Agenda item 6.2

Use of pharmacovigilance data for the assessment of dependence and abuse potential (procedures and methodology)

1. Discussions during the 34th ECDD

The 34th Expert Committee on Drug Dependence (ECDD) discussed the use of pharmacovigilance data for the assessment of dependence and abuse potential (procedures and methodology). The Committee was informed by the Secretariat on the WHO Programme for International Drug Monitoring which started in 1968 and run by the Secretariat, WHO Collaborating Centre (Uppsala Monitoring Centre) and its National Centres (about 100 to date) and Associate Members (about 30 to date). The number of case reports currently approaches 8 million and the accrual rate has increased to about a quarter of a million per year.

The Committee made several suggestions that could improve the usefulness of the data for assessing dependence and abuse potential. These included the use of comparison substances, selection of adverse reactions which are indicators of drug abuse, better specification of the terms used in the data base and use of appropriate denominator data, all of which could improve interpretation of the information. It was agreed that the Secretariat would organize a discussion on how to make the best use of these data and also submit a report at the 35th ECDD.

2. Need for this agenda item in 35th ECDD

This item is included to provide an update of activities on this topic as decided during the 34th ECDD and to discuss further steps.

3. Update on the topic

a. Discussions

WHO PSM/QSM organized an electronic discussion with experts, both from the fields of dependence assessment and from pharmacovigilance, during the first half of 2007. Four rounds of discussions were organized.

During the first round, the use of ADRs for the evaluation of substances for their dependence-producing liability was discussed. There was agreement that pharmacovigilance...
could be one of the many tools to evaluate dependence. ADR reports from clinical trials and spontaneous reports are distinct but complementary. A project to understand whether there are certain ADR terms strongly related to dependence, was proposed.

The purpose of the second round was to discuss issues of terminology. It was clear that definitions cannot be used in a too exact way when using pharmacovigilance data for drug evaluation. Spontaneous reporters do not always use uniform terminologies and various terms can be used in parallel. This round gave a list of ADR terms related to withdrawal and dependence.

The third round discussed numerator and denominator data, frequency and incidence, units of measurement. The discussants agreed that DDD is the unit to establish relative ADR rates, based on ‘reasonable’ therapeutic use. The DDD is the nearest complement to give relative rates from spontaneous reporting data (to measure economic burden) and solicited reports (for comparison between substances), but the numerator and denominator are not derived, with certainty, from the same population. Training on reporting ADRs, with a focus on dependence can improve reporting.

The last round considered comparison with other substances and data interpretation. Opportunity was provided for the participants to bring up any other business. Comparators need to be from the same class as the investigated substance and/or prescribed for the same indication. Several examples were identified. The benefit of a negative control is in establishing a baseline for the method used. A potential “toxicity index” was suggested taking into account dependence and toxicity. A Toxicity Index was developed some years ago in WHO by the International Programme on Chemical safety. Since toxicity grading is used by poison control centres throughout the world (that also have much information on drug abuse), their expertise should be sought.

In summary, the science of using pharmacovigilance for drug dependence liability assessment is not much utilized yet. Among the many ideas discussed was the possibility of data mining. It was attempted by the UMC in 1995, but with simple methodology. The exercise was repeated in 2007, and again recently (2011, see below).

b. Results of explorations using the WHO international pharmacovigilance data base (Vigibase)

The results of the 2007 attempt by Uppsala Monitoring Centre to identify indicators of drug dependence potential from Vigibase are presented in the full report in annex 1.

No single ADR term was found clearly predictive of drug dependence. Cluster analysis to search for possible more complex reporting patterns associated with drug dependence was also performed. The report concludes that the poor results for individual ADR terms, other than those specifying dependence, as general predictors of drug dependence confirms the UMC’s 1995 report, that for early identification of drug dependence potential, more sophisticated ADR
reporting patterns, involving more than one ADR term, and/or other variables, including trends in reporting patterns need to be considered.

The 2011 study used advanced data mining methods. In addition to defining a data mining approach which could be used routinely on Vigibase and that does have some predictive potential, the study results have enabled suggestions of what approaches might be used on other data sets. A publication reporting the real-life predictability finding on Pregabolin is attached (annex 2)

4. Formulation of the discussion point with expected outcome

Based on the information and data presented, realistically can we take this concept forward? Some concrete next steps for progress have to be

- Possible introduction of data mining as a Vigibase routine for dependence
  - How information should be used and by whom?
- To investigate poison control centre information and the possibility of mining that data