® Project
Haiti - Pediatric Hospital N.P.H. Saint Damien, Tabarre; N.P.H. Italia Onlus, Francesca Rava Foundation - Phase 6 of *A.P.P.A.*® Project
Sierra Leone – Hospital "Saint John of God", Mabesseneh, Lunsar; Saint Joseph Fathers Congregation, Rainbow for Africa, Engim ONG - Phase 1 of *A.P.P.A.*® Project

Each lab has so far reached a different state of evolution. All of them are growing day by day, helped by the constant support of all team *A.P.P.A.*®, whose purpose is the one of making them independent from both knowledge in handling galenics and economy in order to buy new raw materials using the gain of medicines sale. Our experience has till now demonstrated that at least 5-6 years are necessary because the laboratory reach its independence if there are not changes of personnel.

GALENICS FOMULATIONS, QUALITY AND STABILITY CONTROL

Magistral and officinal formulations (commonly known as "galenics" in homage to Galen of Pergamum who is regarded as the first pharmacist engaged in the preparation of medications) are required to be prepared, labelled and stored using standard procedures and established methods in order to ensure the quality of finished product which is a mandatory prerequisite for its safety and efficacy [15, 16].

Since *A.P.P.A.*® Project is based on galenics, we had the necessity to perform a survey on the stability of various galenic dosage forms commonly prepared in pharmacy, in order to investigate the actual stability of these medicinal products [17, 18].

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.

Moreover, considering that one of the main aim of *A.P.P.A.*® Project is the fight against counterfeits and then the production of quality medicinal products, we settled up procedures to make quality control tests on galenics produced in our laboratories in order to verify and guarantee their quality.

Results and discussion

Storage conditions, chemical and physical nature of the API, containers, environmental conditions and the compatibility of API with excipients might affect considerably the final quality of galenic preparations.

All these factors, considered as a whole, define the use-by date of medicinal products that must be reported on the label. The current legislation has decided to define precautionary validity limits for galenics depending on the nature of their dosage form, leaving to the pharmacist the option to increase these limits relying on scientific data. [19].

Based on our results it was possible to determinate that in tropical Countries the tested dosage forms are stable for a period of 24 months in "Standard" conditions [17]. In "Accelerate" conditions [17], samples were stable for 3 month provided that they have been stored in glass containers, propylene is not suitable at high temperatures due to probable interactions of active substances with extractables and leachables materials from the container. Stability results of samples stored in "Accelerate" conditions also 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. The results do not imply that it is possible to increase the use-by date of all galenics, but it can be done for those dosage forms tested and prepared following standard general principles [16, 20].

To guarantee the quality of medicinal products made in *A.P.P.A.*® labs we constantly analyse some samples applying procedures in line with the tests of the European Pharmacopea. The results of the analysis must be within the limits imposed by the law in force, otherwise the medicinal products can not be used [16]. In any Country we operate we claim to meet the requirements of quality, safety and effectiveness required; the consequence was a good answer by local technicians and their proposal to better apply the standard procedures established and shared.

CONCLUSION

A.P.P.A.® Project started in 2005, till now we opened an amount of 8 galenic laboratories in 5 different Developing Countries between Africa and America. The laboratories are now working on and they are at various state

of progress. In 8 years about 30 students of Pharmacy have been involved in this Project and about 30 local technicians are working in the opened laboratories.

Through the positive results obtained from the steady execution of quality control tests on galenics made in our labs we demonstrated that it is possible to produce good medicines even in Developing Countries where conditions are not always in favor. It proves that the procedures that we settled up during these years are reliable methods that guarantee the production of medicinal products of high quality.

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