Assessing immunotoxicity: guidelines

E. Putman’a, J.W. van der Laan’a*, H. van Loverenb

‘Preclinical Assessment Group of the Medicines Evaluation Board, Laboratory for Medicines and Medical Devices, National Institute for Public Health and the Environment, Bilthoven, The Netherlands
bLaboratory for Toxicology, Pathology and Genetics, National Institute for Public Health and the Environment, Bilthoven, and Department of Health Risks Analysis and Toxicology, Maastricht University, The Netherlands

KEYWORDS
autoimmunity, developmental immunity, hypersensitivity, immunotoxicity, photosensitivity, predictability, regulatory guidelines

ABSTRACT
Over the last couple of years the assessment of immunotoxic potential of human pharmaceuticals has drawn considerable attention worldwide. Regulatory agencies entrusted with the registration of pharmaceuticals (or other compounds) found an increased need for guidance on this issue. This has resulted in the release of guidance documents on immunotoxicity in Europe, USA and Japan in close succession. In Europe the CPMP has released their immunotoxicity guidance documents that are now in force. The FDA and the Japanese Authorities are in the process of doing so, and will shortly enforce them.

Immune suppression and stimulation, hypersensitivity, photosensitivity, drug-induced autoimmunity and developmental immunotoxicity are the focus of regulatory testing. This review discusses these kinds of immunotoxicity and their clinical implications. The three regional guidelines and screening tools for detection are discussed. Additionally, the scientific background on which these guidelines are based is briefly highlighted.

INTRODUCTION
Administration of immunotoxic pharmaceuticals (or other compounds) may result in various kinds of immunological disturbance. Interaction with the immune system can be the intended pharmacodynamic action of the compound or an unwanted side effect. Immunotoxic response can originate from direct toxicity of the pharmaceutical to component(s) of the immune system. Direct immunotoxicity can result in either immunosuppression or immunostimulation. Alternatively, the immune system may react to the chemical in an antigen-specific way, for instance, in the case of chemicals bound to self-proteins. This type of immunotoxicity is usually expressed as a hypersensitivity reaction or autoimmune reaction. In autoimmunity disease the immune system responds to self-antigens.

An additional area of interest is the effect of (immunotoxic) pharmaceuticals or compounds on the developing immune system. Developmental immunotoxicity occurs when a chemical affects the developing immune system either by direct exposure of the neonate or exposure via the mother. The developmental immunotoxicant can exert its toxicity via direct or indirect mechanisms as described above.

IMMUNE SUPPRESSION/ENHANCEMENT
Immune suppression can result in decreased resistance to (opportunistic) infection, and neoplasia. Clinical relevance of immunomodulation of pharmaceuticals has clearly been demonstrated in the case of immunosuppressive therapeutics (cyclosporin, azathioprine) used in transplant patients. It has been clearly shown that these patients suffer from an increased risk of cancers compared to the general population. Skin cancers, lymphoproliferative disorders, and Kaposi’s sarcomas...