

Recent publications

Drug surveillance: harmonizing regulatory requirements

Relatively rare drug-induced events cannot be investigated effectively within the context of a premarketing drug development programme. The total number of patients studied is far too small to offer a reasonable likelihood of detecting any but the most common adverse effects associated with treatment. Assurance that a defined programme of post-marketing surveillance will be undertaken by the manufacturer is consequently now required by every major national drug regulatory authority as a condition for the registration of a product containing a new drug substance.

Within these programmes, particular attention is accorded to the investigation of potential problems identified in the preregistration studies, both in animals and man. In addition, however, reliance is always vested in spontaneous monitoring to identify, at least, any unwanted effects that become evident within or soon after the timeframe of treatment.

Because spontaneous monitoring notionally involves all doctors and embraces all marketed drugs wherever they may be used, ground rules need to be established to facilitate the interpretation and use of the data obtained. There needs to be reasonable concordance about the types and degree of severity of suspected reactions that should be notified to national monitoring centres; and, if there is to be effective international collaboration, classifications and definitions of specific adverse effects need to be agreed among collaborating national centres. Twenty-five years after the inauguration of WHO's International Drug Monitoring Programme much groundwork remains outstanding in these respects. The efforts required are arduous, time-consuming and they call for compromise. Important progress has been made over the past few years, however, as a result of the recognition by both regulatory bodies and international research-based companies that the Council for International Organizations of Medical Sciences (CIOMS) provides an effective forum for forging a consensus on the norms that still need to be developed.

That such norms are needed is not contested. Administrative as well as scientific advantages will accrue from their adoption — not least because most highly evolved national regulatory authorities have placed companies on notice that product registrations are granted on the understanding that any serious adverse event associated with a licensed product must be notified, formally and promptly, wherever it may have occurred. In the absence of agreement about what is to be reported internationally, companies would be seriously disadvantaged. They would need to prepare case reports on each potentially serious suspected reaction, as well as periodic reviews of specific products, in a format determined by each national regulatory authority. Moreover, in the absence of an internationally standardized adverse reaction terminology, regulatory authorities would have been seriously compromised in their interpretation of reports.

The stimulus to accept compromise as the price of consensus is strong in such circumstances, but this does not detract from the success of CIOMS in steering both regulators and regulated towards mutually supportive goals. In less than one year a first working group comprising regulatory officials and company representatives was able to develop a case report form together with a common set of definitions and procedures to support international requirements. A second working group has since proposed criteria for the preparation and submission of periodic drug-safety update summaries. The hope and expectation is that these proposals will serve as a basis for harmonizing international reporting of drug safety information throughout the world.

The success of the CIOMS initiative derives, in the last analysis, from the dedication of everyone involved and their commitment to ensure immediate implementation of the proposals, at least on a pilot basis.

International reporting of adverse drug reactions. CIOMS, Geneva, 1990. ISBN 92 9036 042 9

CIOMS Working Group II, International reporting of periodic drug-safety update summaries. CIOMS, Geneva, 1992. ISBN 92 9036 053 4

Oral contraceptives and neoplasia

For over 20 years doubts and confusion have existed over the extent to which use of oral contraceptives may predispose to neoplasia. Despite prodigious investment in epidemiological studies, inconsistencies in reported findings have often defied interpretation. Notwithstanding the meticulous design of many cohort and case-control studies, changes in the drugs and dosage schedules that have been introduced over the years have created evident sources of bias; other variables — including, in the case of cervical cancer, differences in patterns of sexual behaviour — have sometimes confounded results; and the possibility remains open that oral contraceptives may affect the risk of neoplasia only in the presence of other unidentified factors. Considerations such as these compound the difficulties that always exist in deciding whether a demonstrated association is likely to be causal. They also raise doubts about the relevance of findings obtained from studies undertaken in industrialized countries to conditions prevalent in the developing world.

It is against this background that a Scientific Group convened by WHO has critically assessed close to 200 relevant studies, including a WHO collaborative study conducted in eight developing and three developed countries. Despite the inevitable difficulties of interpretation, a number of confident conclusions were drawn: use of combined oral contraceptives protects against epithelial ovarian

cancer, reduces the risk of endometrial cancer, and has no influence on the risk of either malignant melanoma of the skin or pituitary tumours. In populations where hepatitis B infection is common, there is no evidence that short-term use of oral contraceptives increases the risk of hepatic carcinoma, but data on the effects of longer-term use are as yet inadequate for evaluation.

Whereas, in general, no overall association appears to exist between oral contraceptive use and breast cancer, a number of recent studies were noted to show a weak association between long-term use of oral contraceptives and breast cancer diagnosed before the age of 36. For women over the age of 45, when breast cancer becomes more common, no evidence of increased risk associated with use of oral contraceptives was found even among high-risk subgroups, including women with a family history of breast cancer. For other cancers, evidence of an association was either weak or inconsistent.

The report includes a discussion of the relevance of existing data to family planning and the protection of women's health in developing countries and it concludes that currently available evidence about neoplasia does not provide grounds for revising the generally favourable assessment of the benefits of oral contraception.

Oral contraceptives and neoplasia: report of a WHO Scientific Group. WHO Technical Report Series, No 817, 1992. ISBN 92 4 1208 17 1

**International Nonproprietary Names (INN)
for Pharmaceutical Substances
Cumulative List No. 8**

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This publication groups together all international nonproprietary names (INN) in Latin, English, French, Russian and Spanish published up to December 1991, together with references to the lists of proposed and recommended INN in which they have been published. It also includes references to other generic names, such as national nonproprietary names and names used by the International Organization for Standardization, pharmacopoeial monographs, the List of Narcotic Drugs under International Control, and other sources. Indexes of molecular formulae and of Chemical Abstracts Service registry numbers are also included.

The procedure for selecting recommended INN is described and the general principles to be followed in devising these names are outlined. All the textual material published in this volume appears in both English and French.

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