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Letter

WHO International Standards and reference preparations for cytokines and growth factors

The ability to quantify the activity of cytokines is an essential part of experimental and clinical investigation and is largely dependent upon the availability of suitable cytokine standards and reference reagents. The International Cytokine and Interferon Society (ICIS) Standards Committee was established to make recommendations regarding interferon and cytokine standards and standardization to the ICIS membership, and thereby to the international cytokine scientific community. The Committee works closely with the World Health Organization (WHO), the National Institute for Biological Standards and Control (NIBSC), the U.S. National Institutes of Health (NIH), the Biodefense and Emerging Infections Resources Repository (BEI Resources), pharmaceutical manufacturers, and regulatory agencies. The Committee includes members from several of these organizations. The role that the Committee plays as a source of information and recommendations to the ICIS membership, and to the international cytokine scientific community as a whole, is very much dependent upon suitable standards and reference materials being made available by the NIBSC. Similarly, the Standardization and Nomenclature Committee of the ICIS reviews the need for cytokine standards and their usage. With the expanding role of cytokines and growth factors in the development and manufacture of biotechnology derived products e.g., monoclonal antibodies targeting cytokines/growth factors, biosimilar medicines, cell and/or gene therapy products, the need for suitable standards is increasing.

The accompanying Table lists WHO International Standards (IS), WHO reference reagents (WRR) and other cytokine and growth factor standards available from the NIBSC (Table 1). ISs and WRRs are publicly available reference standards with defined units (International Unit for IS) established by the WHO Expert Committee on Biological Standardization. Lyophilised and formulated to ensure long term stability, they serve as 'primary' standards for bioactivity and for calibration of secondary reference standards. The use of IS and WRR to calibrate commercially available or laboratory made reagents including immunoassays where feasible as per WHO recommendations facilitates comparisons of data between assays, different laboratories, and individual studies allowing global harmonisation.

Table 1
Cytokine and growth factor standards and reference reagents available from the National Institute for Biological Standards and Control.

Preparation[a]	Product code	Status[b]
Human cytokine standards and reference reagents		
Interleukin 1 alpha	86/632	1st IS
Interleukin 1 beta	86/680	1st IS
Interleukin 2	86/500	2nd IS
Interleukin 3	91/510	1st IS
Interleukin 4	88/656	1st IS
Interleukin 5	90/586	WRR
Interleukin 6	89/548	1st IS
Interleukin 7	90/530	WRR
Interleukin 8	89/520	1st IS
Interleukin 9	91/678	WRR
Interleukin 10	93/722	WRR
Interleukin 11	92/788	WRR
Interleukin 12	95/544	WRR
Interleukin 13	94/622	WRR
Interleukin 15	95/554	WRR
Interleukin 17	01/420	WRR
Interleukin 18	03/200	WRR
M-CSF	89/512	1st IS
G-CSF	09/136	2nd IS
G-CSF(pegylated)	12/188	1st IS
GM-CSF	88/646	1st IS
Leukemia inhibitory factor	93/562	WRR
Oncostatin M	93/564	WRR
Stem cell factor	91/682	WRR
Flt 3 ligand	96/532	WRR
Bone morphogenetic protein-2	93/574	WRR

(*continued on next page*)

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Table 1 (*continued*)

Preparation[a]	Product code	Status[b]
RANTES	92/520	RR
MCP-1	92/794	RR
GRO-alpha	92/722	RR
IFN alpha leukocyte	94/784	1st IS
IFN alpha 1 (D)	83/514	1st IS
IFN alpha 1/8	95/572	1st IS
IFN alpha 2a	95/650	2nd IS
IFN alpha 2b	95/566	2nd IS
IFN alpha 2c	95/580	1st IS
IFN alpha n1 lymphoblastoid	95/568	2nd IS
IFN alpha n3 leukocyte	95/574	1st IS
IFN alpha consensus	94/786	1st IS
IFN omega	94/754	1st IS
IFN beta	00/572	3rd IS
IFN beta ser17	00/574	RR
IFN beta fibroblast	00/576	RR
IFN gamma	87/586	RR
IFN gamma leukocyte	82/587	BWS
IFN lambda1	10/176	WRR
TGF beta 1	89/514	RR
TGF beta 2	90/696	RR
TGF beta 3	09/234	1st IS
Thrombopoietin	03/124	RR
TNF alpha	12/154	3rd IS
TNF beta	87/640	WRR
TRAIL	04/166	WRR
Human growth factor standards and reference reagents		
Basic Fibroblast Growth Factor	90/712	1st IS
Brain-derived neurotrophic factor	96/534	WRR
Ciliary Neurotrophic Factor	94/684	WRR
Epidermal Growth Factor	91/530	1st IS
Epidermal Growth Factor (1–52)	91/550	WRR
Hepatocyte Growth Factor	96/564	WRR
Hepatocyte Growth Factor precursor	96/556	1st IS
Keratinocyte Growth Factor	03/150	WRR
Keratinocyte Growth Factor (24–163)	03/148	WRR
Leptin	97/594	1st IS
Nerve Growth Factor	93/556	WRR
Neurotrophin-3	98/718	RR
Platelet derived Growth factor BB	94/728	1st IS
Vascular Endothelial Growth Factor 165	02/286	WRR
Murine cytokine standards and reference reagents		
GM-CSF	91/658	RR
Interleukin1-α	93/672	RR
Interleukin1-β	93/668	RR
Interleukin 2	93/566	RR
Interleukin 3	91/662	RR
Interleukin 4	91/656	RR
Interleukin 6	93/730	RR
Interleukin 7	93/740	RR
Interleukin 9	93/504	RR
Leptin	97/626	IS
TNF-α	88/532	RR
Standards for cytokine antagonists		
Etanercept	13/204	1st IS
Infliximab	16/170	1st IS

A wide range of WHO International Biological Standards and reference materials are available for the calibration of assays of therapeutic substances and immunoassays and bioassays used in basic research. These materials are available from Standards Processing Division, National Institute for Biological Standards and Control (NIBSC), Blanche Lane, South Mimms, Potters Bar, Herts EN6 3QG, UK. The NIBSC does not charge for these materials, however there is a handling charge to cover the costs of administration, storage, and dispatch. The handling charge is currently £120 per ampoule. A comprehensive catalogue of reference materials is available from the above address or can be accessed online via the NIBSC website (www.nibsc.org/products).

[a] All preparations listed above are rDNA derived unless specified.

[b] IS – International Standard; WRR – WHO Reference Reagent; RR – NIBSC Reference Reagent; BWS – British Working standard; WS – Working standard.

About the National Institute for Biological Standards and Control

The National Institute for Biological Standards and Control (NIBSC) is a global leader in the standardisation and control of biological medicines, playing a major role in assuring the quality of biological medicines worldwide.

NIBSC is a centre of the Medicines and Healthcare products Regulatory Agency which also includes CPRD and MHRA. The Medicines and Healthcare products Regulatory Agency is an executive agency of the Department of Health.

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