Table 7.2 Immunogenicity of Recombinant Drugs

Incidence	Brand Product	Drug Substance
95%	Leukine	Sargramostim
74%	Proleukin	Aldesleukin
25%–45%	Betaferon	Interferon-beta-1b
12%–28%	Rebif	Interferon-beta-1a
14%–24%	Remicade (and its other biosimilars)	Infliximab
12%	Humira	Adalimumab
0%–26%	Rituxan	Rituximab
3.5%–5%	Erbitux	Cetuximab
2%–6%	Avonex	Interferon-beta-1a
0%–2%	Neupogen (and other biosimilars), Procrit, Neorecormon, Aranesp, Avastin, Neulasta, Genotropin (and other biosimilars), Herceptin	Filgrastim, EPO alpha, EPO beta, darbopoietin alpha, bevacizumab, pegfilgrastim, somatropin, trastuzumab

Source: Wadhwa, M., *Immunogenicity: What Do We Know and What Can We Measure?* EPAR 1, National Institute for Biological Standards and Control—Health Protection Agency, 2011. With permission.

interferon alfa 2a (a particular brand) show high incidence, some of which can be attributed to the formulation and manufacturing factors listed in Section 7.2.2.

7.2.1 Regulatory guidance

The assessment of immunogenicity is an important component of drug safety evaluation in preclinical, clinical, and postmarketing studies.

Draft Guidance for Industry Assay Development for Immunogenicity Testing of Therapeutic Proteins has recently been published by the U.S. FDA (http://www.fed.gov/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM192750.pdf). Similarly, guidelines on the immunogenicity assessment of biotechnologyderived therapeutic proteins established by the Committee for Medicinal Products for Human Use of the EMA came into effect in April 2008 (http://www.emea.europa.ed /pdfs/human/biosimilar/1432706en.pdf). These guidelines provide a general framework for a systematic and comprehensive evaluation of immunogenicity that should be modified, as appropriate, on a casebycase basis.

The approach to test immunogenicity is a risk-based approach that is clinically driven and takes into account PK data. Thus, biopharmaceuticals with no endogenous counterpart are considered to be of relatively low risk while drugs with a nonredundant endogenous counterpart are considered to present a high risk. A multitier approach to testing samples is also recommended. This consists of an appropriate screening assay capable of detecting both immunoglobulin M (IgM) and IgG ADAs, the sensitivity