17 May 2011

Ms Julie Dennett
Committee Secretary
Senate Legal & Constitutional Affairs Committee
PO Box 6100
Parliament House
CANBERRA ACT 2600

Dear Ms Dennett

Thank you for inviting Medicines Australia to appear before the Senate Legal & Constitutional Affairs Committee on 28 April 2011.

We wish to respond to the following question on notice:

Q: Which of the medicines listed on page 5 of Medicines Australia's submission to the Committee are identical or substantially identical to naturally-occurring biological compounds?

A: While several of the medicines listed in our original submission contain active ingredients which have natural analogues (see the attached table), Medicines Australia is unable, at this stage, to definitively comment on which of these active ingredients may be "identical" or "substantially identical" to naturally-occurring biological compounds.

This is because the final meaning (or the interpretation) of the words "identical" or "substantially identical" will only be known once they have been tested in the courts, and to our knowledge there have been no legal cases so far which could shed light on whether certain active ingredients in the medicines listed in our submission should (or could) be deemed "identical" or "substantially identical" to naturally-occurring biological compounds.

That said, it is also important to note that the medicines listed in our original submission contain active ingredients which are biological compounds (in each case, a protein) that mimic (or participate in) naturally-occurring biological pathways in human beings. It is therefore possible to describe each of these synthetically produced biological materials as being "substantially identical" to naturally occurring biological compounds.

This reinforces what we said in our original submission, that introducing a ban on patents on all biological materials which are "identical" or "substantially identical" to naturally occurring biological compounds "however (they are) made" would lead to enormous uncertainty around the patent status of many current (under development) and future life-saving medicines. This would undoubtedly have serious effects on patients' access to medicines in Australia, as some companies which develop new medicines containing biological materials as active compounds may choose not to bring their products to Australia, or delay bringing them to Australia until after other markets.

Thank you again for the opportunity to contribute to this inquiry. If you have questions about the views expressed in this letter, or if you would like further information, please do not hesitate to contact Deborah Monk, Director Innovation & Industry Policy, at:

Yours sincerely

Dr Brendan Shaw
Chief Executive

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Brand Name	Active (Biological) Ingredient	Type	Natural Homologue	Major Indications	(Condensed) Description of biological material and Mechanism of Action
Kineret®	Anakinra	protein	interleukin-1 receptor antagonist	rheumatoid arthritis	Anakinra is a recombinant, nonglycosylated form of the human interleukin-1 receptor antagonist (IL-1Ra). Kineret differs from native human IL-1Ra in that it has an additional single methionine residue at its amino terminus. It is produced by recombinant DNA technology using an *E. coli* bacterial expression system. Kineret (Anakinra) blocks the biological activity of interleukin-1 (IL-1) by competitively inhibiting IL-1 binding to IL-1 type 1 receptor which is expressed in a wide variety of tissues and organs. Elevated IL-1 concentrations are associated with inflammation and cartilage degradation in patients with rheumatoid arthritis.
Humira®	Adalimumab	protein		rheumatoid arthritis	Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system. Humira (Adalimumab) binds to a naturally occurring cytokine called tumour necrosis factor (TNF) which is involved in normal inflammatory and immune responses. Elevated levels of TNF are associated with various forms of arthritis. Humira neutralises the biological function of TNF by blocking its interaction with certain cell surface TNF receptors.
NovoRapid®	Insulin aspart	protein	human insulin	Diabetes mellitus	Insulin aspart is a rapid-acting analogue of human insulin that rapidly lowers blood glucose. Insulin aspart is homologous with human insulin with the exception of a substitution of the amino acid proline by aspartic acid at position 28 on the B-chain. Insulin aspart is produced by recombinant DNA technology using *Saccharomyces cerevisiae*. NovoRapid (Insulin apart) acts by binding to insulin receptors to increase glucose uptake and inhibit glucose output.
Tysabri®	Natalizumab	protein		multiple sclerosis	Natalizumab is a recombinant humanised IgG4 monoclonal antibody produced in murine myeloma cells. Natalizumab (rmc) contains human framework regions and the complementarity-determining regions of a murine antibody that binds to α4-integrin. Tysabri (Natalizumab) works by binding to white blood cells and preventing them from moving into the brain and spinal cord where they cause inflammation, an important part of the MS disease process.
Orencia®	Abatacept	protein		rheumatoid arthritis	Abatacept is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1. Abatacept is produced by recombinant DNA technology in Chinese hamster ovary cells. Orencia (Abatacept) modulates a key signal required for full activation of T lymphocytes expressing CD28, which (in activated form) are found in joint areas of patients with rheumatoid arthritis. Activation requires CD 28 to bind with CD80 and CD86, a process which Orencia inhibits by specifically binding to CD80 and CD86.

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Angiomax®	Bivalirudin	protein	hirudin	Anticoagulant	Bivalirudin is a specific and reversible direct thrombin inhibitor. Bivalirudin is a synthetic, 20 amino acid residue peptide. Angiomax (Bivalirudin) prevents unwanted blood clotting during angioplasties by inhibiting the normal functions of thrombin, an enzyme involved in normal blood clotting.
Ovidrel®	Choriogonadotropin α	protein	human chorionic gonadotropin	fertility treatment	Choriogonadotropin alfa is a glycoprotein consisting of two noncovalently linked subunits – designated alfa (α) and beta (β). The primary structure of the α-subunit of the recombinant human chorionic gonadotrophin (r-hCG) is identical to that of the α-subunit of the human chorionic gonadotrophin (hCG), follicle stimulating hormone (FSH) and luteinising hormone (LH). The glycoform pattern of the α subunit of r-hCG is closely comparable to the urinary derived hCG (u-hCG). The β-subunit has both O- and N-glycosylation sites and its structure and glycosylation pattern are also very similar to that of u-hCG. Ovidrel (Choriogonadotropin α)is produced by genetically engineered Chinese hamster ovary (CHO) cells. The physicochemical, immunological and biological activities of recombinant hCG are comparable to those of placental and human pregnancy urine-derived hCG. Ovidrel (Choriogonadotropin α) sitmulates late follicular maturation (etc.) by mimicking the normal function of (the naturally occurring) luteinising hormone. It is used in women undergoing assisted reproductive techniques such as in vitro fertilisation.
Aranesp®	Darbepoetin alfa	protein	human erythropoietin	Anaemia	Darbepoetin alfa is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Aranesp (Darbepoetin alfa) stimulates red blood cell production (erythropoiesis) by the same mechanism as recombinant human erythropoietin (r-HuEPO). Aranesp is a 165-amino acid protein containing 5 N-linked oligosaccharide chains, whereas erythropoietin contains only 3. Aranesp stimulates erythropoiesis (red blood cell production) in patients with chronic renal failure and patients undergoing cancer treatment. Natural production of erythropoietin (a glycoprotein) is impaired in these patients, resulting in anaemia.
Xigris®	Drotrecogin alfa	protein	human activated protein C	severe sepsis	Drotrecogin alfa (activated) rhu is human Activated Protein C produced by recombinant DNA technology. Xigris (Drotrecogin alfa (activated) rhu) is a recombinant version of the endogenous human activated protein C and is produced by genetic engineering from an established human cell line (HEK-293). Xigris, like endogenous activated protein C, has antithrombotic and anti-inflammatory properties. The exact mechanism of action is not clearly understood.

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Forteo®	Teriparatide	protein	parathyroid hormone	osteoporosis	Teriparatide is the active fragment (1-34) of endogenous human PTH, manufactured using recombinant DNA technology. Endogenous 84-amino-acid parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in bone and kidney. Physiological actions of PTH include regulation of bone metabolism, renal tubular reabsorption of calcium and phosphate, and intestinal calcium absorption. The biological actions of PTH and teriparatide are mediated through binding to specific PTH cell surface receptors. Teriparatide binds to these receptors with similar affinity as PTH, and has the same actions in bone and kidney as PTH.
NeoRecormon®	Epoetin beta	protein	human erythropoietin	anaemia	Epoetin beta *rch* is a sterile, purified, stable recombinant human erythropoietin concentrate produced from genetically engineered chinese hamster ovary (CHO) cells containing a cloned human erythropoietin gene. The active ingredient, epoetin beta *rch*, is a highly purified glycoprotein, identical in amino acid sequence to endogenous erythropoietin. (NeoRecormon (Epoetin beta *rch*) stimulates erythropoiesis (red blood cell production) in patients with chronic renal failure and patients undergoing cancer treatment. Natural production of erythropoietin (a glycoprotein) is impaired in these patients, resulting in anaemia.
Integrilin®	Eptifibatide	protein	barbourin	cardiac ischemia	Eptifibatide, is a synthetic cyclic heptapeptide containing six amino acids, including one cysteine amide and one mercaptopropionyl (desamino cysteinyl) residue. Integrilin (Eptifibatide) binds to the platelet receptor glycoprotein IIb-IIIa of human platelets. It reversibly inhibits platelet aggregation by preventing the binding of fibrinogen and adhesive ligands to glycoprotein IIb-IIIa. INTEGRILIN is indicated for patients undergoing nonurgent percutaneous coronary intervention with intracoronary stenting and for the treatment of patients with unstable angina or non-Q-wave myocardial infarction.
Enbrel®	Etanercept	protein		rheumatoid arthritis	Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system. Etanercept is a dimer of a protein genetically engineered by fusing the extracellular ligand binding domain of human tumour necrosis factor receptor-2 (TNFR2/p75) to the Fc domain of human IgG1. Enbrel (Etanercept) binds specifically to a naturally occurring cytokine called tumour necrosis factor (TNF), which is the dominant cytokine in the inflammatory process associated with rheumatoid arthritis. It blocks TNF interaction with cell surface TNF receptors.

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Diphereline®	Triptorelin embonate	protein	human hypothalamic gonadotropin-releasing hormone	prostate cancer	Triptorelin is a decapeptide (pGlu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2) a gonadotropin-releasing hormone agonist (GnRH agonist). By causing constant stimulation of the pituitary, it decreases pituitary secretion of gonadotropins luteinizing hormone (LH) and follicle stimulating hormone (FSH). Diphereline (Triptorelin embonate) works by lowering the production of testosterone in men. In some types of prostate cancer, testosterone may help the cancer cells grow. By lowering testosterone, Diphereline may slow or stop the growth of cancer.
Copaxone®	Glatiramer acetate	protein		multiple sclerosis	Glatiramer acetate is the acetate salt of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine and L-lysine. The precise mechanism by which Copaxone (Glatiramer acetate) exerts its effects in MS patients is unknown. It is thought to act by modifying immune processes that are currently held to be responsible for the pathogenesis of MS.
Remicade®	Infliximab	protein		Crohn's Disease	Infliximab is a chimeric human-murine monoclonal antibody that binds to human tumour necrosis factor alpha (TNFα). TNFα is a pro-inflammatory and immunoregulatory cytokine that, when overexpressed, mediates chronic inflammation in diseases such as Crohn's disease and rheumatoid arthritis. Remicade (Infliximab) neutralises the biological activity of TNFα by binding with high affinity to the soluble and trans-membrane forms of TNFα and inhibits the binding of TNFα with its receptors. Elevated levels of TNFα mediate chronic inflammation in patients with Crohn's disease.
Eprex 2000®	Epoetin alfa	protein	human erythropoietin	anaemia	Erythropoietin is an endogenous glycoprotein that stimulates red blood cell production. It is normally produced by the kidney and regulated by the level of tissue oxygenation. Epoetin alfa (rch) is purified from a Chinese hamster ovary cell line into which the gene coding for human erythropoietin has been inserted. Epoetin alfa (rch) is indistinguishable from human erythropoietin in biological activity and immunological reactivity. Eprex (Erythropoietin alfa) stimulates erythropoiesis in anaemic patients with chronic renal failure in whom the endogenous production of erythropoietin is impaired.
Erbitux®	Cetuximab	protein		colorectal cancer	Cetuximab is a chimeric monoclonal antibody of the immunoglobulin G1 (IgG1) subclass, produced in mammalian cell culture by mouse myeloma cells (Sp2/0). It is obtained by attaching the variable regions of the murine monoclonal antibody M225 against epidermal growth factor receptor (EGFR) to constant regions of the human IgG1. Erbitux (Cetuximab) binds to epidermal growth factor receptor (EGFR) , whose over-expression is detected in many human cancers (including colon cancer), with an affinity that is approximately 5 to 10 times higher than that of natural EGFR binding ligands. Erbitux thus plays a role in down-regulation of EGFR.

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Gonal-F 75®	Follitropin alfa	protein	human follicle stimulating hormone	fertility treatment	Human follicle stimulating hormone (FSH) is a glycoprotein (MW about 30,000) and is characterised by two amino acid chains known as α and β. The β-chain confers biological activity. The α-chain is common to all glycoproteins with specificity residing in the β-chain. GONAL-f contains the active ingredient follitropin alfa (rch). This is produced by a Chinese Hamster Ovary cell line transfected with the human FSH subunit genes (i.e. by recombinant DNA technology). Gonal-F 75 sitmulates late follicular maturation (etc.) by mimicking the normal function of (the naturally occurring) luteinising hormone. It is used in women undergoing assisted reproductive techniques such as in vitro fertilisation.
Lucentis®	Ranibizumab	protein		macular degeneration	Ranibizumab is a humanised monoclonal antibody fragment produced in *Eschericia coli* cells by recombinant DNA technology. Lucentis (Ranibizumab) binds with high affinity to several forms of human vascular endo-thelial growth factor A (VEGF-A), which prevents VEGF-A from binding to its normal receptors VEGFR-1 and VEGFR-2 (a process which is thought to contribute to the progression of age-related macular degeneration).
Neulasta®	Pegfilgrastim	protein	human granulocyte colony-stimulating factor	neutropenia	Neulasta is composed of filgrastim (recombinant methionyl human G-CSF, tradename NEUPOGEN) with a polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionine residue. Filgrastim is a 175 amino acid protein manufactured by recombinant DNA technology. Filgrastim is produced by *Escherichia coli (E coli)* bacteria into which has been inserted the human G-CSF gene. Neulasta (Pegfilgrastim), like its natural analogue, helps the body make new neutrophils (a type of immune cell) in patients who have undergone chemotherapy and who as a result may have a reduced ability to fight post-chemotherapy infections.
PEG-Intron®	Peginterferon alfa-2b	protein	Interferon alpha	hepatitis C	Peginterferon alfa-2b is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. Recombinant interferon alfa-2b is obtained from a clone of *E. coli*, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes. PEG-Intron (Peginterferon alfa-2b) inhibits viral replication. Although the exact antiviral mode of action is unknown, PEG-Intron appears to alter the host cell's metabolism. This action inhibits viral replication or if replication occurs, the resulting viral load is unable to leave the cell.
Fuzeon®	Enfuvirtide	protein		HIV	Enfuvirtide is derived from a naturally occurring motif, amino acid residues (643-678) within the gp41 transmembrane glycoprotein of human immunodeficiency virus type 1 strain LAI (HIV-1LAI). Enfuvirtide is a linear 36-amino acid synthetic peptide, composed of naturally occurring L-amino acid residues. Fuzeon (Enfuviritide) is an inhibitor of the structural rearrangement of HIV-1 gp41 that functions by specifically binding to the virus protein and thus blocking the virus from entering the cell.

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Rapilysin 10 U®	Reteplase	protein	human tissue plasminogen activator	heart attack	Reteplase is a sterile, purified, stable recombinant plasminogen activator (r-PA), produced from genetically engineered E Coli cells containing a cloned human gene for part of the plasminogen activator protein structure. Reteplase is obtained by genetic engineering technology, and is a variant of plasminogen activator comprising only the kringle 2 and protease domains. Rapilysin 10 U (Reteplase) is used to generate plasmin, a downstream protein which degrades certain other proteins in order to reduce the incidence of blood clots.
Mabthera®	Rituximab	protein		leukaemia	Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is a glycosylated IgG_1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences (Fab domain) and human constant region sequences (Fc domain). Mabthera (Rituximab) binds specifically to CD20, a protein found on the surface of B-Lymphocytes. This stops the abnormal growth of B-Lymphocytes (which is responsible for certain types of non-Hodgkin's lymphomas and chronic lympho-cytic leukaemia.
Metalyse®	Tenecteplase	protein	human tissue plasminogen activator	heart attack	Tenecteplase is a tissue plasminogen activator (tPA) produced by recombinant DNA technology, using an established mammalian cell line (Chinese Hamster Ovary cells). Tenecteplase is a 527 amino acid glycoprotein developed by introducing the modifications to the complementary DNA (cDNA) for natural human tPA. Tenecteplase is a recombinant plasminogen activator that is derived from native tPA by modifications at three sites of the protein structure. It binds to the fibrin component of the thrombus (blood clot) and converts thrombus-bound plasminogen to plasmin, which degrades the fibrin matrix of the thrombus. Tenecteplase has a higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor compared to native tPA.
Thyrogen®	Thyrotropin alfa	protein	human thyroid stimulating hormone	thyroid cancer	Thyrotropin alfa contains a highly purified recombinant form of human thyroid stimulating hormone (TSH), a glycoprotein which is produced by recombinant DNA technology. Thyrotropin alfa is synthesized in a genetically modified Chinese hamster ovary cell line. The amino acid sequence of thyrotropin alfa is identical to that of human pituitary thyroid stimulating hormone. Thyrogen (Thyrotropin alfa) is an exogenous source of human thyroid stimulating hormone, used to replace the deficiency of the hormone in patients who have undergone a thyroidectomy.