General Policy Topics

Shelf-life and stability

The time is long past since pharmacopoeial standards alone could be regarded as sufficient to assure the quality of pharmaceutical products. Two generic products meeting the same compendial requirements may differ in the quality of their ingredients, the nature of their excipients, and the stability of their dosage forms. On occasion, these differences have important implications for the shelf-life of the products and even for the welfare of patients. Yet in the absence of effective licensing systems, reliable certification procedures and facilities for analytical control, they will simply pass undetected.

The stability of pharmaceutical products is put to greatest test in tropical countries. Not only is the degradation of intrinsically unstable chemical compounds accelerated when ambient temperature and humidity are raised, but lack of resources may result in supplies being inadequately protected within the distribution chain. The consequences of such inadequacies can be dire in the case of life-saving drugs. Parenteral ergometrine maleate, for example, is needed everywhere to prevent excessive uterine bleeding following childbirth. Post-partum haemorrhage accounts for about one-third of perinatal maternal deaths in those countries where maternal mortality remains high. Yet, in a recent survey of 24 samples of injectable ergometrine drawn from peripheral health facilities in three developing countries, less than half met pharmacopoeial specifications for potency and, in over a quarter, potency was reduced more than fivefold (1). Degradation is not a phenomenon that is exclusive to developing countries, however, it is recognized to be a matter of practical moment everywhere. Several regulatory authorities have extensively revised their requirements for the testing of dosage forms within the past few years (2-6), and a detailed Note for Guidance has recently been issued by the Committee for Proprietary Medicinal Products of the European Economic Community (7).

It is not widely appreciated that the active ingredients of drugs are sometimes more stable in the pure state than in the finished dosage form. Indeed, since the magnitude and even the direction of these formulation-dependent changes are unpredictable, stability and shelf-life can only be determined on a product-by-product basis. Information on the stability of the active substance is, none the less, important: it provides a basis for rational pharmaceutical development and selection of packaging for the dosage form and it enables appropriate methods to be devised for detecting degradation in the finished product.

The EEC Guidelines acknowledge that — for known active substances — data contained in the published literature will often suffice to support the use of a specific active ingredient in a product. However, manufacturers are placed on notice that when changes are made in the way a substance is manufactured, and particularly if the route of synthesis is changed, comparative accelerated stability studies may well be required on material from at least two independently-manufactured batches. The testing programme proposed for finished products is yet more demanding. Emphasis is placed on the ultimate need to establish shelf-life on the basis of "real time" studies sustained for at least six months under controlled conditions. These should be undertaken on samples drawn from at least three batches with a view to determining the stability of the product between 20° and 30°C at one or more specified mean humidities. Initially, however, information derived from accelerated stability studies conducted under more extreme conditions is acceptable to:

- tentatively justify the proposed shelf-life;
- provide a basis for proposing suitable storage conditions;
- demonstrate the consequences of adverse storage; and
- support important changes in formulation, methods of preparation, and packaging materials.

In every case, manufacturers are expected to detect and investigate any changes in the physical and chemical properties of the product or of its packaging that could be indicative of degradation. In doing so, they are required to validate each test procedure and to discuss critically the clinical implications of any detected degradation.

Knowledge of whether such requirements are already imposed by a national drug regulatory authority has immediate practical relevance to the competent authorities within any importing country. Where they are operative, assurances obtainable through the "WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce" (8) that a given product is registered for marketing in the country of origin indicate that a substantial body of data must have been generated to support the labelled shelf-life in that country. For the most part, however, this information will only define the properties of the product under temperate conditions. When a product is intended for distribution in tropical regions, more exacting information on its potential stability may be needed. Ultimately, results of real-time studies should be provided under anticipated storage conditions but, in the first instance, reliance may reasonably be vested in provisional estimates obtained from accelerated studies conducted at high temperature (up to 60°C in extreme situations) and high humidity. The manufacturer has an acknowledged responsibility to undertake such studies. It is an important element of good manufacturing practice to ensure that each product together with its package will be adequately stable under recommended storage conditions in the countries to which it is to be exported.

In reality, the situation remains far from satisfactory. Significant stocks of valuable medicines are too often written off as a consequence of gross degradation. Sometimes this is attributable to deficiencies in procurement practices or stock management, and these should always be reviewed in the light of such incidents. At the same time, considerably more needs to be known about the stability of commonly used formulations of long established drugs under demanding climatic conditions. As an initial screening exercise, WHO has commissioned comparative accelerated stability studies on a wide variety of drug substances (9) included in its Model List of Essential Drugs. Those in which evidence of degradation was detected are listed below. Further research is now ongoing, both on the stability of selected dosage forms of a variety of multisource products, and on the development of simplified tests to detect significant degradation. These data and methods will subsequently be used to design field studies intended to explore the magnitude of the problem in greater detail and to provide a basis for guidance to small regulatory authorities on practical approaches to stability assurance for registration purposes.

Potentially degradable pharmaceutical substances*

acetylsalicylic acid
aminophylline
amitriptyline hydrochloride
amphotericin B
ampicillin sodium
ampicillin trihydrate
ascorbic acid
bacitracin
bacitracin zinc
benzathine benzylpenicillin
benzylpenicillin potassium
benzylpenicillin sodium
calcium gluconate
chloral hydrate
chloramphenicol sodium succinate
chlorphenamine hydrogen maleate
chlorpromazine hydrochloride
cloxacillin sodium (monohydrate)
coal tar
codeine phosphate
dapsone
dexamethasone sodium phosphate
diethylcarbamazine dihydrogen citrate
doxycycline hyclate
ephedrine
ephedrine sulfate
epinephrine
ergocalciferol
ergometrine hydrogen maleate
ergotamine tartrate
ethosuximide
ferrous sulfate
fluphenazine decanoate
gentamicin sulfate
hydralazine hydrochloride
hydrocortisone sodium succinate
hydroxocobalamin
ipecacuanha powder
lidocaine hydrochloride
melarsoprol
metrifonate
naloxone hydrochloride

(Continued)

neomycin sulfate	quinine dihydrochloride
nystatin	retinol (vitamin A)
penicillamine	salbutamol sulfate
pethidine hydrochloride	senna leaf
phenobarbital sodium	silver nitrate
phenoxymethylpenicillin	sodium stibogluconate
phenoxymethylpenicillin potassium	sulfacetamide sodium
pilocarpine hydrochloride	sulfadimidine sodium
pilocarpine nitrate	suxamethonium chloride
procainamide hydrochloride	tetracaine hydrochloride
procaine benzylpenicillin	tetracycline hydrochloride
procarbazine hydrochloride	thiamine hydrochloride
promethazine hydrochloride	thiopental sodium
pyridoxine hydrochloride	tolbutamide
quinine bisulfate	warfarin sodium

* Standardized conditions were applied in this survey which was commissioned by WHO. Light was excluded, while temperature and humidity were adjusted to simulate tropical conditions. All substances were initially exposed for 30 days to air at 50° C and 100% humidity. If no degradation was demonstrable at this time, the temperature was raised to 70° C for a further period of 3 - 7 days. The extent of the degradation was assessed in most cases by thin-layer chromatography. A semi-quantitative method was used to determine the proportion of unaltered substance.

References

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2. *Guidelines for the stability testing of drugs* (B/279/35/585). Drug Control Council, Zimbabwe. (1985).

3. *Requirements for the registration of drugs for human use*. Pharmaceutical Services Department, Ministry of Health, Ethiopia (1986).

4. *Drug registration requirements in Japan*. 3rd edition. Isao Saito, ed., Yakuji Nippo Ltd, Japan (1988) pp. 33-42.

5. *Guidelines for submitting documentation for the stability of human drugs and biologics*. Center for Drugs and Biologics, Food and Drug Administration, USA (1987).

6. *Richtlinie des Instituts für Arzneimittelwesen der DDR zur Bearbeitung von Stabilitätsgutachten von Arzneimitteln*. Institut für Arzneimittelwesen der DDR, German Democratic Republic (1987).

7. Stability tests on active substances and finished products. Note for guidance concerning the application of section F part 1 of the Annex to the Directive 75/318/EEC with a view to marketing authorization in respect of a proprietary medicinal product (III/66/87/EN) issued by the EEC (1988).

8. *WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce* (WHO/PHARM/82.4 Rev.3). World Health Organization, Geneva.

9. *Accelerated stability studies of widely used pharmaceutical substances under simulated tropical conditions* (WHO/PHARM/86.529). World Health Organization, Geneva.