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# Experience of a Mexican paediatric hospital preparing oral extemporaneous formulations

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Aim: **An audit was performed to evaluate whether the extemporaneous formulations produced at the Hospital Infantil de México Federico Gómez (HIM) were prepared in accordance with nationally accepted standards or specifications in order to satisfactorily meet the requirements of oral paediatric formulations.**

Methods: **The number of extemporaneous pharmaceutical formulations produced from 1996 to 2002 by the Laboratorio de Fórmulas Magistrales was reviewed. A pharmaceutical formulation corresponded to the minimum quantifiable unit of each drug, i.e. one tablet, one capsule or an oral liquid preparation.**

Results: **For outpatients, the number of extemporaneous formulations per 100 patients ranged from 246 in 1996 to 251 in 2002. For inpatients, the number of extemporaneous formulations per 100 patients ranged from 1,562 in 1996 to 2,656 in 2002. The total amount of formulations was equivalent to 65,300 pharmaceutical formulations per pharmacist (n = 7) per year. Chemical, bacteriological or analytical evaluations were not used in any of the extemporaneous formulations because of lack of equipment. Clinical information about the patient was rarely specified in the prescriptions requesting an extemporaneous formulation.**

Conclusions: **The number of oral extemporaneous formulations being prepared at the laboratory significantly increased over time and may be beneficial to offset the current deficit of paediatric pharmaceutical formulations and to decrease costs. However, it is imperative to work to recognised standards and specifications and to rationalise preparations made extemporaneously, since excessive and unnecessary numbers of products are currently being prepared.**

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## Introduction

As a result of anatomical and physiological differences, the pharmacokinetics and pharmacodynamics of a wide range of drugs vary from children to adolescents to adults[1-3]. However, it is recognised that there are insufficient appropriate pharmaceutical formulations for many drugs to be used in the paediatric population[4,5]. The use of drugs manufactured to satisfy the requirements of adult patients, results in a significant waste when they are used in children and may also predispose to medication errors. The costs resulting from this waste may be relevant for public health services and may also result in improper drug utilisation[5,6].

The presence of a hospital pharmacy service has decreased drug related costs and morbidity in a wide range of medical services[7-9]. However, there is no such service yet available in Mexico. The Hospital Infantil de México Federico Gómez (HIM), with 208 beds in 2003, is a tertiary care public hospital devoted to sick children ranging in age from newborn to adolescents. These patients commonly are of a low or very low socio-economic income level and do not have access to the social security systems or private medical care. The HIM has the Laboratorio de Fórmulas Magistrales y Recetas devoted to prepare oral and topical extemporaneous formulations as requested by different hospital services. This laboratory could be used to decrease the amount of drugs and resources that are being wasted due to the lack of appropriate paediatric pharmaceutical formulations. However, it was recently demonstrated that oral extemporaneous formulations for paediatric patients are subject to large variation in European hospitals while there is little harmonisation of formulations[10]. The experience of this unique laboratory in Mexico has not been documented and therefore its role in the preparation of extemporaneous formulations has not previously been evaluated.

## Methods

We audited the laboratory's registry books from 1996 to 2002. The seven year period was selected according to the availability of information properly documented by the laboratory. Information was not stored in any electronic form and was therefore retrieved manually. Any minimum quantifiable unit (a tablet, a capsule, or an oral liquid formulation) produced as a result of crushing the licensed tablet formulation or opening the capsule and using the content was considered as an extemporaneous pharmaceutical formulation. For the purpose of the study, we only considered oral extemporaneous formulations prepared by the laboratory.

The number of outpatients and inpatients during the study period were obtained from the Archivo General of the HIM, and results were adjusted to per 100 patients per year according to the patients for whom the extemporaneous formulations were prepared.

The Laboratorio de Fórmulas Magistrales is staffed by seven technicians and a supervisor, four of them have Bachelor of Science degrees in Chemistry and three of them are laboratory technicians. All are recognised as being able to work in a pharmacy in Mexico. The number of extemporaneous formulations prepared each year per pharmacist was also recorded. In order to identify the drugs commercially available as paediatric formulations each year of the study period, the Diccionario de Especialidades Farmacéuticas (Ediciones PLM, S.A. de C.V. México DF, México) of the corresponding year, was checked. Finally, the personnel were asked to inform whether they used Good Manufacturing Practice or the Mexican Pharmacopoeia (Farmacopea de los Estados Unidos Mexicanos, Secretaría de Salud, México) to standardise their procedures.

## Results

The drugs prepared as oral extemporaneous formulations during the study period are listed in Table 1. A total of 2,200,622 extemporaneous

**Table 1** List of drugs prepared extemporaneously

**Antibiotics**
Amoxicillin ± clavulanate, ampicillin, cefuroxime, cephalexin, ciprofloxacin, clarithromycin, clindamycin, cotrimoxazole, dicloxaxillin, erythromycin, metronidazole, nalidixic acid, neomycin, nitrofurantoin

**Antiretroviral drugs**
Abacavir, didanosine, efavirenz, lamivudine, stavudine

**Cardiovascular drugs**
Acetazolamide, amiodarone, captopril, clonidine, digoxin, dipyridamole, frusemide, hydralazine, hydrochlorothiazide, losartan, metoprolol, nifedipine, nimodipine, prazosin, propranolol, spironolactone, verapamil, vigabatrin

**CNS drugs**
Amitriptyline, carbamazepine, haloperidol, lamotrigine, levodopa/carbidopa, phenobarbital, phenytoin, primidone, valproate (magnesium)

**Drugs for gastrointestinal disorders**
Cisapride, domperidone, loperamide, metoclopramide, omeprazole, ranitidine, sucralfate, ursodeoxycholic acid

**Non-steroidal anti-inflammatory drugs and paracetamol**
Acetylsalicylic acid, diclofenac, ibuprofen, ketorolac, metamizol, naproxen, paracetamol

**Steroids**
Dexamethasone, prednisone

**Vitamins**
Ascorbic acid, folic acid, pyridoxine

**Miscellaneous**
Allopurinol, atorvastatin, azathioprine, calcium carbonate, chloroquine, chlorpheniramine, ethambutol, ketoconazole, levothyroxine, loratadine, phenazopyridine, rifampin, tacrolimus, theophylline

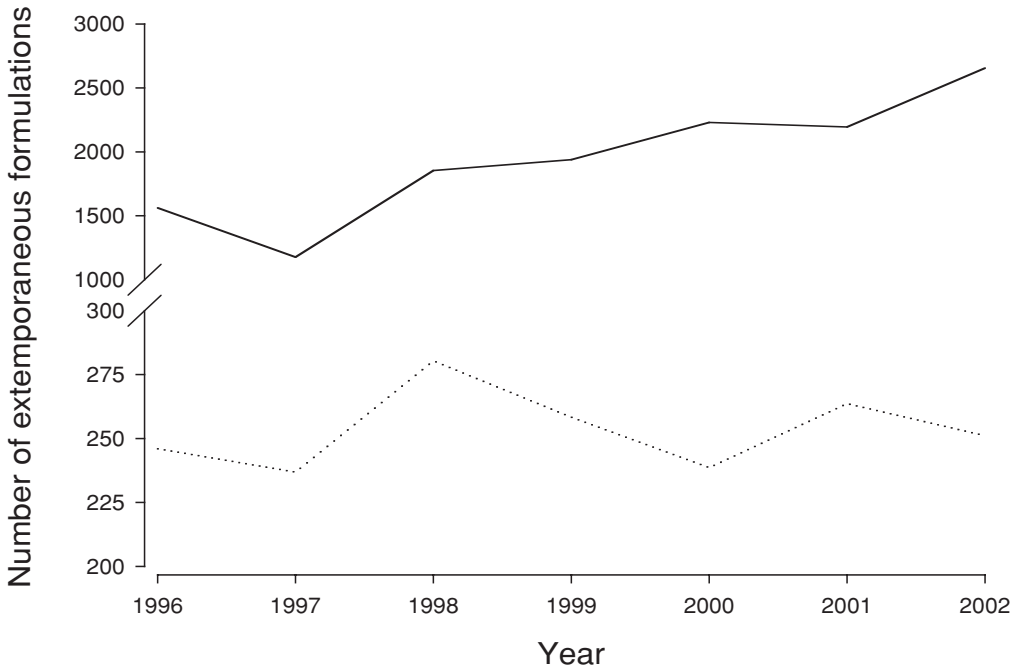


**Figure 1** Number of oral extemporaneous formulations prepared per 100 inpatients ( _____ ) or per 100 outpatients ( ..... ) from 1996 to 2002 by the Laboratorio de Fórmulas Magistrales y Recetas of the HIM.

formulations were prepared for outpatients and 999,802 for inpatients. The number of extemporaneous formulations prepared for outpatients ranged from 246 per 100 patients in 1996 to 251 per 100 patients in 2002 (Figure 1). For inpatients, the number of oral extemporaneous formulations ranged from 1,562 per 100 patients in 1996 to 2,656 per 100 patients in 2002. No chemical, physical or microbiological evaluation was used for any extemporaneous formulation because of the lack of equipment. Clinical information such as age, weight or health status of patients was not provided in any prescription for inpatients while it was only occasionally provided in prescriptions for outpatients. An average of 65,300 doses was prepared every year by each member of the laboratory.

Of the drugs produced as extemporaneous formulations, 37–40% were available as marketed paediatric formulations during the study period. No Good Manufacturing Practice Guidelines were available in the laboratory and the Mexican Pharmacopoeia was not being used.

## Discussion

The prescription of generic drugs in order to decrease health care costs has prompted an intense worldwide debate[10-14]. In Mexico, the pharmaceutical companies that produce generic drugs have tried to decrease the time of patents protecting original drugs and the topic is now polarised by intensive and aggressive public campaigns in favour or against the generic drugs. However, despite the decreased drug utilisation costs associated with the proper use of generic formulations, according to two surveys recently published elsewhere, one performed among general physicians and the other among general anaesthetists, drug selection in this country is not supported by economic factors[6,15]. Extrapolating these observations, it is very unlikely that the extemporaneous formulations were requested by paediatricians in order to reduce costs.

Another important factor that may justify the extensive request of extemporaneous formulations is the lack of appropriate paediatric formulations. For example, lisinopril is not available in a paediatric formulation and therefore an extemporaneous liquid formulation of this drug was prepared[16]. However, paediatric formulations were available for almost 40% of the drugs during the study period. Because of the improper manufacturing conditions in the laboratory, these formulations should be preferred over the extemporaneous formulations produced at HIM.

Extemporaneous formulations were manually prepared without any chemical, bacteriological or analytical control. There was no clinical information in the prescription that may help to control, for example, the amount of sugar in the new liquid formulation. Furthermore, misuse of human and material resources was also identified, as is illustrated by the following two cases.

A physician requested an extemporaneous formulation of 50 mg of verapamil to be prepared from a pill of verapamil containing 80 mg. In Mexico, pills containing 40 mg of verapamil are available. Furthermore, 10– 20% of the drug content is lost during the preparation procedures of extemporaneous formulations[17]. This request should not have been processed. The second example is a prescription requesting the extemporaneous formulation of 10 mg of frusemide from a grooved tablet of 20 mg frusemide. It would have been simpler to divide the original grooved tablet in two equal parts. The working time and resources devoted to prepare the extemporaneous formulations exemplified above were undoubtedly misallocated.

According to the list in Table 1, some of the drugs prepared as extemporaneous formulations by the laboratory were formerly prepared as pills (e.g. sucralfate), coated pills (e.g. omeprazole) or as extended release formulations (e.g. clarithromycin). Since the extemporaneous formulations did not respect the original formulations, plasma drug concentrations achieved after the ingestion of the new formulation may be different compared to those expected with the original formulation. We do not have, however, evidence of an increased rate of adverse events or a decreased rate of efficacy secondary to this potential problem.

We believe that procedures to ensure a substantial quality improvement of this laboratory must be implemented urgently. The Mexican Pharmacopoeia, for example, contains specifications, tolerances and procedures to assure the official Mexican requirements for quality of drugs produced and prepared in this country. However, according to our study, the Pharmacopoeia is not being used in the laboratory at HIM. Furthermore, a critical appraisal of drugs administered to children should be performed in order to assure that rational evidence of safety and efficacy are available in children. Drugs administered for the first time in children should be carefully monitored under a protocol reviewed by the hospital research and ethic boards, and effects should be observed. Also, drugs that are no longer in use because of the report of serious drug adverse events, e.g. cisapride and metamizol, should not be prepared. Although the professional responsibility upon pharmacists at the laboratory is limited to quality of extemporaneous formulations, the HIM must ensure that the drugs requested by physicians as oral extemporaneous formulations are not only prepared in accordance with nationally accepted standards but also drugs must be approved for paediatric patients or must be used under strict protocols.

## Conclusions

The number of oral extemporaneous formulations being prepared at the laboratory significantly increased over time and may be beneficial to offset the current deficit of paediatric pharmaceutical formulations and to decrease costs. However, it is imperative to work to recognised standards and specifications and to rationalise preparations made extemporaneously, since excessive and unnecessary numbers of products are currently being prepared.

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