Clinical gelenics: examples of applications in the national context and in developing countries

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(Article begins on next page)
CLINICAL GELENICS: EXAMPLES OF APPLICATIONS IN THE NATIONAL CONTEXT AND IN DEVELOPING COUNTRIES

Francesca Baratta

Department of Scienza e Tecnologia del Farmaco, University of Turin, Italy
THE GALENICS: AN ANSWER TO THE HOSPITAL PECULIAR NEEDS

- Modulation of the amount of API in the preparation
- Formulation of associations of API which, if present in the same preparation, may show greater efficacy
- Therapeutic treatments for patients with different ages with special needs and/or different problems (children and elderly)
- Treatments of patients with cancers or degenerative pathologies that cause a severe pain with characteristics that greatly vary from patient to patient

- Customize the dosages and pharmaceutical forms according to the local needs of patients
- Employ local staff, teaching them a new “job”, so that it will be possible to open suitable school
- Minimize the financial commitment necessary to prepare these medicines, respecting the quality of medicinal products

DIFFERENT COUNTRIES, SAME NEED OF QUALITY
**THE GALENICS: AN ANSWER TO THE HOSPITAL PECULIAR NEEDS**

**ITALY**

| PROJECT “POLO ONCOLOGICO DI TORINO” | 1. Extension of the stability of anticancer drugs  
2. Development of a method for monitoring the microbiological stability of the cytotoxic preparations |
| CLINICAL STUDY PROTPROS | Evaluation of chemopreventive activity of galenics, comparable to dietary supplement, containing lycopene, selenium and green tea polyphenols |
| CLINICAL STUDY MONAPOL | Evaluation of cholesterol-lowering activity of a galenic, comparable to a dietary supplement, containing monacolin k and policosanol in subjects with mild to moderate hypercholesterolemia uncomplicated unfamiliar: randomized controlled double-blind study |

**DEVELOPING COUNTRIES (DC)**

| A.P.P.A.® GALENIC LAB IN HAITI | 1. Study of oral liquid pediatric formulations  
2. Stability study of the prepared liquid pharmaceutical forms  
3. Development of a method for the preparation of sterile solutions (antibiotics and cytostatic drugs)  
4. Project for the introduction of new oral and sterile formulations for pediatric use |
ACCESS TO HEALTH SERVICES: INEQUALITIES BETWEEN NORTH AND SOUTH OF THE WORLD

Countries with a critical shortage of health service providers (doctors, nurses and midwives)

The World Health Report 2006 - working together for health
Chapter 1: Health workers: a global profile
PROBLEMS RELATED TO THE LIFE STYLE

«...water-borne diseases are not caused by lack of antibiotics but by dirty water, and by the political, social, and economic forces that fail to make clean water available to all; heart disease is caused not by a lack of coronary care units but by the lives people lead, which are shaped by the environments in which they live; obesity is not caused by moral failure on the part of individuals but by the excess availability of high-fat and high-sugar foods ...»

“Closing the gap in a generation: Health equity through action on the social determinants of health” – WHO Commission on Social Determinants of Health - 2008

Borana Singing wells, Kenya
Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford.

**BUT...**

- More than **fifty percent of the population** in the Region **have no regular access to essential medicines.**
- **Medicine supply** and **regulatory systems** are weak
- **Financial** as well as **human resources** are inadequate to ensure delivery of pharmaceutical services and ensure access to essential medicines.
- Circulation of **poor quality medicines**, high medicine **prices**, unethical promotion and **irrational use** of medicines poses additional challenges.
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 - General information on counterfeit medicines

"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.
F. Baratta, A. Germano, P. Brusa

**Diffusion of counterfeit drugs in developing Countries and stability of galenics stored for months under different conditions of temperature and relative humidity**

F. Baratta, A. Germano, P. Brusa

Diffusion of counterfeit drugs in developing countries and stability of galenics stored for months under different conditions of temperature and relative humidity

PHARMACEUTICAL FORMS TESTS (Ph Eur)
- Uniformity of content (2.9.6)
- Uniformity of mass (2.9.5)
- Disintegration (2.9.1)
- Friability (2.9.7)
- Hardness (2.9.8)
- Sterility (2.6.1)
A.P.P.A.® PROJECT
PLANNING, CARRYING OUT, STARTING LABS IN ORDER TO PREPARE GALENIC MEDICINAL PRODUCTS AND RELATIVE QUALITY CONTROL IN DEVELOPING COUNTRIES

With the patronage of:

Università degli Studi di Torino

FEDERAZIONE ORDINI FARMACISTI ITALIANI
ORDINE DEI FARMACISTI PROVINCIA DI TORINO

www.progettoappaitalia.it        appa.onlus@unito.it
BASIC CONDITIONS FOR OPENING
A LAB FOR THE PREPARATION OF GALENIC MEDICINAL PRODUCTS

- **HIGH PERCENTAGE OF COUNTERFEIT MEDICINES** IN THE AREA
- **LOCAL POOR AVAILABILITY** OF QUALITY MEDICINES
- **HIGH COST** OF INDUSTRIAL MEDICINES
- **APPROVAL** OF LOCAL AUTHORITIES
A. STUDY OF ORAL LIQUID PEDIATRIC FORMULATIONS
B. STABILITY TESTS OF THE ACTIVE MOLECULES AND OF THE PREPARATION IN ACCORDANCE WITH THE EMA GUIDELINES
C. DEVELOPMENT OF A METHOD FOR THE PREPARATION OF STERILE SOLUTIONS (ANTIBIOTICS AND CYTOSTATIC DRUGS)
# HAITI: WHY?

## MEDICINAL PRODUCTS

<table>
<thead>
<tr>
<th>LOT</th>
<th>API</th>
<th>PROVENANCE</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>6C090</td>
<td>Acetazolamide 250 mg</td>
<td>Haiti</td>
<td><strong>Unsatisfied:</strong> Uniformity of content (2.9.6), Friability (2.9.7)</td>
</tr>
<tr>
<td>0302609</td>
<td>Ampicillin 1g</td>
<td>India</td>
<td><strong>Unsatisfied:</strong> Bacterial endotixins (2.6.14.)</td>
</tr>
<tr>
<td>071202</td>
<td>Chloramphenicol 1g</td>
<td>USA</td>
<td><strong>Suitable</strong></td>
</tr>
<tr>
<td>09K4840 A</td>
<td>Phenobarbital 30 mg</td>
<td>Haiti</td>
<td><strong>Unsatisfied:</strong> Friability (2.9.7), Hardness (2.9.8)</td>
</tr>
<tr>
<td>08E2978-A</td>
<td>Phenobarbital syrup 18mg/5ml</td>
<td>Haiti</td>
<td><strong>Suitable</strong></td>
</tr>
<tr>
<td>08111487</td>
<td>Propanolol 40mg</td>
<td>Brasil</td>
<td><strong>Unsatisfied:</strong> Uniformity of content (2.9.6)</td>
</tr>
<tr>
<td>L08111487</td>
<td>Spironolactone 25mg</td>
<td>Domenican Republic</td>
<td><strong>Suitable</strong></td>
</tr>
</tbody>
</table>
PAEDIATRICS: WHY?

PREPARATION OF CAPSULES FOR CHILDREN FROM INDUSTRIAL HIGH-DOSE TABLETS

PROBLEMS:
✓ Method of preparation
✓ Quality of industrial tablets
✓ Stability of the preparations
✓ Administration of capsules for the neonatal and paediatric treatment

<table>
<thead>
<tr>
<th>LOT</th>
<th>API</th>
<th>PROVENANCE</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>200910-A</td>
<td>Acetazolamide 25 mg</td>
<td>St Damien Hospital</td>
<td>Unsatisfied: Uniformity of content (2.9.6)</td>
</tr>
<tr>
<td>A-200S10-A</td>
<td>Acetazolamine 25 mg</td>
<td>St Damien Hospital</td>
<td>Suitable</td>
</tr>
<tr>
<td>121110-B Exp</td>
<td>Captopril 1,25 mg</td>
<td>St Damien Hospital</td>
<td>Unsatisfied: Uniformity of mass (2.9.5)</td>
</tr>
<tr>
<td>230610-C</td>
<td>Phenytoin 10 mg</td>
<td>St Damien Hospital</td>
<td>Suitable</td>
</tr>
<tr>
<td>230610-G</td>
<td>Phenytoin 10 mg</td>
<td>St Damien Hospital</td>
<td>Suitable</td>
</tr>
</tbody>
</table>
A. STUDY AND FORMULATION OF ORAL LIQUID PAEDIATRIC FORMULATIONS:

**METHODOLOGICAL APPROACH**

- In agreement with local medical doctors, the drugs for the paediatric therapy are chosen and then formulated: 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 has been tested to check its quality and its stability under different environmental conditions in accordance with the EMA guidelines.
## PREPARATIONS PEDIATRIQUES

<table>
<thead>
<tr>
<th>SIROPS</th>
<th>SOLUTIONS</th>
<th>GOUTTES</th>
<th>SUSPENSIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACIDE ASCORBIQUE 10 mg/ml</td>
<td>CAPTOPRIL 1 mg/ml</td>
<td>NIFEDIPINE 1 mg/gtt</td>
<td>VITAMINE B COMPLEX 5,8 mg/ml</td>
</tr>
<tr>
<td>CANREONATE DE POTASSIUM 1 mg/ml</td>
<td>FUROSEMIDE 1 mg/ml</td>
<td>RANITIDINE 4 mg/gtt</td>
<td>MAGNESIUM ET ALUMINIUM HYDROXYDE 200 mg/ml</td>
</tr>
<tr>
<td>FER SULFATE 5 mg/ml</td>
<td></td>
<td>SALBUTAMOL 0,2 mg/gtt</td>
<td></td>
</tr>
<tr>
<td>IBUPROFENE 20 mg/ml</td>
<td></td>
<td>VITAMINE B6 0,5 mg/gtt</td>
<td></td>
</tr>
<tr>
<td>PROPRANOLOL 0,5 mg/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RANITIDINE 15 mg/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SALBUTAMOL 0,4 mg/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VITAMINE B6 1 mg/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PROPRANOLOL CHLORHYDRATE SIROP 0,5 mg/ml**

Formulation pour 100 ml

- Propranolol chlorhydrate: 0,05 g
- Carboxyméthylcellulose sodium: 1,00 g
- Sodium citrate: 0,21 g
- Acide citrique monohydrate: 0,28 g
- Eau dépurée: 72,25 ml
- Nipagine sodique: 0,07 g
- Saccharose drop: 3,23 g

Caractéristiques chimiques-physiques:

Poudre cristalline blanche ou blanchâtre, il est inodore et avec un goût amer.

Solvable dans l'eau (1:20) et dans l'alcool (1:20).

p.f. = 163-166 °C.

Propriétés pharmacologiques:

Le propranolol a une activité β-bloquante. Il est un antagoniste compétitif des deux récepteurs β1 et β2, non cardioselectif.

Il est utilisé dans l'hypertension.

**Pharmacologie pédiatrique:**

2.5-5mg correspondant à 5-10 ml.

**Préparation:**

1. Sulphurer la nipagine sodique dans l'eau dépurée.
2. Ajouter le sodium citrate et l'acide citrique monohydrate dans la solution.
3. Ajouter la propranolol chlorhydrate.
4. Ajouter la carboxyméthylcellulose sodique peu à la fois, mélanger très lentement.
5. Ajouter le saccharose drop.
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.
B. STABILITY STUDY OF THE PREPARED LIQUID PHARMACEUTICAL FORMS

Method:

<table>
<thead>
<tr>
<th>STORAGE CONDITION</th>
<th>T (°C)</th>
<th>RH</th>
<th>PERIOD COVERED BY DATA</th>
<th>ANALYTICAL METHOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>25±2</td>
<td>60±5%</td>
<td>12 months, analysis at time zero (T0) and every 30 days (from TS-1 to TS-12)</td>
<td>UV-VIS spectrophotometric assay</td>
</tr>
<tr>
<td>Refrigerator</td>
<td>5±3</td>
<td>-</td>
<td>12 months, analysis at time zero (T0) and every 30 days (from TR-1 to TR-12)</td>
<td></td>
</tr>
<tr>
<td>Accelerated</td>
<td>40±2</td>
<td>60±5%</td>
<td>3 months, analysis at time zero (T0) and every 30 days (from TA-1 through TA-3)</td>
<td></td>
</tr>
</tbody>
</table>

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

EVALUATION OF THE EXPIRATION DATE
VALIDITY PERIOD:
3 MONTHS

housing and environmental conditions are not suitable for a proper storage of the preparations

STABILITY STUDY: RESULTS

<table>
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<tr>
<td>MAGNESIUM ET ALUMINUM HYDROXYDE 200 mg/ml</td>
</tr>
</tbody>
</table>

The stability has been demonstrated for 12 MONTHS for all formulations

![RANITIDINE DROPS](image)

<table>
<thead>
<tr>
<th>Abs</th>
<th>190</th>
<th>240</th>
<th>290</th>
<th>340</th>
<th>390</th>
</tr>
</thead>
<tbody>
<tr>
<td>T5-12</td>
<td>1.6</td>
<td>1.2</td>
<td>1.0</td>
<td>1.0</td>
<td>1.4</td>
</tr>
<tr>
<td>TR-12</td>
<td>1.5</td>
<td>1.0</td>
<td>1.2</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>T0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>TA-1</td>
<td>0.5</td>
<td>0.2</td>
<td>0.4</td>
<td>0.6</td>
<td>1.0</td>
</tr>
</tbody>
</table>

VALIDITY PERIOD:
3 MONTHS
Galenics, in accord with the European Law (Ph Eur), must guarantee “the quality as a fundamental support to the security and the efficacy”

**QUALITY CONTROL AND QUALITY ASSURANCE**

**D.C.**

**PHARMACEUTICAL FORMS TESTS**
- Ointments for skin application; Suppositories:
  - Verify of accuracy of followed procedures
  - Control of aspect
  - Control of the amount to sell
  - Control of the solidity of packing

- Stiff capsules:
  - Verify the accuracy of followed procedures
  - Control of aspect and solidity of capsules
  - Control of the number of capsules prepared
  - Mass uniformity of capsules

- Liquid medicinal products:
  - Verify the accuracy of followed procedures
  - Control of the amount of product to sell
  - Control of the solidity of packing

**RAW MATERIALS:** Organoleptic control
   - Melting point

**ITALY**

**STABILITY TESTS** (EMA)

**PHARMACEUTICAL FORMS TESTS** (Ph Eur)
- Uniformity of content (2.9.6)
- Uniformity of mass (2.9.5)
- Disintegration (2.9.1)
- Friability (2.9.7)
- Hardness (2.9.8)
- Sterility (2.6.1)
### QUALITY CONTROL AND QUALITY ASSURANCE

<table>
<thead>
<tr>
<th>ANALYSIS</th>
<th>METHOD REF.</th>
<th>ACCEPTANCE CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>General aspect</td>
<td>Visual</td>
<td>Posological unit integrity</td>
</tr>
<tr>
<td>Uniformity of content</td>
<td>Ph. Eur. 7 ed. Assay 2.9.6</td>
<td>Each individual content is between 85% and 115% of the average content (10 dosage units)</td>
</tr>
</tbody>
</table>

---

**SPECTOPHOTOMETRY UV/VIS**

- **STANDARDIZATION OF RESULTS**
- **LOW COSTS**
- **SIMPLE EXECUTION**

---

“...reuse, repair equipment and goods instead of throwing them in a landfill, exceeding the consumerist obsession of the obsolescence of objects and the tension to the new...”

C. DEVELOPMENT OF A METHOD FOR THE PREPARATION OF STERILE SOLUTIONS (ANTIBIOTICS AND CYTOSTATIC DRUGS)

Application of specific procedures for the preparation of:

- Lyophilized medicinal products
- Infusion bags
- Solutions
## THE GALLENICS: AN ANSWER TO THE HOSPITAL PECULIAR NEEDS

### NATIONAL CONTEXT

#### DEVELOPING COUNTRIES

### DIFFERENT COUNTRIES: SAME NEED OF QUALITY

## ITALY

**PROJECT “POLO ONCOLOGICO DI TORINO”**

1. Extension of the stability of anticancer drugs
2. Development of a method for monitoring the microbiological stability of the cytotoxic preparations

**CLINICAL STUDY PROTPROS**

Evaluation of chemopreventive activity of galenics, comparable to dietary supplement, containing lycopene, selenium and green tea polyphenols

**CLINICAL STUDY MONAPOL**

Evaluation of cholesterol-lowering activity of a galenic, comparable to a dietary supplement, containing monacolin k and policosanol in subjects with mild to moderate hypercholesterolemia uncomplicated unfamiliar: randomized controlled double-blind study

## DEVELOPING COUNTRIES (DC)

**A.P.P.A.® GALENIC LAB IN HAITI**

1. Study of oral liquid pediatric formulations
2. Stability study of the prepared liquid pharmaceutical forms
3. Development of a method for the preparation of sterile solutions (antibiotics and cytostatic drugs)
4. Project for the introduction of new oral and sterile formulations for pediatric use
To verify the profiles of effectiveness and tolerability of a galenic comparable to a dietary supplement containing a dry extract of fermented red rice by Monascus purpureus associated with another one titrated in policosanols
A. EVALUATION OF THE CORRECT DOSAGE AND SET UP OF GALENIC FORMULATION

Literature evaluation
Evaluation of the legislation in force
Application of specific procedures for the preparation of stiff cps
Quality and assurance control based on FU XII - Ph Eur assays

GALENIC FORMULATION: STIFF CAPSULES
Administration: 2 cps / day

Group 1 (galenic preparation similar to a food supplement):
Dose administered per day: monacolin k 3 mg/day, policosanol 20 mg/day
Components:
- Red yeast rice extract: title in monacolin k equal to 3.1%;
- Biocosanol®: title in policosanol equal to 91.2% of which hexacosanol 14.7%, octacosanol 56.1%, triacontanol 20.4%;
- Maize starch pregelatinised: q.b.

Group 2 (active pharmaceutical ingredient):
Dose administered per day: lovastatin 3 mg/die
Components:
- Lovastatin: 1,5 mg/cps;
- Maize starch pregelatinised: q.b.

Group 3 (placebo):
Components: Maize starch pregelatinised : q.b.
B. GALenic FORMULATION: STABILITY STUDY

Method:

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

Results:
All formulations have proved to be stable in “Refrigerated” conditions (RT-24) and “Standard” conditions (ST-24) for **24 months**, in “Accelerated” conditions (AT-3) for **3 months**
C. EVALUATION OF PLASMATIC CONCENTRATION BY HPLC ANALYSIS

Developing of an HPLC method (UV detector) to evaluate the monacolin k concentration in the plasma of enrolled subjects

Mobile phase: 0.1% phosphoric acid - acetonitrile, flow rate: 0.5 ml / min, $\lambda = 238$ nm
HiQ sil column C18HS, 3um, 4.6 mm L IDx100mm
HPLC composed by: Biotech model 2003 degasser; CBM-10A Shimadzu communications bus module; SPD-10° VP Shimadzu UV-Vis detector; LC-10AD VP Shimadzu liquid cromatograph

Stoch solution (SSm) of monacolin K

Plasma enriched with SSm

Stoch solution (SSI) of lovastatin

Plasma enriched with SSI
Overlapping of a baseline analysis (green) and quarterly (red) in the plasma of a subject.

CONCLUSIONS

- The application of a standard procedure for the preparation the galenics administered during the study can guarantee their **stability for 24 months**.
- The developed HPLC procedure allows to highlight the concentration of monacolin k in the **plasma of enrolled subjects**
- Actually **31 subjects** have been enrolled.
- The phase I of the study is finished and the phase II of the study is in progress.
Riso rosso fermentato (Monascus purpureus)
monacolina
Avvertenza supplementare:
Per l’uso del prodotto si consiglia di sentire il parere del medico.
Non usare in gravidanza, durante l’allattamento e in caso di terapia con farmaci ipolipidemizzanti

LOVASTATINA 10 mg
Indicazioni terapeutiche riportate in RCP
Ipercolesterolemia primaria inclusa l’ipercolesterolemia familiare o l’iperlipemia mista (tipo IIa e IIb) quando la sola risposta alla dieta e ad altre misure non farmacologiche (aumento dell’attività fisica e se indicato riduzione del peso corporeo) sia risultata inadeguata.
Ipercolesterolemia non corretta dalla sola dieta in soggetti ad alto rischio di un evento cardiovascolare maggiore (soggetti con rischio superiore del 20%, colesterolo totale maggiore di 190 mg/dl e colesterolo LDL maggiore di 115 mg/dl). Ipercolesterolemia non corretta dalla sola dieta in pazienti con cardiopatia ischemica, per la riduzione del rischio di infarto del miocardio.