by offering training opportunities, harmonized methods, tools, and data resources.

Disclosure of Interest: None declared.

Reference

THE BACKGROUND TO THE NEW WHO/IUPHAR/CIOMS MANIFESTO ENTITLED “CLINICAL PHARMACOLOGY IN HEALTH CARE, TEACHING AND RESEARCH” AND THE IMPORTANCE OF THE FOCUS ON HEALTH CARE
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Summary: In 1970, the World Health Organization (WHO) published its well-known manifesto on clinical pharmacology, which for many years was the gold standard of the discipline.1 However, for the last 10 years or so it has been clearly in need of updating. This was finally achieved in 2012 after 3 to 4 years of work by the above-named editors and a team of distinguished clinical pharmacologists from around the world. Their work was supported not only by the WHO but also by the Council for International Organizations of Medical Sciences (CIOMS) and the International Union of Basic and Clinical Pharmacology (IUPHAR). The document covers a number of different facets of the work of clinical pharmacologists but in particular highlights the role of clinical pharmacology in the delivery of health care.2 A recent questionnaire study in 31 European countries3 has identified the weakness of clinical pharmacology in health care, particularly in its failure to provide clinical pharmacologic services that will promote the rational use of medicines (RUM).

The main chapter on “The Clinical Pharmacologist in Patient Care” covers a number of different ways in which the discipline can help deliver better patient care. The importance of the various modalities discussed will depend on the way in which health care is delivered in different countries. In a few countries, the clinical pharmacologist (CP) will be directly involved in the care of both inpatients and outpatients. However, in the majority of countries, the CP will be more involved indirectly in patient care. In all countries, the CP will be closely involved in the critical evaluation of new and old therapies; in the work of Drug and Therapeutic committees, both national and local; and in services such as drug information, pharmacovigilance, and drug utilization studies. In addition, the CP in many countries is directly involved in therapeutic drug monitoring (TDM) and pharmacogenetic services aiming to facilitate personalized medicine. The overall purpose of the manifesto is to strengthen the role of clinical pharmacology in achieving RUM, and this is the focus of the last chapter in the manifesto.

Disclosure of Interest: None declared.

References

WHO PROGRAMME FOR INTERNATIONAL DRUG MONITORING
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Summary: The thalidomide disaster detected in 1961 initiated the first systematic international effort to address medicine safety issues at the global level. The Sixteenth World Health Assembly (1963) adopted a resolution (WHA 16.36) that reaffirmed the need for early action in regard to rapid dissemination of information on adverse reactions due to medicines and led to the WHO Programme for International Drug Monitoring. Under this program, systems have been developed in member states for the collection of individual case safety reports (ICSRs) and their evaluation. The reports are held in a central database, managed and maintained by the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) in Sweden. The work of the UMC, with policy directives from WHO, serves the important function of contributing to the work of national drug regulatory authorities and other relevant stakeholders, by improving the knowledge of safety profiles of medicines. As of June 2013, there are 144 countries participating in the program, with access to a WHO database containing > 8 million ICSRs. This presentation will trace the growth of the program these last 40 years, address gaps in pharmacovigilance at national and international levels, determine trends and the most urgent PV priorities in defined settings, and identify the broad elements of a pharmacovigilance strategy that will promote quality health care and assure patient safety.

Disclosure of Interest: None declared.

NOVEL MECHANISTIC BIOMARKERS OF DRUG-INDUCED LIVER INJURY
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Summary: Drug-induced liver injury (DILI) represents a significant cause of patient morbidity and mortality and is a major contributor to attrition in drug development. Prediction of clinical DILI remains difficult, particularly in cases characterized by marked interindividual variation. A lack of sensitivity, specificity, and an indirect mechanistic basis of currently used markers of hepatic injury remains a factor for the delayed identification of DILI. There is a need to discover, develop, and validate new biomarkers to better inform the medicinal chemist and the clinician. The ideal biomarker is 1 that is mechanism-based, organ (cell) selective, and that can be used in both the clinic and laboratory models. Traditional biomarkers of DILI include leakage markers of cell death and markers of hepatic function. Preclinical DILI biomarker identification and validation have been focused on molecular biomarkers such as cytokeratin-18, high mobility group box-1 protein, and microRNA-122, which are more informative with respect to chemical stress, adaptation, and mechanisms of cellular damage. Recent reports have shown that these hold translational application to inform both the sensitive identification of DILI and also its mechanistic basis in man. Furthermore, a number of these biomarkers provide enhanced prognostic information during clinical acetaminophen overdose. The integrated use of these and other markers will be discussed from a backdrop of imperfect current standards
in the context of understanding fundamental hepatology, translational applications, and the challenges associated with the clinical qualification of novel DILI biomarkers.

Disclosure of Interest: None declared.

IMMUNOLOGICAL ASPECTS OF DRUG HYPERSENSITIVITY—FROM MOLECULE TO MAN
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Summary: Drug-induced liver injury (DILI) accounted for >50% of cases of acute liver failure and 15% of patients undergoing liver transplantation between 1990 and 2002. One of the biggest fears is unpredictable idiosyncratic drug-induced liver injury (IDILI), which is a major contributor to the failure of a drug to process through development and is a major cause of withdrawal and black box warnings. Due to the low concordance of the hepatotoxicity of drugs in animals and humans, a fundamental understanding of the mechanistic basis from novel human-relevant in vitro models and biomarkers is critical for the development of effective strategies to prevent and predict DILI.

Hepatocellular activation of drugs has been widely implicated in immune-mediated DILI with concomitant activation of the adaptive immune system. Consistent with this hypothesis, a number of HLA alleles that are associated with DILI have been identified. Studies with patient PBMC and PBMC from drug-naive donors carrying HLA risk alleles have shown that drugs form specific associations with HLA risk alleles generating T-cell antigens and hence provide the immunogenetic basis for the reaction. The identification of HLA alleles as predisposing factors for IDILI suggests that the adaptive immune system also participates in reactions targeting the liver. Furthermore, the release of damage-associated molecular pattern molecules (DAMPs), such as high mobility group box-1, may serve to activate cells of the innate immune system. Certain mediators produced by innate cells may cause liver injury, but other factors are actually important to promote tissue repair and regeneration. However, to fully define cause and effect (bioactivation vs liver failure), an integrated approach based on clinical studies, in vitro experiments, and animal models will be required, underpinned by appropriate bioanalysis. We have been able to characterize covalent protein adducts in man formed by reactive drug metabolites (nevirapine, diclofenac) using techniques developed for β-lactam antibiotics that associate with various types of drug hypersensitivity. We have also developed in vitro models to look at the interplay between, genetic, chemical, and immunologic factors using cells from both hypersensitive and drug-naive individuals. Such techniques and concepts should enable us to elucidate various mechanistic pathways and thus define both chemical and biological variables that underpin this rare but serious form of DILI.

Disclosure of Interest: None declared.

NOVEL CLINICAL TRIAL DESIGNS FOR ASSESSING THE EFFICACY OF DRUGS
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Summary: There is a pressing need for faster and more efficient evaluation of new cancer agents to improve outcomes. Although many of the new targeted agents have proved disappointing, there is a large range of new agents from varying classes that need to be evaluated alongside a need to evaluate biomarkers to identify more responsive patient subgroups effectively. The current evidence on biomarkers that predict the response to a therapy in oncology has often arisen from post hoc retrospective analyses of Phase III trial data. More recent trials are exploring novel ways to identify potential biomarkers of response much earlier in the drug development process, albeit in a more exploratory fashion. We suggest a new approach to trial design, which links novel treatment evaluation with the concurrent evaluation of a biomarker within a confirmatory Phase II–III trial setting.

We describe such an approach used in a new protocol in advanced colorectal cancer called FOCUS4. The protocol will ultimately answer 3 research questions for a number of treatments and biomarkers: (1) After a period of standard first-line chemotherapy, do targeted novel therapies provide strong signal of activity in different biomarker-defined populations? (2) If so, do these definitively improve outcomes? (3) Is evidence of activity restricted only to the biomarker-defined groups?

Disclosure of Interest: None declared.

THE FUTURE OF MODELING AND SIMULATION APPROACHES IN DRUG DEVELOPMENT
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Summary: High development cost, low development success, cost-disciplined health care policies, and intense competition demand an efficient drug development process. New compounds need to bring value to patients by being safe, efficacious, and cost-effective compared with existing treatment options.

The goal of pharmacometrics/quantitative clinical pharmacology (also called Modeling and Simulation) is to optimize therapies for adult and pediatric patients through integration, innovation, and impact.1
- Quantitatively integrate multisource data and clinical, biological, statistical, and mathematical concepts
- Collaborate and innovate across disciplines, enhancing scientific understanding and knowledge
- Impact and enhance key decisions in drug research and development

Pharmacometric approaches, including model-based meta-analyses, allow for integration and utilization of biomarker, efficacy, and safety data and:
- Provide a quantitative framework for comparative efficacy/safety assessments of drugs
- Create opportunities to test assumptions through “virtual” experiments and optimized clinical trials
- Facilitate research and development of new therapies for adults and pediatrics

A sustained collaborative effort between academia, biotech/pharma, hospitals and scientific societies involved in research, development, and use of medicines is required to bring pharmacometrics/quantitative clinical pharmacology to its full potential.

Reference

PHARMACOLOGY OF CHOCOLATE
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Summary: Rationale: Chocolate is a popular food. Its consumption is largely associated with pleasure. Beliefs on its positive impact on health, physical, and mental strengths have been well established for