WHO Drug Information

Contents

Access to Medicines

WHO prequalification: progress in 2007

The Prequalification Programme for medicinal products is a service provided by the World Health Organization (WHO) to facilitate access to medicines that meet international unified standards of quality, safety and efficacy for HIV/AIDS, malaria, tuberculosis and reproductive health.

Work is carried out through:

- stringent assessment of pharmaceutical product dossiers;
- inspection of pharmaceutical manufacturing sites (both for finished dosage forms and active pharmaceutical ingredients) and contract research organizations (CROs);
- prequalification of pharmaceutical quality control laboratories (QCLs); and
- advocacy for medicines of assured quality.

The Programme also provides high-level training, capacity building and technical assistance to stakeholders from both the private and public sectors. The Bill & Melinda Gates Foundation as well as UNITAID are currently the principle financial supporters of the WHO Prequalification Programme.

New prequalified products

Twenty-one products were added to the list of prequalified medicines in 2007 – all but one being generics. The number of prequalified medicines now stands at 156.

A major achievement in 2007 was the prequalification of five new products to treat tuberculosis and three antimalaria products. This offers a considerable increase in the choice of prequalified medicines for these diseases.

The total number of prequalified products in 2007 was the lowest since 2001. The main reasons for this are:

- decreasing number of new submissions;
- submitted dossiers did not include sufficient evidence to prove quality, safety and efficacy of products; and
- little additional substantive evidence was provided in support of dossiers previously submitted.

Certain product groups are urgently in need of expansion to increase available treatment options, i.e., second-line antituberculosis and paediatric antiretroviral combination products. In 2007, only one antituberculosis treatment submission and two new submissions for paediatric antiretrovirals were presented for WHO Prequalification.

In the past year, the number and quality of product dossiers submitted for assessment was very uneven. Conversely, a considerable number of new applicants approached WHO. However, most of the newcomers have limited or no experience in production to international standards and are not yet capable of generating the required evidence. The manufacturing conditions and quality specifications presented for reproductive health and antimalarial products were particularly poor.

Efforts needed to reach prequalification status

The products prequalified in 2007 were, on average, under assessment and

Summary of activities in 2007

The WHO Prequalification Programme:

- Prequalified a total of 21 medicinal products, including 5 anti-tuberculosis and 3 anti-malarial medicines
- Intensified and widened the scope of prequalification of quality control laboratories
- Doubled the number of training workshops for capacity building in resource-limited countries
- Organized 10 technical assistance missions for manufacturers to support improvements in the quality of their products
- Planned and implemented a comprehensive sampling and testing programme
- Developed guidelines and standards to facilitate global quality assurance activities, including pharmacopoeial monographs and chemical reference substances
- Undertook special efforts to facilitate development of paediatric formulations
- Recruited additional full-time staff to maintain sustainability and improve performances of prequalification process
- Streamlined the process between receiving a complete dossier and the first assessment or inspection of manufacturing sites
- Developed tools to increase transparency and allow monitoring of the prequalification process

adjustment for two years before attaining compliance with international standards. During this period, eight to nine assessment sessions and five inspections were required before the ultimate positive conclusions were reached. Thus, considerable time and resources are needed from applicants, as well as dedication to implementing the necessary corrective action, to meet international quality standards.

All involved stakeholders agree and understand that expansion of the list of prequalified medicines can only be realized if capacity building and technical assistance activities increase in resource-limited countries. Therefore, such actions have become one of the core objectives of the Prequalification Programme.

Maintaining the list of prequalified medicines

Inclusion in the list does not mean that the prequalified status of a product lasts forever. All prequalified medicines have to be checked regularly in order to ensure that any changes undertaken by manufacturers do not undermine the quality, safety and efficacy of the products.

In order to reach this objective, WHO assesses variations in manufacture and carries out random quality control tests of prequalified medicines, as well as re-inspections of manufacturing sites. As the prequalified products list is constantly growing, maintaining and updating the information becomes increasingly important in order to ensure the quality and safety of the medicines.

Training Workshops organized in 2007

Date	Location	Content of training
16–20 April	Cape Town, South Africa	Pharmaceutical development with a focus on paediatric medicines
6–7 June	Cairo, Egypt	WHO Prequalification Programme – introduction for EMRO countries
25–27 June	Kiev, Ukraine	Dissolution, pharmaceutical product inter-changeability and biopharmaceuticals classification system
10–14 September	Dar Es Sallam, Tanzania	Assessment of dossiers based on WHO Prequalification guidelines for staff of East Africa Community national medicine regulatory authorities
15–19 October	Tallinn, Estonia	Pharmaceutical development with a focus on paediatric medicines
5–9 November	Jiaxing, China	Pharmaceutical quality, Good Manufac turing Practice and bioequivalence with a focus on anti-tuberculosis products
26–29 November	Rabat, Morocco	Quality assurance, Prequalification and quality control in quality control laboratories
10–14 December	Dakar, Senegal	Good Manufacturing Practice training course for countries of francophone Africa
5–7 December	Dar Es Sallam, Tanzania	Quality assurance, Prequalification and development of standards in quality control laboratories

Capacty building for regulatory authorities

Recognizing the importance of capacity building through training and hands-on practice, the WHO Prequalification programme organized nine training courses in 2007 and co-organized four training activities together with other partners in nine different countries. These exercises offered tuition on general or specific technical issues for larger groups, including staff from regulatory agencies and quality control laboratories, and for manufacturers. Such training includes group sessions as well as communication between involved parties, such as manufacturers and the presenters, who are themselves part of the assessment or inspection teams working with the Prequalification Programme.

In 2007, four national regulatory experts from Ethiopia, Tanzania, Uganda and

Zimbabwe were offered a full-time position at WHO for three months. The objective was to create a rotational network between WHO and resource-limited countries, increase capacity building of national regulatory authorities and enhance information exchange between all parties.

Technical assistance to manufacturers

Since 2006, the WHO Prequalification programme has provided coordinated technical assistance aimed at resolving specific practical problems encountered by manufacturers or quality control laboratories. Assistance is given by a qualified professional in the form of an audit and training in technical or regulatory areas.

In 2007 alone, the WHO Prequalification programme provided a total number of 13 technical assistance sessions in nine different countries, compared to six in four countries in 2006.

To avoid conflict of interest, WHO uses a pool of specialists working either for nonprofit organizations or acting as individual technical consultants unrelated to prequalification activities. These experts are not involved in assessments and inspections.

Dossier assessments and expert advice

In 2007, six assessment sessions were organized at the UNICEF Supply Division in Copenhagen where the product dossiers are received and stored. In total, 39 external assessors from both well and less resourced regulatory authorities participated in the assessment sessions. It is worth noting that regulators from the WHO Africa Region have been especially active in the process.

In addition to regular assessment activities, considerable increase in expert scientific advice provided to applicants was observed in 2007 – a total of 16 bioequivalence study protocols were reviewed, with more than 80 bioequivalence queries answered, and 35 separate quality issues handled by the respective expert panels.

Inspections

A total of 45 inspections were carried out in seven different countries in 2007, with 35 taking place in India. As in the previous year, considerable assistance with inspections was received from national inspectorates belonging to The Pharmaceutical Inspections Convention and Pharmaceutical Inspection Cooperation Scheme (jointly referred to as PIC/S). As in 2006, France, was the leading country in terms of providing inspection support.

Technical assistance organized by WHO Prequalification Programme in 2007

Date	Location	Content of technical assistance
6–9 February	Ukraine	Stability studies and GMP
5–10 March	China	GMP of manufacture under aseptic conditions
26 March – 2 April	Cambodia	GMP of packaging combination products
1–5 May	Zimbabwe	GMP of antiretroviral products
20–26 May	India	Manufacturing process validation and GMP
17–29 July	Cambodia	GMP of packaging combination products
23–29 August	Bangladesh	Pharmaceutical engineering and GMP
04–09 November	Zimbabwe	GMP of antiretroviral products
17–21 December	India	Manufacturing process validation and GMP
17–22 December	China	GMP of manufacture under aseptic conditions

Prequalification assessment and inspection statistics: 2007

Dossier Assessment	
Assessment sessions in Copenhagen	6
Total number of assessment days	42
Total number of assessment reports	463
Assessment reports on HIV/AIDS products	298
Assessment reports on TB products	100
Assessment reports on malaria products	54
Assessment reports on reproductive health products	11
Inspections	
Manufacturing sites of finished product manufacturers	26
Manufacturing sites of active pharmaceutical ingredients	6
Contract research organizations	13
National pharmaceutical quality control laboratories	1

Prequalification of quality control laboratories

One laboratory was prequalified in 2007, while 12 laboratories expressed interest in prequalification but only seven submitted the required information file. The Programme carried out six pre-audit visits and inspectors concluded that all applicants needed training and technical assistance.

Strengthening and transparency of activities

In January 2007, there were five full-time professional staff members working for the WHO Prequalification Programme — a number that increased to 12 by the end of the year. A database to log and track dossier assessment and inspections was developed and became operational in 2007.

Developments to the website at http://www.who.int/prequal include:

- creation of a public tool to monitor dossier status of products currently under evaluation;
- more and better guidance for applicants;
- new invitations to manufacturers of HIV, antimalaria, antituberculosis and reproductive health products;
- publication of the annual report in six languages;
- creation of a section in Chinese to accommodate the translated documents on prequalification; and
- creation of a searchable and customized registry of prequalified medicines.

Safety and Efficacy Issues

Update on safety of heparin

World Health Organization — On 17 January 2008, Baxter Healthcare Corporation began voluntary recall of nine lots of heparin sodium in the USA. The adverse events are described as acute allergic-type reactions and have been documented by the US Centers for Disease Control (CDC) (1). The number of recent adverse reactions associated with the Baxter heparin preparations is over 700, including 19 deaths. The US Food and Drug Administration (FDA) and Baxter are conducting an investigation into these clusters of adverse reaction reports.

The active pharmaceutical ingredient (API) for the batches of heparin associated with adverse reactions originated from the Scientific Protein Laboratories (SPL) Changzhou facility in China. The FDA investigation included inspections of the manufacturing plants in China and the USA. The FDA's report of its inspection of the Changzhou SPL manufacturing plant was critical of several aspects of its processes.

The US FDA has found that heparin batches associated with adverse reactions contain 5–20% by weight of a "heparin-like compound which is not heparin" contaminant. The contaminant has been identified as an oversulfated chondroitin sulfate (2). The FDA has published two screening methods which can identify the presence of the heparin-like contaminant oversulfated chondroitin sulfate; one of them involves proton nuclear magnetic resonance (NMR) spectroscopy, and the other involves capillary electrophoresis (CE). These tests are now mandatory for batch release of all heparin API preparations in the USA (3).

In Germany, 80 or more recent cases of similar adverse events (no deaths) relating to specific batches of heparin products manufactured by Rotexmedica GmbH have also been reported. Rotexmedia initiated a recall on several batches of heparin injection in early March 2008 (4). The origin of the heparin in these products is the Changzhou Quianhong Bio Pharma Co. Ltd., China, and the Yantai Dongcheng Biochemicals Co., China.

Further recalls of heparin products from other suppliers have followed more recently, in the USA and elsewhere. Heparin is on the WHO Model List of Essential Medicines, and WHO distributes the 5th International Standard Heparin for measurement of the potency of unfractionated heparin preparations according to methods outlined in the International Pharmacopoeia. Other WHO International Standards for heparin are the low molecular weight heparin standards for both biological activity and for molecular weight calibration. All the WHO International Standards for heparin have been found to be free of contamination according to criteria defined in the most recent version of the FDA's "Impurity evaluation of Heparin Sodium by NMR Spectroscopy" (5).

Adverse reactions to heparin products should be reported to the appropriate National Regulatory Authority. WHO has a programme on International Drug Monitoring, co-ordinated by the Uppsala Monitoring Centre, Uppsala, Sweden (6).

WHO can offer advice and help to national regulatory authorities in countries with limited resources for the characterization of suspect batches of heparin API, including testing by NMR and CE as recommended by the FDA, through the WHO Collaborating Centre for Biological Standards.

The WHO Expert Committee on Specifications for Pharmaceutical Preparations, which oversees the activities related to The International Pharmacopoeia, together with the WHO Expert Committee on Biological Standardization, will review the above information as well as appropriate validated tests for impurity evaluation of unfractionated heparin.

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4. http://www.rotexmedica. com/index.php? page_id=18

5. http://www.fda.gov/cder/drug/infopage/ heparin/Heparin_NM_method.pdf

6. http://www.who-umc.org/DynPage.aspx

7. World Health Organization. http:// www.who.int/medicines and http://www.who. int/biologicals

Nicorandil–associated ulceration

Australia — Nicorandil (Ikorel®) is a synthetic nicotine derivative, which causes arterial and venous dilatation. It is indicated for the treatment of chronic stable angina pectoris at a dose of 10–20 mg daily.

Nicorandil-associated ulceration was initially reported in oral mucosa (1). Subsequently, ulceration has been reported at other sites, including anal, perianal, vulvar, perivulvar, gastrointestinal and parastomal tissues, and various cutaneous sites, including the lower anterior leg, natal cleft, umbilicus and areas affected by flexural psoriasis; ulcers may occur at multiple sites (2, 3). The reaction occurs rarely, appears to be dose-related and the time to ulcer onset may be up to months after starting nicorandil. The ulcers are persistent, deep and 'punched out' in appearance, with non-specific inflammatory histology. Their pathogenesis remains unclear.

Unless nicorandil is recognized as a potential cause and the drug withdrawn, the ulcers are likely to persist despite other treatment. Conservative ulcer management is ineffective and surgery may exacerbate the tissue damage. Typically any discomfort resolves quickly after nicorandil is withdrawn, although healing may take considerably longer.

Seven of 51 reports received by the Therapeutic Goods Administration (TGA) for nicorandil describe ulceration. Six of the seven reports described tongue or mouth ulcers. Failure to recognize nicorandil-induced ulceration can lead to substantial morbidity, inappropriate investigation and treatment, and unnecessary surgery.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 27, Number 2, April 2008

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Topiramate and other drugs causing glaucoma

Australia —Topiramate is an antiepileptic indicated for either monotherapy or add-on therapy in adults and in children aged two years and over; and for the prophylaxis of migraine in adults. It has an authority required Pharmaceutical Benefits Schedule (PBS) listing for the treatment of epilepsy, and was recently PBS-listed as a third-line agent for the prophylaxis of migraine.

Topiramate has been rarely associated with the development of angle-closure glaucoma. To date, the Therapeutic Goods Administration (TGA) has received 11 reports of glaucoma associated with the use of topiramate out of 175 total reports for the drug, Five patients had recovered at the time of reporting, three had not yet recovered, and recovery status was unknown in the other three.

Although all of these cases have involved adults, a literature report has described bilateral angle-closure glaucoma presenting as headache, nausea, and fatigue in a five year old girl 10 days after starting topiramate (1).

A published review of reports of ocular reactions to topiramate included 86 cases of acute glaucoma, 83 of which were bilateral (2). In this series, time to onset was one to 49 days after starting topiramate, with 85% of cases occurring in the first two weeks of treatment. Permanent vision loss was described in seven reports. Topiramate was also associated with a number of other ocular adverse effects, including acute myopia, suprachoroidal effusions, periorbital oedema, and scleritis (2).

Management of topiramate-induced glaucoma involves immediate cessation of topiramate and urgent medical treatment of the glaucoma as required. A number of mechanisms have been proposed for this reaction, but because pupillary block is not involved, pilocarpine and iridotomy are generally ineffective. Permanent vision loss can occur if the condition is not managed appropriately (3). Of note is that migraine itself may cause eye pain and it is important that non-migraine causes should be considered in patients treated with topiramate for migraine, who present with eye pain.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 27, Number 2, April 2008

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Varenicline: serious psychiatric reactions

Canada — Varenicline tartrate (Champix®) has been marketed in Canada since April 2007 and is indicated for smoking-cessation treatment in adults in conjunction with smoking-cessation counselling (1). The efficacy of varenicline in smoking cessation is believed to be a result of the drug's partial agonist activity at the nicotinic acetylcholine receptor. By binding to these receptors, varenicline induces 2 results (2). First, it signals the release of dopamine and creates similar reinforcing effects, but not to the full extent that nicotine does because of its partial binding of the receptor (2). Second, it acts as a physical antagonist by binding to the

Table 1: Summary of reports of aggression, depression and suicidal tendency suspected of being associated with varenicline submitted to Health Canada from 1 April 2007 to 23 Noveber 2007*

Case/Patient age/sex	History of psychiatric condition	Adverse reaction(s)†	Time to onset of reaction, d‡	Outcome after discontinuation of varenicline
1. 51/F	No	Aggressiveness	4	Unknown
2. 65/M	Yes	Aggressiveness	36	Recovered
3. 46/M	Yes	Depression	1	Recovered
4. 55/F	Unknown	Depression	<2	Recovered
5. 64/M	No	Depression	2	Recovered
6. NA/F	Yes	Depression	<42	NA§
7. 64/F	Unknown	Depression	Unknown	NA¶
8. 33/F	No	Suicidal tendency	11	Unknown
9. 55/F	Unknown	Suicidal tendency	<14	Unknown
10. 53/F	No**	Suicidal tendency/ depression	<29	Recovered
11. 30/F	Unknown	Suicidal tendency/ depression	<31	Unknown
12. 46/M	No	Suicidal tendency/ depression	<32	Recovered
13. 54/M	No	Suicidal tendency/ depression	<72	Recovered
14. 58/F	Yes	Suicidal tendency/ depression/anger	<13	Recovered

Note: NA = not available.

* These data cannot be used to determine the incidence of adverse reactions (ARs) because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.
† Terms are listed according to the World Health Organization Adverse Reaction Terminology (WHOART).
‡ Estimated from the beginning of treatment.
§ At the time of reporting, the patient was still taking varenicline and had not yet recovered.
¶ The onset of depression was after the discontinuation of the drug.
** Family history of depression was reported.

nicotine receptor and by blocking the effects of nicotine or a nicotine-replacement agent (2).

Smoking cessation with or without treatment is associated with various symptoms such as depressed mood, insomnia, irritability, frustration or anger, and anxiety (1). From 1 April to 23 November 2007, Health Canada received 107 reports of adverse reactions (ARs) suspected of being associated with varenicline. Of these reports, 46 described psychiatric ARs of which 14 reported cases of aggression, depression or suicidal ideation (table 1). The remaining cases of psychiatric disorders included ARs such as amnesia, abnormal dreams, anxiety, insomnia, abnormal thinking and somnolence.

The impact of a smoking-cessation product with partial nicotinic-receptor agonist properties in patients with underlying psychiatric illness is unknown, and care should be taken with these patients (1). Two case reports recently described the exacerbation of schizophrenia in one patient (3) and a manic episode in a patient with bipolar disorder taking varenicline (4).

The Canadian Product Monograph for varenicline was recently revised to indicate that there have been postmarket reports of depressed mood, agitation, changes in behaviour, suicidal ideation and suicide (1). The product monograph states that not all patients had known pre-existing psychiatric illness and not all had completely discontinued smoking (1).

Extracted from Canadian Adverse Reaction Newsletter, Volume 18, Issue 2, April 2008

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Montelukast : safety review

United States of America — The Food and Drug Administration (FDA) is investigating a possible association between the use of montelukast (Singulair®) and behavior/mood changes, suicidality and suicide. Montelukast is a leukotriene receptor antagonist used to treat asthma and symptoms of allergic rhinitis, and to prevent exercise-induced asthma.

Over the past year, the manufacturer has updated the prescribing and patient information to include the following post-marketing adverse events: tremor (March 2007), depression (April 2007), suicidality (October 2007), and anxiousness (February 2008).

FDA is working with the manufacturer to further evaluate a possible link between the use of Singulair® and behavior/mood changes, suicidality and suicide. Until further information is available, healthcare professionals and caregivers should monitor patients for suicidality or changes in behavior and mood.

Other leukotriene modifying medications include zafirlukast (Accolate®), which is also a leukotriene receptor antagonist and zileuton (Zyflo® and Zyflo CR®), which is a leukotriene synthesis inhibitor. FDA is reviewing postmarketing reports it has received of behavior/mood changes, suicidality and suicide and will assess whether further investigation is warranted.

Reference: Information from FDA dated 27 March 2008 at http://www.fda.gov/medwatch

Neurocognitive effects of chemotherapy

Australia —There is growing evidence that some patients who survive cancer can suffer neurocognitive impairment after chemotherapy.

Although the symptoms are generally subtle and improve after ceasing chemotherapy, for some survivors the symptoms are sustained and can impact significantly on their quality of life. Some studies have reported that 15–50% of patients have cognitive impairment after chemotherapy for solid tumours. Areas most affected are usually attention, concentration, verbal and visual memory and processing speed.

Studies published in the past few years report that up to 30% of patients with solid tumours may have cognitive impairment before receiving chemotherapy. It is likely that the regimen, dose and duration of chemotherapy influence the incidence and severity of cognitive impairment. Studies have found higher rates of cognitive dysfunction in patients receiving high doses of chemotherapy compared to those on standard doses. There are no proven interventions to prevent impairment and the mainstay of therapy is to treat any depression and anxiety.

Reference: Australian Prescriber Media Release, 4 February 2008 at http://www.tga.gov.au

New MMRV vaccine recommendations

United States of America — On 27 February 2008, new information was presented to the Advisory Committee on Immunization Practices (ACIP) regarding the risk for febrile seizures among children aged 12—23 months after administration of the combination measles, mumps, rubella, and varicella (MMRV) vaccine (ProQuad®). ACIP updated recommendations remove ACIP's previous preference for administering combination MMRV vaccine over separate injections of equivalent component vaccines (i.e., measles, mumps, and rubella [MMR] vaccine and varicella vaccine).

The combination tetravalent MMRV vaccine was licensed by the Food and Drug Administration (FDA) on 6 September 2005, for use in children aged 12 months–12 years (1). MMRV vaccine can be used in place of trivalent MMR vaccine and monovalent varicella vaccine to implement the recommended 2-dose vaccine policies for prevention of measles, mumps, rubella, and varicella (1, 2). The first vaccine dose is recommended at age 12–15 months and the second at age 4–6 years.

In MMRV vaccine prelicensure studies, an increased rate of fever was observed 5–12 and 0–42 days after the first vaccine dose, compared with administration of MMR vaccine and varicella vaccine at the same visit (3, 4). Because of the known association between fever and febrile seizures (5), CDC and Merck initiated postlicensure studies to better understand the risk for febrile seizures that might be associated with MMRV vaccination.

ACIP also recommended establishing a work group to conduct in-depth evaluation of the findings regarding the increased risk for febrile seizures after the first dose of MMRV vaccine to present for consideration of future policy options. CDC, FDA, and ACIP will communicate updates and implement further necessary actions based on these evaluations (6).

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Oseltamivir label updated with neuropsychiatric warning

United States of America —The product label for oseltamivir phosphate (Tamiflu®) has been revised to include a warning about possible neuropsychiatric events. The updated label is based on recommendations from the agency's Pediatric Advisory Committee meeting in November 2007.

Postmarketing reports indicate that some patients with influenza who were receiving oseltamivir had delirium and abnormal behavior, leading to injury and even death. Most of the cases occurred in children and in Japan. The label now cautions clinicians to monitor their patients for abnormal behavior when taking the drug.

Reference: Physician's First Watch, 5 March 2008.

Ketoconazole tablets: risk of hepatotoxicity

United Kingdom — Following a systematic review of all available data, the manufacturer of ketoconazole (Nizoral ®) tablets has released information on a change to the Summary of Product Characteristics (SmPC) because of a risk of serious hepatotoxicity and the availability of other effective antifungal treatments. Nizoral® tablets are now indicated for:

- Treatment of dermatophytosis and Malassezia (previously called Pityrosporum) folliculitis that cannot be treated topically because of the site, extent of the lesion or deep infection of the skin, in patients resistant to, or intolerant of, fluconazole, terbinafine and itraconazole.

- Treatment of chronic mucocutaneous candidiasis, cutaneous candidiasis, and oropharyngeal candidiasis that cannot be treated topically because of the site, extent of the lesion or deep infection of the skin, in patients resistant to or intolerant of both fluconazole and itraconazole.

In addition to the existing drug interactions and contraindications, several other drugs have been added to the list of contraindicated drugs, including: disopyramide; sertindole; nisoldipine; eplerenone; and ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine)

Very rare cases of serious hepatic toxicity, including cases with a fatal outcome or requiring liver transplantation, have occurred with the use of oral ketoconazole. Some patients had no obvious risk factors for liver disease.

The risk of serious hepatic toxicity increases with longer duration of treatment; courses of greater than 10 days should only be given after full consideration of the extent of treatment response and the risk benefit of continuing treatment. Liver function must be monitored in all patients receiving treatment with Nizoral® tablets.

The following Postmarketing adverse drug reactions have been added: anaphylactoid and anaphylactic reactions; angioneurotic oedema; adrenocortical insufficiency; cirrhosis, the reporting rate being very rare.

Reference: Communication from Janssen-Cilag Ltd January 2008 \\mhralonfs01\home$\tilstonec\Website\Feb 2008\Nizoral DDL.doc on the Medicines and Healthcare products Regulatory Agency (MHRA) website at http://www.mhra.gov.uk/Safetyinformation

Alemtuzumab: infection–related deaths

United Kingdom — Bayer Schering Pharma AG and Genzyme Europe BV have informed physicians of six infection-related deaths, reported from a trial (CALGB10101) in which previously untreated, symptomatic B-cell chronic lymphocytic leukemia (CLL) patients were treated with fludarabine and rituximab followed by alemtuzumab for remission consolidation.

Alemtuzumab (MabCampath®) is approved for the treatment of patients with B-cell chronic lymphocytic leukaemia (B-CLL) for whom fludarabine combination chemotherapy is not appropriate and should not be used as consolidation therapy following induction with fludarabine + rituximab outside of a clinical trial.

Fludarabine, rituximab and alemtuzumab all have known immunosuppressive properties, and it is possible that the fatal infectious complications which occurred in this trial are the result of a prolonged period of immunosuppression resulting from the sequencing of these drugs without sufficient time for recovery, as well as other factors specific to this trial.

The five fatal infections were reported as: viral meningitis, Listeria meningitis, Legionella pneumonia, cytomegalovirus infection and *Pneumocystis jiroveci* pneumonia, all in patients who achieved a complete response after induction therapy.

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3. CALGB10101 abstract available online at http://www.hematology.org.

Mycophenolate mofetil: progressive multifocal leukoencephalopathy

European Union — In agreement with the European Medicines Agency (EMEA), the manufacturer of mycophenolate mofetil (CellCept®) has advised physicians of new safety information. CellCept® has been on the market for over 10 years, as an immunosuppressive agent indicated in combination with ciclosporin and corticosteroids.

Isolated cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving CellCept®.

The case reports have been associated with confounding factors in particular the nature of the underlying disease, concomitant immunosuppression and the latency between the use of CellCept® and the onset of PML. However, based on the temporal relationship observed in some cases, the contributory role of CellCept® cannot be excluded.

Leukoencephalopathy (PML) is a rare, progressive, demyelinating disease of the central nervous system (CNS) that usually leads to death or severe disability. PML is caused by the reactivation of the JC virus, a polyomavirus that resides in latent form in 70 – 90% of the adult population worldwide. JC virus usually remains latent, typically only causing PML in immunocompromised patients. The factors leading to activation of the latent infection are not fully understood although abnormalities in T-cells have been described as important for reactivation of JC virus and PML. Patients usually present with focal CNS abnormalities and radiographic evidence of white matter disease without mass effect.

Reference: Communication from Roche, P212828, 18th February 2008 at http://www.mhra.gov.uk

Modafinil: serious rash and psychiatric symptoms

United Kingdom —The manufacturer of modafinil (Provigil®) has informed physicians of new warnings and safety information regarding:

- Serious skin rash and psychiatric symptoms. The safety concern involves serious skin rashes requiring hospitalization and discontinuation of treatment in adults and children occurring within 1 to 5 weeks after treatment initiation [isolated cases have been reported after prolonged treatment (e.g. 3 months)].

  Modafinil should be discontinued at the first sign of rash and not restarted unless the rash is clearly not drug-related.

- Psychiatric adverse experiences (psychosis, mania, delusion, hallucinations, suicidal ideation and aggression) have been reported in patients treated with modafinil. If psychiatric symptoms occur, modafinil should be discontinued and not restarted.

  Caution should be exercised when administering modafinil to patients with a history of psychosis, depression or mania given the possible emergence or exacerbation of psychiatric symptoms.

Modafinil is not approved for use in children for any indication.

Modafinil is indicated for the symptomatic relief of excessive sleepiness associated with narcolepsy, Obstructive Sleep Apnoea/Hypopnoea Syndrome (OSAHS) or moderate to severe chronic Shift Work Sleep Disorder (SWSD) in adult patients.

Reference: Communication from Cephalon dated 14/02/2008 at http://www.mhra.gov.uk product information available on the electronic medicines compendium site http://emc.medicines.org.uk

Moxifloxacin: serious hepatic and skin reactions

United Kingdom/European Union — In agreement with EU regulatory authorities, including the Medicines and Healthcare Products Regulatory Agency (MHRA), the manufacturer of moxifloxacin (Avelox®) has released important safety information. A recent assessment of adverse reactions associated with the use of moxifloxacin resulted in the following information and recommendations:

- Treatment with moxifloxacin is associated with a risk of developing fulminant hepatitis potentially leading to life threatening liver failure and risk of potentially life threatening bullous skin reactions like Stevens-Johnson-Syndrome (SJS) or toxic epidermal necrolysis (TEN).
- Due to limited clinical data, moxifloxacin is contraindicated in patients with impaired liver function (Child Pugh C) and in patients with transaminases increased > 5 fold the upper limit of normal.
- Patients should be advised to stop treatment and to contact their physician if early signs and symptoms of these reactions occur.

Liver injuries possibly related to moxifloxacin were more frequently of cholestatic or mixed hepatocellular-cholestatic type than of hepatocellular type. Eight reports of fatal hepatic injuries were considered as possibly related to moxifloxacin therapy. Cases of positive re-challenge gave further evidence of a causal relationship. However, the majority of patients experiencing serious liver injuries where the outcome was reported improved or recovered.

TEN was reported in several cases where a causal relationship was considered possible; this included two cases with fatal outcome. Additionally, a total of 35 individual cases of SJS were reported, including three cases where there was a fatal outcome and seven cases which were considered life-threatening. In these 10 cases of severe SJS, a progression to TEN was documented in three patients. Based on the large patient exposure, the incidence of both life threatening liver injuries and TEN is very low, although a definite frequency cannot be calculated from these reports.

As a consequence of this review, the manufacturer has revised the product information for moxifloxacin across the European Union.

Reference: Communication from Bayer Schering Pharma, Bayer plc February 2008, at Medicines and Healthcare products Regulatory Agency (MHRA) http://www.mhra.gov.uk

Rimonabant: depression; psychiatric reactions

United Kingdom — Rimonabant (Acomplia®) is contraindicated in patients with ongoing major depression or those taking antidepressants. Prescribers are encouraged to take a detailed history from patients before prescribing. However, depressive reactions may occur in patients who have no obvious risk factors, apart from obesity itself.

Up to the end of January 2008, 673 ADR reports (reporting 1971 individual reactions) had been received with rimonabant in the UK, 423 of which were serious. Four reports had a fatal outcome. The most common reported ADRs, which are labelled in the Summary of Product Characteristics, were:

- Psychiatric disorders (depression, anxiety, nervousness, irritability, sleep disorders, parasomnias)
- Nervous-system disorders (memory loss, dizziness, hypoaesthesia, paraesthesia)
- Gastrointestinal disorders (nausea, diarrhoea, vomiting)
- General disorders (fatigue, asthenia)
- Skin and subcutaneous disorders (pruritus, sweating)

876 psychiatric reactions were reported (44% of all 1971 reported reactions). The most common psychiatric reactions were depression and related disorders of mood and associated symptoms. 52 reactions involved suicidal and

self-harming thoughts or behaviours, most of which were suicidal ideations (42 reports).

Many patients who receive rimonabant are diabetic. There have been seven reports of hypoglycaemia/decreased blood glucose. This type of reaction may be due to inadequate monitoring of blood-glucose control in patients who have managed to reduce calorie intake without appropriate adjustment of oral antidiabetics (and possibly insulin).

Reference: *Drug Safety Update*. Volume 1, Issue 10, May 2008

Exenatide: risk of acute pancreatitis

United Kingdom — Exenatide (Byetta®), the first-in-class incretin mimetic, is a glucagon-like-peptide-1 analogue that stimulates insulin release from pancreatic cells in a glucose dependent manner. Exenatide is indicated for treatment of type 2 diabetes mellitus in combination with metformin, with or without sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. Exenatide was first marketed in the European Union in November 2006.

Several reports of acute pancreatitis have been received in association with exenatide use worldwide. Up to 30 September 2007, 89 reports of pancreatitis had been received: 87 from the USA and two from Germany. One case had a fatal outcome. A UK report of acute and chronic pancreatitis was received in November 2007.

If pancreatitis is suspected, exenatide and other potentially suspect medicines should be discontinued.

Reference: *Drug Safety Update*. Volume 1, Issue 10, May 2008

Zanamivir: neuropsychiatric events

United Kingdom — The manufacturer of zanamivir (Relenza®) Inhalation Powder has updated the package insert as a result of postmarketing reports (mostly from Japan) of delirium and abnormal behaviour leading to injury in patients with influenza who were receiving neuraminidase inhibitors, including zanamivir .

Therefore, patients should be observed for signs of unusual behaviour and a healthcare professional should be contacted immediately if the patient shows any signs of unusual behaviour.

Zanamivir is indicated for treatment of uncomplicated acute illness due to influenza A and B virus in adults and paediatric patients 7 years of age and older who have been symptomatic for no more than 2 days.

Reference: Communication from GSK at www.gsk.com posted at http://www.fda.gov/medwatch

Inosine ponophosphate dehydrogenase inhibitors: congenital anomalies

United States of America —The Food and Drug Administration (FDA) is aware of reports of infants born with serious congenital anomalies, including microtia and cleft lip and palate, following exposure to mycophenolate mofetil (MMF) during pregnancy. MMF, the active drug substance in CellCept®, is an ester of the active metabolite mycophenolic acid (MPA), the active drug substance in Myfortic®. In most cases, the mothers were taking MMF following an organ transplant to prevent organ rejection. However, some mothers taking MMF were being treated for immune-mediated conditions such as systemic lupus ery-

thematosus (SLE) and erythema multiforme. Treatment began before their pregnancies and continued into the first trimester or until the pregnancy was detected. MMF is approved in the US for use in the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants and MPA is approved in the US for use in the prophylaxis of organ rejection in patients receiving allogeneic renal transplants. In patients who are transplant recipients, these drugs are almost always used in combination with other immunosuppressant drugs.

MMF and MPA increase the risk of spontaneous abortion in the first trimester and can cause congenital malformations in the offspring of women who are treated during pregnancy. The labelling for both MMF and MPA was revised in November 2007 to change the Pregnancy Category to "D" (positive evidence of human fetal risk, but potential benefits may warrant use of the drug in pregnant women despite the potential risk) and to add these findings about the risk of early pregnancy loss and congenital malformations to the boxed warning.

Reference: *FDA Alert,* 16 May 2008 at http://www.fda.gov/medwatch

Strontium ranelate : life-threatening allergic reactions

Singapore — Strontium ranelate (Protos®, Servier) has been registered since July 2006 for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures. Since its launch in Europe in 2004, Protos® has been registered in 64 countries and has a total of about 570 000 patient-years of exposure.

In November 2007, the European Medicines Agency's (EMEA) Committee for Medicinal Products for Human Use (CHMP) was alerted to an increasing number of reports of drug rash with eosinophilia and systemic symptoms (DRESS) associated with the use of Protos®. DRESS is a rare but serious and life-threatening type of allergic reaction to a drug. The condition starts with a skin rash, accompanied by a fever, swollen glands, eosinophilia, adenopathy and systemic involvement which may include hepatic, renal and pulmonary impairment. In most cases, the symptoms resolved upon discontinuation of Protos® and with the initiation of corticosteroid therapy. However, it has been reported that recovery can be slow and there is a risk of symptoms returning during the recovery period.

As of November 2007, 16 cases of DRESS were reported to the CHMP. In light of these reports , the CHMP concluded that the use of Protos® is linked to an increased risk of DRESS and recommended that warnings on severe hypersensitivity syndromes, including DRESS and Stevens Johnson syndrome be included in the product and patient information

To date, the Health Sciences Agency (HSA) has not received any ADR reports associated with Protos® and DRESS. There is one case of a patient who developed Stevens Johnson syndrome after taking both Protos® and Arcoxia® (etoricoxib) simultaneously for about one month.

In view of this emerging safety concern, prescribers are reminded to alert their patients of the risk of severe allergic reactions and to inform them to stop Protos® immediately should a rash occur and to seek medical advice. For patients who have stopped treatment due to hypersensitivity reactions, Protos® should not be re-introduced.

Reference: Strontium (Protos®) - A safety update. 25 Mar 2008: at http://www.hsa.sg

Lapatinib and hepatoxicity

Singapore — In consultation with HSA, the manufacturer of lapatinib (Tykerb®) has informed healthcare professionals of new safety information on hepatotoxicity.

From the manufacturer's worldwide safety database, 39 cases of hepatotoxicity were identified, of which 38.5% of subjects were receiving lapatinib monotherapy while 53.8% were receiving lapatinib in combination with other chemotherapies, such as capecitabine.

Majority of the key cases were from clinical trials, which yielded a crude incidence of 0.4% for hepatobiliary events in the entire lapatinib clinical program while 7 cases of hepatotoxicity were from spontaneous sources. There have been 13 incidences of death with reported liver-related events.

Healthcare professionals are advised to monitor their patients' liver functions before initiating treatment and at approximately monthly intervals thereafter or as clinically indicated. Tykerb® should be discontinued and not restarted in patients with severe changes in liver function.

Reference: Tykerb® (lapatinib) and new safety information on hepatotoxicity, 1 April 2008 at http://www.hsa.sg

Telbivudine and peripheral neuropathy

Singapore — Telbivudine (Sebivo®) is indicated for the treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B in patients who have compensated liver disease, evidence of viral replication and active liver inflammation, and who are nucleoside analogue naive.

In a pilot clinical trial, 8 cases of peripheral neuropathy were reported out of the 48 patients treated with telbivudine and a standard dose of pegylated interferon alfa-2a. The time to onset for the event was approximately 2 to 6 months. In contrast, the rate of peripheral neuropathy in the 2-year pivotal study with telbivudine monotherapy was uncommon.

As the risk of developing peripheral neuropathy appears to be increased in the telbivudine and pegylated-interferon alfa-2a combination, the manufacturer is working with the Health Sciences Agency (HSA) to update the product information.

Reference: Peripheral neuropathy seen with the combination treatment of Sebivo® (telbivudine) with pegylated interferon alfa-2a, 17 March 2008 at http://www.hsa.sg

Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious and unexpected adverse drug reactions. A signal is defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information". All signals must be validated before any regulatory decision can be made.

International Nonproprietary Names

International Nonproprietary Names for monoclonal antibodies: IFPMA proposal

This summary represents the IFPMA proposal presented to the 46th Consultation on International Nonproprietary Names (INNs) for Pharmaceutical Substances held at the World Health Organization in Geneva in April 2008. The proposal was developed by the IFPMA (International Federation of Pharmaceutical Manufacturers & Associations) Biotech Working Group, which includes twenty companies, two regional and three national associations located in Europe, Japan and USA.

The pioneering work of Kohler and Milstein (1) in the 1970s provided the means to produce monoclonal antibodies (MAbs) derived from a single clone of cells which bind to a single antigenic determinant with predefined specificity. This paved the way to use this class of biomolecules as diagnostic tools as well as therapeutic drug substances for treatment of cancer, auto-immune, and other diseases. Technological advances in the generation of antibodies with reduced immunogenicity permitted the development of MAb-based therapies as a major strategy in biomedicine (2). Today, more than 20 MAb-based medicines have been approved for marketing, and a further 160 MAbs were in development in 2006 (3).

The appearance of the first MAb-based drugs in the late 1980s created the impetus for the WHO INN programme to establish a naming system for monoclonal antibodies in 1990/91. By 2006, more than 140 INNs had been selected for MAbs. The system was gradually expanded but the general policy for naming of MAbs remained unchanged [reviewed in (4)]. The nomenclature rules for monoclonal antibodies are complex. Furthermore, current developments in the use of different antibody types with different functions, antibody fragments and antibody glycoengineering add to this complexity. Therefore, it was decided (5) that consideration should be given to establishing a small expert group to review these developments and to make specific recommendations on INN policy for monoclonal antibodies.

In order to support this process, the IFPMA has developed *Proposals for principles for INNs of new monoclonal antibodies* (6). This summary is intended to give a short overview on MAbs, their molecular structure and aspects relevant to their use as pharmaceutical drug substances, and to communicate and explain the IFPMA naming proposal. It should be emphasized that the additional explanations given in this paper do not necessarily represent a harmonized IFPMA position but reflect the personal views of the authors.*

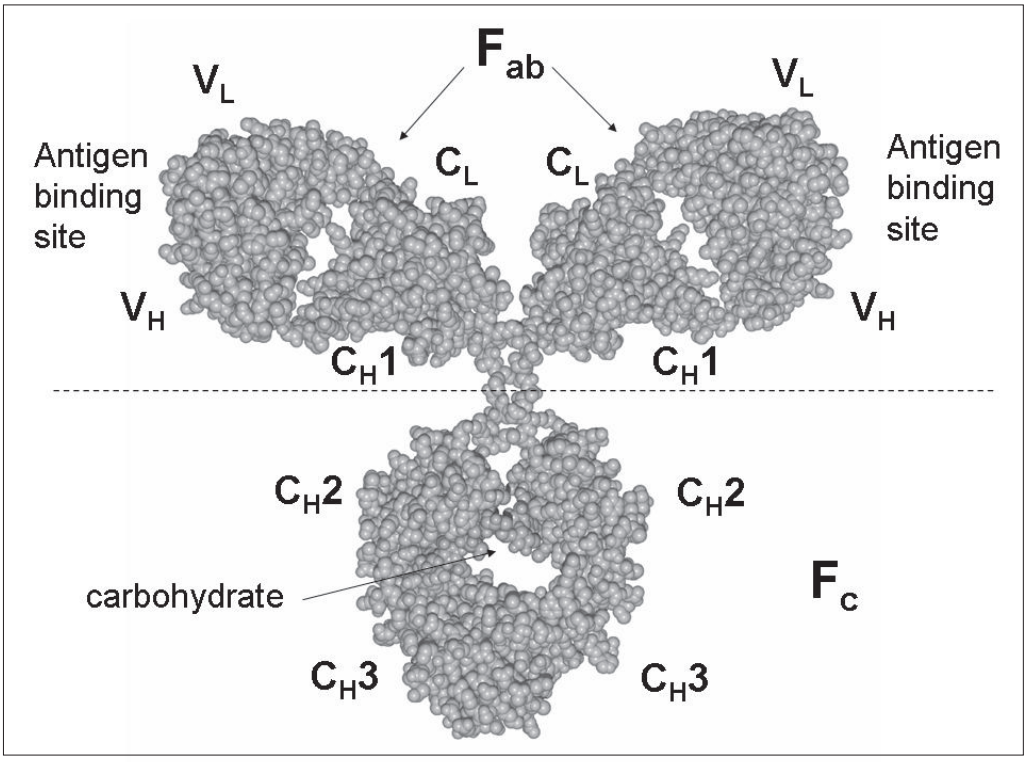
* *The article was prepared by Anna-Maija Autere, Nicole Wagner and Georg-Burkhard Kresse from Roche on behalf of International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) Biotech Working Group: http://www.ifpma.org/Issues/Biologicals/. Correspondence: Ryoko Krause, IFPMA at r.krause@ifpma.org*

Molecular structure of antibodies – the immunoglobulin molecule

Antibodies, also called immunoglobulins, are a large group of closely related glycoproteins with a molecular weight of up to 150 kDa. Each immunoglobulin molecule is composed of two identical heavy chains and two identical light chains, linked together by disulfide bonds (Fig.1). The amino acid sequences of the amino-terminal regions, referred to as V_H and V_L, are highly variable and are involved in antigen binding. The constant part of the light chain is called C_L, and the constant part of the heavy chain is sub-divided into three domains C_H1, C_H2, and C_H3. Two heavy and two light chains form a "Y-shaped" hetero-tetrameric superstructure. It consists of three structurally independent moieties connected by a flexible hinge region, which are termed F_{ab} (the antigen-binding fragments comprising one light chain and the V_H and C_H1 parts of one heavy chain), responsible for antigen specificity and binding, and F_c ("fragment crystallizable", comprising the C_H2 and C_H3 parts of two heavy chains).

Based on the amino acid sequence differences in the constant part of the heavy chains, immunoglobulins are classed by isotypes (e.g. human IgA, IgG, IgM, IgD, and IgE). All licensed therapeutic antibodies belong to the IgG isotype. Human IgG–F_c contains carbohydrate residues bound to residue Asn297 in each of the C_H2 domains, thus characterizing IgG as a glycoprotein. In addition, 15–20% of human IgG molecules have N-linked oligosaccharides within the F_{ab} region (7). The oligosaccharides provide important recognition sites mediating a variety of interactions (see 8) and play specific structural roles.

Figure 1. Structure of an IgG Molecule



Within the IgG isotype, there are four different sub-classes (IgG_1, IgG_2, IgG_3, and IgG_4) differing in their amino acid sequence, hinge length, binding to F_c receptors and complement, and biological function. In development of therapeutic monoclonal antibodies, scientists have focused on the IgG_1, IgG_2, and IgG_4 subclasses (9).

Immune effector functions and glycoengineering

Antibodies specifically bind to their antigens via their F_{ab} fragment regions. In general, they thereby can prevent pathogens from entering or damaging cells, interfere with signal transduction mediated by interactions of ligands with cell surface receptors, and induce cell-death mechanisms through apoptosis or by blocking the action of survival pathways.

Furthermore, by virtue of interaction sites located in the F_c part of IgG, antibodies can also stimulate removal of a pathogen or tumour cell by macrophages and other cells of the immune system. This is mediated by interaction with F_c-gamma receptors (FcgRs) present on the immune cells and eliciting antibody-dependent cellular cytotoxicity (ADCC). Antibodies can also trigger direct pathogen or cell destruction by stimulating other immune responses such as the complement pathway (complement-dependent cytotoxicity, CDC). These effects have been termed “immune effector functions” of antibodies.

It has been shown (10,11) that the presence and structure of the F_c-bound carbohydrate moieties of the IgG molecule are essential for binding to a certain subtype of FcgRs (FcgRIIIa) and promotion of effector functions: IgG molecules with an ungycosylated F_c portion retain little ability in activating complement and binding to FcgRs. On the other hand, the lack of a fucose residue in human IgG_1 enhances the binding to FcgRIIIa and thereby increases in-vitro ADCC more than 50-fold. The presence or absence of galactose and sialic acid residues also influences ADCC (12) and CDC.

Several studies (e.g. 13,14) have highlighted the importance of FcgR-mediated killing of target cells for the efficacy of antibody treatment in cancer therapies, which represents an essential mechanism for efficacy. Modulation of IgG glycosylation (“glycoengineering”) which results in removal of part or all of the fucose residues in order to enhance potency is considered a promising technology to enhance the efficacy of therapeutic MAbs (15), as already demonstrated in murine xenograft models (16). MAb-based medicines containing glycoengineered antibodies have entered clinical development.

In contrast to the importance of F_c interactions in cancer, in some disease areas (e.g. for treatment of inflammatory diseases) F_c-mediated effects can lead to safety issues and it may be desirable to minimize or even eliminate F_c-mediated interactions. Thus, glycosylation of antibodies can be crucial for their clinical profile, including aspects of safety and efficacy, and the consistency of glycosylation has to be carefully controlled.

Monoclonal antibody production and heterogeneity

According to the original Kohler-Milstein technology, monoclonal antibodies are obtained from hybridoma cells. Today, therapeutic MAbs are usually produced using recombinant DNA technology. Due to the requirement for glycosylation, all antibody therapeutics that are currently licensed are manufactured from mammalian cell culture, using e.g. Chinese hamster ovary (CHO) and mouse myeloma (NS0 or Sp2/0) cells. Other systems based on transgenic animals, yeast, plants, etc. are under development. Unglycosylated F_{ab} fragments can be produced from prokaryotic systems.

Manufacturing of recombinant MAbs, which is a complex multi-step process, requires the same high standards in process development, validation and control as for other recombinant therapeutic proteins. Sound product and process knowledge (preferentially based on "quality by design" concepts) is indispensable in order to ensure and maintain product quality. The safety and efficacy of antibody therapeutics, including their stability and immunogenic potential, are critically dependent on post-translational modifications such as, but not limited to, glycosylation which are highly depending on the manufacturing and control characteristics of the process.

In this context, it should be emphasized that even highly purified recombinant proteins, due to the complexity of both their molecular structure and their manufacturing process, are never single and uniform molecular entities, but families of closely related molecular variants (18,19). These variations will be introduced by the manufacturing cell itself, as well as by the production process. For an IgG antibody, it has been estimated that, even considering only a limited number of glycoform variants (17), up to 10^8 variants are theoretically possible; in fact, variability may be even greater since there may be many more glycoforms than considered in this analysis (7). In contrast to the situation with small, chemically synthesized molecules, current protein-analytical methods are not able to characterize complex proteins completely, and the functional impact is known only for particular attributes (or defined combinations of some attributes). Therefore, for recombinant proteins including monoclonal antibodies manufactured by different, independently developed processes, differences in microheterogeneity have to be expected whose impact on clinically relevant properties usually cannot be predicted.

Lowering the immunogenicity

Monoclonal antibodies obtained by the original Kohler-Milstein procedure, and the first MAb which was licensed in 1986 for use in therapy (muromonab-CD3), were murine proteins. However, rodent MAbs can elicit an immunogenic response referred to as human anti-mouse antibodies (HAMA). Furthermore, therapeutic efficacy may be reduced by relatively faster clearance (as compared to human antibodies) and weak effector functions in humans (19). Therefore, efforts were made to make MAbs more "human-like" by genetically fusing rodent variable domains to human constant domains (resulting in "chimeric" antibodies which still contain about 35% rodent sequences). "Humanized" antibodies with only approximately 10% rodent sequences have also been produced by grafting only the six loops, termed complementarity determining regions (CDRs), of the antibody sequence which can potentially interact with the target molecule to a human antibody framework, combined with some additional sequence optimization. These chimeric or humanized antibodies indeed exhibit less immunogenicity, and most of the monoclonal antibody products presently licensed contain either chimeric or humanized antibodies.

More recently, methods have become available to obtain MAbs with "fully human" sequence (20), either by using phage display selection techniques, or by generating the antibodies in mice transgenic for the human immunoglobulin genes. Currently, two therapeutic "fully human" MAbs (adalimumab, panitumumab) are licensed, with many more being in clinical development. Alternatively, efforts are ongoing to reduce the immunogenicity of chimeric MAbs by "de-immunization" based on *in-silico* identification of potential linear T-cell epitopes which then are removed by altering the sequence. Several of these MAbs which

strictly cannot be designated as "chimeric" nor "humanized" or "human" have entered clinical development.

However, even "fully human" MAbs have a significant immunogenic potential in patients. The formation of antibodies may be due to the presence of foreign sequences or epitopes, but also to product quality issues (e.g., presence of aggregates) and/or patient- and disease-related factors. Thus, even small differences in therapeutic protein products may lead to unexpected immunogenicity.

Bi-specific antibodies, antibody fragments, antibody conjugates

Whereas unmodified, intact antibodies represented the first wave of licensed immunotherapeutic reagents, it soon became clear that it is often desirable to improve clinically relevant properties, such as pharmacokinetics, potency, avidity, or half-life. Among the approaches to address these topics is the construction of bi-specific antibodies (containing two different binding specificities connected together) which in some cases are even designated as "trifunctional" due to immune effector functions mediated by the F_c part (e.g. catumaxomab).

It is possible to minimize F_c-mediated effects in therapeutic MAbs by selecting IgG subclasses with low effector functions, such as IgG_2, IgG_4, or IgG_1 mutants. Another option to eliminate unwanted F_c functionalities is the use of antibody fragments obtained by proteolysis of intact antibodies or by recombinant expression of monovalent fragments (such as F_{ab}, F_v, or single-chain F_v fragments) which are devoid of the F_c part of the IgG molecule (21). Due to their smaller size, these antibody fragments may exhibit better pharmakokinetics for tissue (e.g., tumour) penetration. If multivalent binding is desired to increase retention times on the target, such fragments can be engineered into di- or oligomeric conjugates. Several F_{ab} fragments have already been licensed for use as drugs (e.g., abxicimab, ranibizumab, 99mTc-sulesomab). As a result of their smaller size, antibody fragments usually exhibit shorter *in-vivo* half-life than intact antibodies. However, their in-vivo half life can be increased by conjugation with poly(ethylene glycol)(PEG).

Due to their exquisite antigen binding specificity, antibodies (or their F_{ab} fragments) can be used for targeting cytotoxic drugs, cytokines, toxins, or radio-isotopes to the desired location, e.g. tumour cells (22). Licensed products following this principle include e.g. ibritumomab tiuxetan, gemtuzumab ozogamicin, or (^{131}I)tositumomab.

The F_c part of the IgG molecule, when fused genetically to otherwise short-lived protein sequences, can serve to extend the *in-vivo* half-life considerably. Several fusion proteins relying on this concept have been licensed (e.g., etanercept, rilonacept, alefacept).

The present policy of MAb naming

International Nonproprietary Names (INNs) are unique names which are globally recognized. They are assigned to allow the clear and unambiguous identification, safe prescription and dispensing of active pharmaceutical ingredients based on molecular characteristics and pharmacological class (23). Since initiation of the INN system in 1950, INNs have become essential for health professionals as a tool for correct prescription and are used by drug manufacturers, regulatory authorities, authorities involved in reimbursement and some other interested parties. They play a key role in communication, prescription, interchangeability and reimbursement of medicines as well as pharmacovigilance.

The concept of INNs was initially developed for small chemical entities that can

be fully characterized by physicochemical means. Due to the progress in biomedical and biotechnological research, medicinal products containing significantly more complex substances of biological origin have been and will continue to be developed. As a consequence, INNs need to be assigned for these complex products. The challenge is that these active pharmaceutical ingredients (APIs) are often very large macromolecules which cannot be fully characterized analytically. Moreover, these APIs are not single specific ingredients but mixtures of molecular species which are differently glycosylated, or otherwise modified post-translationally.

A systematic scheme for INNs of MAbs was implemented in the early 1990s. The common stem is '-mab', sub-stems indicate the source of the product (e.g. -o- for mouse, -u- for human, -xi- for chimeric, -zu- for humanized), and further sub-stems indicate the disease or target class (e.g. -li- for immunomodulators, -vi(r)- for viral) or tumour type (e.g. -co- for colon, -ma(r)- for mammary, -me(l)- for melanoma, -tu(m)- for miscellaneous). The prefix is chosen randomly, but should contribute to a euphonious and distinctive name. If necessary, a second word is added, indicating radiolabelling or conjugations, e.g. to toxins. In this case, the infix -toxa- can be inserted. Several further rules and restrictions apply (i.e., avoid conflicts with trademarks and brand names). To accommodate new technical developments the system has become increasingly complex. Due to the increasing number of INNs selected for MAbs, difficulties have arisen especially in those MAb groups which attract the biggest research interest, e.g. cancer and autoimmune diseases. As a consequence, new INNs tend to become longer, more complicated, and there is the potential for confusion.

Therefore, it was decided at the 44th Consultation on International Nonproprietary Names (INNs) for Pharmaceutical Substances held at WHO Headquarters on 22–24 May 2007 (5) that consideration should be given to review these developments and to make specific recommendations on a revised INN policy for monoclonal antibodies.

IFPMA proposals for principles on INNs for new MAbs

With the intention of supporting this process, IFPMA has developed the following ideas for principles which, from the industry view, should preferably be followed in the naming of new MAbs (6). The following proposals should serve to focus attention on a number of important aspects. Proposals approved by the IFPMA Biotech Working Group are printed in bold italic.

1. ***The naming convention for monoclonal antibodies should follow the same policy as established for all (glyco)proteins. Thus, protein drug substances (including MAbs) with differences in amino acid sequence should always have different INNs***.

Monoclonal antibodies are glycoproteins, and there is good reason to use the same general policy as for naming of other glycosylated proteins where the INN system is well established and proved to be useful for all stakeholders.

2. ***IFPMA proposes to continue the use of the common stem –mab for monoclonal antibodies. For antibody fragments (such as F_{ab} fragments), the use of –fab instead of –mab might be considered.***

We propose to differentiate between complete (intact) antibodies and antibody fragments which presently are also named using the same stem –mab (e.g., abxicimab, ranibizumab). Differentiation would be helpful for the INN users. However, it is open for discussion

whether other distinct stems should be defined for products based on other immunoglobulin fragments such as Fv, scFv, or other fragments (see 21), or whether a general stem (such as –fab) might be used to indicate that the product is derived from a Mab type structure.

3. ***An invented part of the INN is still considered necessary. IFPMA proposes that WHO makes efforts to provide related names for MAbs directed against the same molecular target (although these MAbs nevertheless may differ in amino acid sequence, epitope specificity, immune effector functions, binding constants, etc.).***

The specificity of a MAb for its antigen (which represents the molecular target) is the most important element of information characterizing a monoclonal antibody as a drug substance. Presently, antigen specificity is not apparent from the INNs selected for MAbs. Since the number of clinically validated MAb targets is limited, it can be expected that there will be several MAbs entering clinical studies or obtaining marketing approval which are directed against the same antigen – in fact, this is already reality (e.g., cetuximab and panitumumab both adress the epidermal growth factor (EGF) receptor although this is not evident from the respective INNs). It would help the users of INNs if related, although different, INNs would be provided for MAbs addressing the same antigen. However, it is not suggested that the INN system should develop systematic naming principles for all potential antigens, which clearly is not possible.

4. ***Consistent with the naming conventions for other glycoproteins, it is mandatory that differences in post-translational modifications (for example, but not limited to, the glycosylation pattern) are indicated in the INN of MAbs.*** This might be done using designators (e.g., Greek letters, details to be decided by WHO) as for other glycosylated proteins. This requirement is justified scientifically since it has clearly been shown that differences in glycosylation (e.g., fucosylation, galactosylation, sialylation) influence immune effector functions and thus may have an impact on clinically relevant properties. Consequently, MAbs with an identical amino acid sequence but a different glycosylation pattern have to be considered different drug substances and therefore should have different INNs.

In accordance with the naming policy for glycosylated proteins, MAbs with a different glycosylation pattern (or other differences in post-translational modifications) should have distinct INNs even if their amino acid sequence is the same. This is important because cases are expected where MAbs with the same amino acid sequence, but proven or potential differences in glycosylation are developed which may possess different clinical properties. Such differences may either be intended, e.g. in glycoengineered antibodies, or unintended but inevitable due to the use of different, independent manufacturing processes, e.g. in subsequent-entry (stand-alone follower or biosimilar) products.

5. ***At the time of INN application it may not yet be clear whether modification (e.g., glycosylation) is identical or different. Therefore, monoclonal antibodies made independently (i.e., by different manufacturers using different processes) should generally obtain distinct INNs.*** These distinct INNs should have the same stem but include different designators or identifiers.

It should be noted that this policy in practice will only be efficient if WHO and the drug regulatory authorities agree to make it mandatory for the second manufacturers to present their substances to WHO and apply for a distinct INN.

Manufacturers usually apply for INNs during early clinical development when the final manufacturing process may still be under development and the quality profile, including the modification (e.g. glycosylation) pattern of the product to be commercialized, has not yet been finally established. So, as a matter of precaution, distinct INNs should be given at that time to MAbs made by different manufacturers using different, independent processes. Even if it turns out later on that the glycosylation pattern of two products is the same, the issue of having two products with identical properties but distinct INNs can be considered minor compared to the risk of having two products with the same INN but different clinical properties because in this latter case, "clear identification, safe prescription and dispensing" as requested by WHO (23) based on the INN would be impossible.

This concept does not contradict the fact that there may be some batch-to-batch variability of the glycosylation pattern, as well as slight glycosylation differences after manufacturing changes in a given product. In these cases, the range of variability is validated by the results of clinical development and by the comparability exercise to be performed by the manufacturer according to the ICH Q5E guideline (24) in case of process changes. Thereby it is ensured that within the design space defined by these data, there is no adverse impact on the quality, safety or efficacy of the drug product. So there is no need to select a distinct INN after manufacturing changes provided that pre- and post-change comparability is demonstrated.

6. ***Generally, the INNs contain information on the "pharmacological class" of the substance. Until now, this has been done for MAbs by including a sub-stem for the "disease or target" class.*** However, targeted therapies such as monoclonal antibodies often address biological mechanisms (and molecular targets) which may be involved in more than one indication or disease. Therefore, it is likely (and already reality in some cases) that MAb drug substances will be used in more than one disease (e.g., cancer and inflammatory diseases). While it is recognized that information on the disease is useful for the physician, IFPMA believes that WHO should discuss whether it is appropriate to include information on the disease, or rather on the molecular target (e.g., CD20, HER-2, etc.) in the INN.

In cases where the same MAb is used in therapy for more than one disease (e.g., rituximab in non-Hodgkin lymphoma as well as rheumatoid arthritis), it is confusing when the INN includes information relating to only one of these diseases only. Although this can also be the case with chemically synthesized, low-molecular weight drug substances, it is more likely to occur with monoclonal antibody-based medicines because biopharmaceuticals discovery and development is based on interfering with complex signaling pathways, which may be involved in multiple diseases, rather than solely on organ pathology. Therefore, it should be considered to include information on the antigen/molecular target (cf. proposal 3 above) rather than on the disease in the name.

7. ***IFPMA does not believe that more detailed information on the mechanism of action (e.g., inhibitory, stimulatory, etc.) has to be part of the INN to avoid too much complexity of the names.*** This information should rather be part of the substance description. However, this should be left to WHO's discretion.

8. Specific information for which subtype of disease (e.g., kind of tumour) an antibody drug substance is used (e.g., colon, testis, ovary, etc.) is not useful because many MAbs in oncology may be used for several tumour types. Naming

according to the first indication (which often will turn out not to be the most important) would be misleading. IFPMA proposes to remove this information from the INN.

9. ***In order to simplify the INNs for MAbs, IFPMA also considers INN differentiation dependent on the "source of product" (human, mouse, chimeric, humanized, etc.) no longer necessary.*** This distinction is scientifically questionable due to the fact that there are emerging approaches to design MAb sequences *in silico*, in order to reduce immunogenicity, for removal of T-cell epitopes. The resulting MAbs can neither be classified "murine" or "chimerized", "humanized", or "human". The same principle applies to MAbs generated by, for example, phage display. This type of information should be part of the description of the substance rather than the INN.

Proposals 8 and 9 are intended to support simplification of the MAb INNs. This can only be done if some of the above mentioned informative parts — which according to the present policy are included in the names — will be removed. Information on the "kind of tumour" as well as on the "source of product" both are scientifically questionable and can even be misleading for the user, and therefore need not necessarily be part of the name itself. However since this information certainly is helpful in some situations, it should be retrievable within the substance description which is associated with the INN.

10. ***Distinct names should be assigned to derivatives of antibodies including e.g. bispecific antibodies, antibody-peptide or antibody-toxin conjugates, and radio-labelled antibodies.*** INNs for conjugates might be composed (e.g. as two separate words) from the names assigned to the individual components. In accordance with the naming policy for other pegylated proteins, pegylated MAbs and Fabs should obtain the prefix "peg-". Differences in conjugation (e.g., site of modification, conjugate chemistry, linker chemistry, chain length of polymer, etc.) would require differentiation as for other types of modification. As far as possible, the naming of antibody conjugates should follow the naming convention applied to non-antibody conjugates.

11. ***Fusion constructs containing parts of an immunoglobulin molecule genetically fused to another sequence have to be treated as a new protein and should obtain individual INNs.*** WHO should discuss whether it is more appropriate to follow the policy for MAb naming, or for non-antibody proteins in these cases.

In the present INN policy (4), fusion constructs containing the immunoglobulin F_c part connected to a receptor molecule (or part of a receptor molecule) have been designated with the stem –cept (e.g., alefacept, abatacept, rilonacept). From these names, it is not apparent that the products contain part of an immunoglobulin sequence. In future, there may be fusion products which contain e.g. F_c sequences fused to other peptide (but not necessarily receptor) sequences. While it is evident that each of these products will need a distinct INN, it is proposed to consider whether the presence of antibody (F_c) sequences should be indicated in the INN.

Conclusion

Due to technological progress and the increasing number of MAb-based drugs under development and on the market, a revision of the present policy for INNs of MAbs should be performed. With the proposals described in this paper, IFPMA would like to support this process and contribute to the establishment of a MAb naming system that is able to accommodate the recent and emerging technical developments in the field of monoclonal

antibodies, while at the same time being as clear and simple as possible.

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Regulatory Action and News

Dydrogesterone withdrawn for commercial reasons

United Kingdom — Dydrogesterone (Duphaston ®) is to be withdrawn from the market from March 2008 for commercial reasons. Dydrogesterone was licensed for use in several indications, including threatened or recurrent miscarriage, dysfunctional uterine bleeding, and hormone replacement therapy.

A Public Assessment Report has reviewed evidence for the efficacy of progesterone and dydrogesterone in the maintenance of pregnancy in women with threatened miscarriage or recurrent miscarriage.

For several decades, progesterone and progestogens (such as dydrogesterone) have been used to maintain early pregnancy. However, this practice seems to have been based on theoretical considerations rather than robust evidence of efficacy. Although the methodological and ethical difficulties associated with conducting efficacy trials in these indications need to be considered, the quality of much of the evidence is generally poor relative to today's standards.

Reference: Medicines and Healthcare products Regulatory Agency (MHRA) information release. http://www.mhra.gov.uk/Safetyinformation

Withdrawal of lumiracoxib

Australia — Lumiracoxib is a selective COX-2 inhibitor, which was registered in Australia in 2004 for the symptomatic relief of osteoarthritis (at 200 mg daily) and for the treatment of acute pain and pain due to primary dysmenorrhoea (400 mg daily for up to five days). Lumiracoxib was not widely used in Australia until it was included on the Pharmaceutical Benefits Schedule (PBS) in July 2006.

Following the evaluation of trial data showing that the efficacy of a 100 mg daily dose was comparable to that of the 200 mg dose, a 100 mg tablet was registered for use in Australia in June 2007 for the relief of symptoms of osteoarthritis. In the 12 month period up to the end of July 2007, 567,903 prescriptions for lumiracoxib were dispensed in Australia.

In March 2007, the first Australian report of serious hepatotoxicity associated with the use of lumiracoxib was received. Concerns about this case stimulated a priority review of the general safety profile of lumiracoxib, with a focus on hepatotoxicity.

By the time of the Australian Adverse Reactions Advisory Committee (ADRAC) meeting on 10 August, the Therapeutic Goods Administration (TGA) had received eight reports of serious liver injury associated with the use of lumiracoxib. There were also three reports of minor increases in liver enzymes. There were five reports of hepatic failure, including two fatalities and two liver transplants, and an additional three reports of severe jaundice or acute hepatitis without liver failure.

ADRAC was informed of a further three overseas reports of hepatic failure with lumiracoxib, all from South America. ADRAC also reviewed data provided by the sponsor of lumiracoxib regarding liver abnormalities seen in the clinical trial programme.

At the August meeting, it was known that a 100 mg dose of lumiracoxib had been registered recently in Australia. However, the Committee was concerned there was insufficient evidence for an adequate margin of safety with the 100 mg daily dose because of the possibility that the hepatotoxicity of lumiracoxib may be idiosyncratic; that lower doses may be hepatotoxic in specific populations such as the elderly, low-weight individuals, or those with other underlying disease; or that the 100 mg daily dose may be exceeded by patients seeking more pain relief. ADRAC also considered that the apparent rate of severe liver injury with lumiracoxib appeared greater than for other marketed nonsteroidal anti-inflammatory drugs.

After the above review and advice from ADRAC that the risks of lumiracoxib outweighed its benefits, the TGA acted immediately to cancel the registration of all forms of lumiracoxib in Australia, on the grounds that failure to cancel the registration would create an imminent risk of death, serious illness or serious injury.

Following the cancellation, the TGA advised that all patients should stop taking lumiracoxib immediately, and should be assessed by their doctor for any evidence of liver damage (see TGA website at www.tga.gov.au/alerts/prexige.htm)

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 27, Number 2, April 2008

Enoxaparin contamination: batches recalled

Australia —The Therapeutic Goods Administration (TGA) has recalled five batches of the anticoagulant medicine enoxaparin (Clexane®) due to the detection of an impurity in the affected batches.

The TGA has required testing of all heparin containing products in Australia since March 2008, following the identification of a contaminant known as "oversulphated chondroitin sulphate (OSCS)" implicated in several severe allergic reactions in the USA and Europe.

As a result of this testing contamination with OSCS has been detected in five batches of the low molecular weight heparin product Clexane®. These batches have been quarantined pending further assessment.

To date, there have been no reports of adverse events in Australia of the type reported in the United States associated with heparin products. Nevertheless, the TGA has decided to quarantine the affected batches so no patients are put at undue risk at this time.

Responses from regulatory agencies around the world have varied, with some agencies initiating recalls and others continuing to allow contaminated product to remain in the market, based on the view that in many clinical settings the benefits of continued use of these blood thinning agents outweigh the possible risks from contamination.

Reference: Therapeutic Goods Administration Alert, 22 April 2008. http://www.tga.gov.au/alerts/medicines/clexane.htm

Sweden — On 23 April 2008, the Medical Products Agency decided to recall the contaminated batches of enoxaparin (Klexane®) found on the Swedish market. The level of contamination is low and the recall was made as a precautionary measure.

During January and February 2008 Baxter recalled almost all of their heparin products from the US market after reports on serious adverse events. At the begin-

ning of March 2008, the US Food and Drug administration (FDA) announced that the adverse events were associated with the presence of an unknown heparin-like impurity that could only be detected with new analytical methods presented on the FDA website.

The Medical Products Agency decided that all Companies supplying heparin products for the Swedish market should test their products for this specific contamination. A few batches of the low molecular weight heparin, Klexane®, were found to be contaminated with low levels of the same impurity as in the unfractionated heparin detected in the USA, i.e. oversulphated chondroitin sulphate (OSCS). Therefore, the Medical Products Agency decided to recall these contaminated batches as a precautionary measure.

No reports of similar severe adverse reactions as seen in the USA have been reported to the MPA. The batches of Klexane® that have not been withdrawn can be used according to the approved indications. They do not contain any impurity.

Reference: Medical Products Agency, 29 April 2008. http://www.lakemedelsverket.se/Tpl/NewsPage____7312.aspx

Recombinant antihemophilic factor approved

United States of America — The Food and Drug Administration (FDA) has licensed a treatment for hemophilia A, a rare, hereditary blood-clotting disorder that affects approximately 15 000 individuals, almost exclusively males, in the United States.

The new treatment, called Xyntha® Antihemophilic Factor (Recombinant) Plasma/Albumin Free, is a genetically engineered version of factor VIII Xyntha® is licensed for the control and prevention of bleeding, which can occur spontaneously or after an accident or injury in patients diagnosed with hemophilia A. This recombinant Factor VIII is produced without additives from human or animal material, which further minimizes any risk of infection from the product.

In clinical trials, Xyntha® was shown to be effective at preventing or controlling bleeding, including preventing bleeding in surgery, for hemophilia A patients. Generally, the most frequently reported adverse reaction was headache. Most adverse reactions reported in either study were considered mild or moderate in severity. In addition, two of 89 individuals who received 50 days of treatment with Xyntha®, developed factor VIII inhibitors, which are antibodies that counteract treatment with factor VIII.

Reference: *FDA News*, 21 February 2008 at http://www.fda.gov

Esomeprazole magnesium approved for children

United States of America — The Food and Drug Administration (FDA) has approved esomeprazole magnesium (Nexium®) for short-term use in children 1–11 years of age for the treatment of gastroesophageal reflux disease (GERD). The agency approved Nexium® in two forms, a delayed-release capsule and liquid form, in 10 mg or 20 mg daily for children 1–11 years old compared to 20 mg or 40 mg recommended for pediatric patients 12–17 years of age.

Children prescribed this drug should be monitored by their physicians for any adverse drug reactions.

Esomeprazole magnesium is part of a class of drugs known as proton pump inhibitors (PPIs). PPIs decrease the

amount of acid produced in the stomach and help heal erosions in the lining of the esophagus known as erosive esophagitis.

FDA approved the use of esomeprazole magnesium in patients 1 to 11 years for short-term treatment of GERD based upon the extrapolation of data from previous study results in adults to the paediatric population, as well as safety and pharmacokinetic studies performed in paediatric patients. In one study, 109 patients 1-11 in age, diagnosed with GERD, were treated with esomeprazole magnesium once-a-day for up to eight weeks to evaluate its safety and tolerability. Most of these patients demonstrated healing of their esophageal erosions after eight weeks of treatment.

The most common adverse reactions in children treated with esomeprazole magnesium were headache, diarrhea, abdominal pain, nausea, gas, constipation, dry mouth and sleepiness. The safety and efficacy of Nexium® has not been established in children less than one year of age.

Reference: *FDA News*, 28 February 2008 at http://www.fda.gov

Rotavirus vaccine approved

United States of America — The Food and Drug Administration (FDA) has announced the approval of Rotarix®, the second oral US licensed vaccine for the prevention of rotavirus, an infection that causes gastroenteritis (vomiting and diarrhea) in infants and children. Rotarix is a liquid and given in a two-dose series to infants from 6–24 weeks of age.

Although the disease is usually self-limiting, rotavirus causes about 2.7 million cases of gastroenteritis in US children each year — about 55 000 to 70 000 of those require hospitalization; and between 20 and 60 deaths are attributed to it. Without vaccination, nearly every child in the United States would likely be infected at least once with rotavirus by age 5. There are many different strains of rotavirus. The vaccine protects against rotavirus gastroenteritis caused by the G1, G3, G4, and G9 strains.

The most common adverse reactions reported during clinical trials were fussiness, irritability, cough, runny nose, fever, loss of appetite and vomiting.

To help ensure that Rotarix® does not increase the risk of intussusception, its manufacturer conducted a study of more than 63 000 infants. In that study, there was no increase in the risk of intussusception in those who received Rotarix® (31 673 infants) compared to those who received placebo (31 552 infants).

Increased rates of convulsion and pneumonia-related deaths were observed in the Rotarix® recipients in the intussusception study, however these events were not observed in other studies conducted by the manufacturer. Although the FDA has concluded that the available data do not establish that these events are related to the vaccine, the agency has requested the manufacturer to conduct post-marketing safety studies involving more than 40 000 infants to provide additional safety information.

Reference: *FDA News*, 3 April 2008 at http://www.fda.gov

New version of genetically engineered Factor VIIa approved

United States of America — The Food and Drug Administration (FDA) has approved a new formulation of the genetically engineered version of Factor VIIa, a plasma protein essential for the clotting of blood. The new formulation allows the product to be stored at room temperature for up to two years.

The new formulation of NovoSeven Coagulation Factor VIIa (Recombinant)®—contains sucrose and L-Methionine, which allow for storage at room temperature.

NovoSeven RT uses include treatment of hemophilia A or B; treatment of bleeding and prevention of surgical bleeding in patients with congenital Factor VII deficiency; and prevention of surgical bleeding in patients with acquired hemophilia.

The most commonly observed adverse reactions with NovoSeven RT® are fever, bleeding, injection site reaction, joint discomfort, headache, elevations or falls in blood pressure, nausea, vomiting, pain, swelling, and rash. Some elderly patients experienced an increased risk of arterial clotting when they were treated with NovoSeven RT® outside of its approved indications.

Reference: *FDA News*, 9 May 2008 at http://www.fda.gov

International Pharmacopoeia

Role of *The International Pharmacopoeia* in quality assurance

In the pharmaceutical sense, a pharmacopoeia is an official, legally binding publication containing recommended quality specifications for the analysis and determination of drug substances, specific dosage forms, excipients and finished drug products. A quality specification is a set of appropriate tests which will confirm the identity and adequate purity of the product, ascertain the strength or amount of the active substance and, when needed, performance characteristics. General requirements are also given in the pharmacopoeia on important subjects related to drug quality, such as microbiological purity, dissolution testing, or stability.

The underlying principles of a pharmacopoeia are that pharmaceutical substances and products intended for human use should be manufactured at sites that are adequately equipped, dispose of appropriate professional and technical knowledge and are operated by qualified staff. General rules of appropriate pharmaceutical manufacture are contained in the good manufacturing practices (GMP) guidelines recommended by WHO (1) and/or those laid down by the competent national or regional authority in the country of manufacture.

Protection provided by compendial standards will depend not only on technical content but also to a great extent on how they are used in the context of other control measures. When pharmacopoeial standards are used to establish regulatory product compliance, the following principles should be applied:

- the interpretation of a monograph must be in accordance with all general requirements and testing methods, texts, or notices pertaining to it;
- a product is not of pharmacopoeial quality unless it complies with all the requirements stated.

There is a practical distinction between pharmacopoeial standards and manufacturers' release specifications, although both comprise sets of tests to which a given product should conform. Release specifications are applied at the time of manufacture of a pharmaceutical product to confirm its appropriate quality but they also need to have a predictive value, to support the notion that the manufacturer is responsible for the product during its entire shelf-life. In many cases, pharmacopoeial monographs are based on the specifications developed by the manufacturers of innovator products.

Therefore, pharmacopoeial specifications are not used to launch innovator products because the manufacturer's quality specifications will be evaluated by the competent regulatory authorities using rigorous scientific assessment in conjunction with pre-clinical and clinical safety and efficacy data. It is important to note that the regulatory focus has been shifting from finished dosage form quality control to the control of the whole complex of processes and procedures involved in the manufacture of both active pharmaceutical ingredients (APIs) and finished dosage forms. The objective of a regulatory approval nowadays is to ensure that the

manufacturer has built quality into the product from A to Z. In the case of a multisource (generic) medicine, well resourced regulatory authorities require that it should contain the same active ingredients as the innovator drug and:

- be identical in strength, dosage form, and route of administration
- have the same use indications
- be bioequivalent (as a marker for therapeutic interchangeability)
- meet the same batch requirements for identity, strength, purity and quality
- be manufactured under the same strict standards of GMP required for innovator products.

In the case of multisource (generic) medicines, which are formulated after patents and other exclusivity rights expire, pharmacopoeial monographs are important as they enable manufacturers to develop products to meet the requirements of pharmacopoeial standards (both for APIs and finished dosage forms) rather than elaborate their own specifications. It should be noted that not all pharmacopoeias present monographs (quality standards) for finished dosage forms.

Pharmacopoeial standards should be used in the framework of all regulatory measures such as good manufacturing practice (GMP) inspection of the manufacture of active pharmaceutical ingredients and finished dosage forms, and scientific assessment of all quality specifications, interchangeability data and labelling information. Their greatest value is revealed during post-marketing surveillance of the quality of multisource (generic) medicines.

Pharmacopoeial standards have also certain limitations. For example, testing using pharmacopoeial methods will not necessarily identify all possible dangerous impurities. Pharmacopoeial methods are usually designed to catch the impurities that are likely to occur during the route of synthesis that has been utilized by the originator. In case of a different route of synthesis or accidental contamination with other chemicals, it may not necessarily pick up impurities even if they pose a danger to health. This is why well resourced regulatory authorities never base marketing authorization of multisource (generic) products on quality control testing based on pharmacopoeial monographs alone. In fact, pre-marketing quality control testing has diminished constantly and more accent is put on market surveillance after the product is released onto the market.

Pharmacopoeial monographs help to verify the quality and, in the case of multisource (generic) medicines, they may indicate pharmaceutical interchangeability with the originator product.

Beginnings and history of *The International Pharmacopoeia*

The history of *The International Pharmacopoeia* dates back to 1874 when the need to standardize terminology and to specify dosages and composition of drugs led to attempts to produce an international pharmacopoeial compendium. A first conference, called by the Belgian Government and held in Brussels in 1902, resulted in the Agreement for the Unification of the Formulae of Potent Drugs, which was ratified in 1906 by 19 countries. A second agreement, the Brussels Agreement, was drawn up in 1925 and ratified in 1929. This 41-article agreement stipulated that the League of Nations would be responsible for the administrative work to produce a unified pharmacopoeia, and a permanent secretariat of an international organization would coordinate the work of national pharmacopoeial commissions. General principles for the preparation of galeni-

International Pharmacopoeia milestones

1874	Discussion on Unification of terminology and composition of drugs
1902	First Conference organized by the Government of Belgium
1906	Agreement on Unification of the Formulae of Potent Drugs ratified by 19 states
1925	Brussels agreement (signed 1929)
1937	First meeting - Health Organization of the League of Nations
1947	Interim Commission of WHO takes up health-related work of League of Nations
1948	First World Health Assembly (WHA) establishing the Expert Commit tee on Unification of Pharmacopoeias
1950	WHA approved publication of Pharmacopoeia Internationalis
2006	Publication of 4th edition of *The International Pharmacopoeia* (3)

cals, maximal doses, nomenclature, and biological testing of arsenobenzones were included in the articles of this agreement, as was a table of dosage strengths and descriptions for 77 drug substances and preparations.

In response to repeated calls from pharmaceutical experts in various countries that the Brussels Agreement be revised and extended to cover an international pharmacopoeia, the Health Organization of the League of Nations set up a Technical Commission of Pharmacopoeial Experts in 1937. This first committee comprised seven experts from Belgium, Denmark, France, the Netherlands, Switzerland, United Kingdom, and United States of America.

In 1947 the Interim Commission of WHO took over the work on pharmacopoeias previously undertaken by the Health Organization of the League of Nations, and set up an Expert Committee on the Unification of Pharmacopoeias to continue the work of the League's Technical Commission. In 1948 the First World Health Assembly approved the establishment of the Expert Committee by the Interim Commission. In 1951 this became the Expert Committee on the International Pharmacopoeia; and subsequently, in 1959, the Expert Committee on Specifications for Pharmaceutical Preparations. The panel of experts serving this Committee was named the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations.

Managing *The International Pharmacopoeia*

Work on *The International Pharmacopoeia* is carried out in collaboration with members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations as well as with specialists from the pharmaceutical industry and other institutions. This is followed by consultation with national and regional pharmacopoeias and a working procedure based on wide

international consultation. The specifications and general methods included in *The International Pharmacopoeia* benefit from an international worldwide validation process, using a global network of expertise. This is undertaken with a view to serve all 193 WHO Member States, the global market and increasing trade around the world. This is a major difference with other pharmacopoeias that provide control specifications for the medicines sold within their country or region.

Development of monographs for inclusion in The International Pharmacopoeia

Procedure

Step 1: Identify specific pharmaceutical products for which quality control (QC) specifications need to be developed, obtain confirmation from all WHO parties concerned (e.g. Department of Medicines Policy and Standards, Prequalification project team and specific disease programmes).

Step 2: Provide contact details for manufacturers of the above products in collaboration with all parties concerned.

Step 3: Contact manufacturers to request provision of QC specifications and samples.

Step 4: Identify and contact QC laboratories to collaborate in the project (2–3 laboratories depending on how many pharmaceutical products have been identified in step 1. Contract for laboratory work.

Step 5: Prepare the contract for drafting the specifications and undertaking the necessary laboratory work.

Step 6: Search for information on QC specifications available in the public domain.

Step 7: Conduct laboratory testing, development and validation of QC specifications.

Step 8: Support WHO Collaborating Centre in the establishment of International Chemical Reference Substances.

Step 9: Follow the consultative process: send copies of draft specifications to Expert Advisory Panel and to specialists for comments.

Step 10: Discuss comments with contract laboratories and WHO Collaborating Centres. Conduct additional laboratory testing to verify and/or validate specifications.

Step 11: Hold a consultation to discuss the comments and test results received as feedback.

Step 12: Re-circulate draft monograph for comments.

Step 13: Repeat step 10.

Step 14: Present final draft to the WHO Expert Committee on Specifications for Pharmaceutical Preparations for possible formal adoption (for example, see the Committee report from 2006, reference 6)
.
If not adopted, repeat steps 11–13.

The aim within this process is to keep the number of reference standards to a minimum, thus balancing the cost of analysis with identification of potential health risks for users.

Advantages of *The International Pharmacopoeia*

Unlike national (and regional) pharmacopoeias *The International Pharmacopoeia* has no determined legal status and WHO Member States are free to adopt and incorporate it, either in part or in whole, into national legislation. Advan-

tages of *The International Pharmacopoeia* are:

- International validation of specifications through an independent scientific process.
- Input from WHO Collaborating Centres and national drug quality control laboratories in the six WHO regions of Africa, the Americas, Eastern Mediterranean, Europe, South-East Asia and Western Pacific.
- Collaboration with manufacturers around the world, especially for new projects where no public standards exist.
- Collaboration with standard-setting organizations and parties, including regional and national pharmacopoeias.
- Networking and close collaboration with WHO Member States and drug regulatory authorities.
- Maintaining minimum cost of analysis through use of robust test methods and minimum number of references standards.
- Input and feedback from other WHO activities, such as the WHO/UNICEF/ World Bank Prequalification Project.
- Free for use by all WHO Member States.

Published editions of *The International Pharmacopoeia*

First edition

The first edition, published with the aim of creating a worldwide, unified pharmacopoeia, relied on collaboration with national pharmacopoeia commissions for its preparation. It was published in two volumes (1951 and 1955) and a supplement (1959) in English, French and Spanish, and was also translated into German and Japanese. Altogether, it included 344 monographs on drug substances, 183 monographs on dosage forms (capsules, injections, tablets and tinctures) and 84 tests, methods, and general requirements.

A large number of national pharmacopoeias and official lists were examined and assistance was also obtained from the International Pharmaceutical Federation (FIP) to determine the selection of substances and products to be described in the pharmacopoeia.

Second edition

The second edition was published in 1967 as *Specifications for the Quality Control of Pharmaceutical Preparations*. The selection of monographs and appendices was based largely on the availability, at the time, of specifications intended for publication in national pharmacopoeias and in other volumes of specifications for pharmaceutical quality control. Specifications for 162 pharmaceutical preparations not included in the first edition were introduced in the second edition, while 114 monographs were deleted, based on feedback from the first edition. New analytical methods were also added.

Third edition

In 1975, *The International Pharmacopoeia* was re-focused on the needs of developing countries and recommended simple, classical chemical techniques that had been demonstrated as sound. Priority was given to medicines that were widely used throughout the world and medicines important to WHO public health programmes, also targeting those substances likely to contain impurities arising from degradation or due to difficulties in manufacture. Robust analytical test methods and procedures were preferred whenever applicable without compromising public health. A flexible approach was employed to facilitate accessibility of control specifications for less well equipped national quality control laboratories. Since 1979, the medicines appear-

ing in *The International Pharmacopoeia* have been selected from the WHO Model List of Essential Medicines.

The five volumes of the third edition contained 62 general methods of analysis and requirements, quality specifications for 255 active pharmaceutical ingredients — the majority of essential drug substances in the WHO Model List of Essential Medicines — 65 quality specifications for pharmaceutical excipients, and 67 finished dosage forms.

Fourth edition

The fourth edition of *The International Pharmacopoeia* was published in 2006 (2). It comprises two volumes: General Notices and monographs for pharmaceutical substances (A to O) are to be found in Volume 1 and the remaining monographs for pharmaceutical substances (P-X), together with those for dosage forms and radiopharmaceutical preparations, methods of analysis and the reagent sections are to be found in Volume 2.

This new edition consolidates the texts of the five separate volumes of the third edition and includes new monographs for antiretrovirals together with updates and revisions of the existing, previously published texts. Significant changes and improvements have been made in the presentation, cross-referencing to general methods.

The new notice on Definition, for example, serves to define dosage forms as being manufactured with active ingredients of pharmacopoeial quality and to clarify the mandatory status of certain statements in monographs. The new notice on Manufacture governs the interpretation of statements included under this heading in monographs such as the general monographs for dosage forms, the monographs for the different grades of water and certain other individual monographs. The need for a notice on Impurities arose from the inclusion of information at the end of certain new monographs for antiretroviral substances. Such lists of known and potential impurities that have been shown to be controlled by the tests in a monograph are likely to be included more widely in future.

Most importantly, a new series of monographs has been added for antiretrovirals. These monographs have been developed as part of the WHO strategy to make quality antiretroviral medicines widely available. Such specifications support the joint WHO/UNICEF/World Bank Prequalification Project managed by WHO (3). These new monographs provide an element of choice in relation to test methods used for identification and, where possible, a titration method for assay, in line with established policy. However, in order to provide adequate control of impurities, it has been found necessary to place reliance on HPLC.

CD-ROM

The fourth edition was published simultaneously both in print and on CD-ROM (2). This provides users of *The International Pharmacopoeia* with a choice of format with which to consult the publication depending on the circumstances and the type of enquiry. The response from users of the CD-ROM has demonstrated the usefulness of making the publication available electronically. The simplified structure of the fourth edition and the improved functionality of the CD-ROM will facilitate both reading and searching text.

Future role of *The International Pharmacopoeia*

Work is in progress on the preparation of new monographs for antiretroviral substances, the associated dosage forms and for a number of fixed-dose combination products for the treatment of HIV/AIDS, malaria and tuberculosis. Special attention is also being given to paediatric formulations.

Revision of monographs is also continuing to improve specifications, for example, by providing better means of impurity control or by the addition of a dissolution test. Additions and revisions to the fourth edition will be made available at appropriate intervals.

Meanwhile, attention is drawn to the WHO Medicines website (htpp://www.who.int/medicines), where texts of monographs adopted by the Expert Committee on Specifications for Pharmaceutical Preparations are provided together with other detailed information.

International Chemical Reference Substances

International Chemical Reference Substances (ICRS) are primary chemical reference standards. They are supplied for use in physical and chemical tests and assays described in the specifications for quality control of drugs published in *The International Pharmacopoeia* or proposed in draft monographs. The ICRS may be used to calibrate secondary standards.

Analytical data on ICRS are given in certificates enclosed with the reference substances. ICRS may also be used in tests and assays not described in *The International Pharmacopoeia*. The responsibility for assessing the suitability of the reference substances then rests with the user.

For ordering information, please visit the website of the WHO Collaborating Centre for Chemical Reference Standards: http://www.apl.apoteket.se/who.

Links to other WHO activities

An important feature of *The International Pharmacopoeia* is that it forms a basic element of quality assurance activities. WHO gives advice on the establishment and management of national quality control laboratories, prepares guidelines on functioning, publishes guidance and gives advice on good manufacturing practices and other regulatory issues, following the underlying principle that quality must be built into a product from the very beginning of the manufacturing process.

There is also a close link with the International Nonproprietary Names (INN) programme which is responsible for naming new pharmaceutical entities. The lists of International Nonproprietary Names are published in a regular manner (3). The whole area of work is overseen by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The WHO Expert Committee on Specifications for Pharmaceutical Preparations is an advisory body on quality assurance to WHO and its Member States. Advice and recommendations provided by this Expert Committee are intended to support national and regional authorities (in particular drug regulatory authorities), procurement agencies, and international bodies and institutions such as the Global Fund, and international organizations such as UNICEF, to combat problems of counterfeit and substandard medicines and underpin important WHO initiatives.

Conclusion

The role of WHO in quality assurance of medicines, especially for those countries that have no or little means to develop their own quality control specifications, is important. WHO has numerous activities to support Member States such as creating nomenclatures and developing guidance, while also delivering training courses and workshops on various topics of quality assurance to build national capacity to regulate medicines. *The International Pharmacopoeia* in conjunction with International Chemical Reference Substances are regarded as essential tools in the overall framework of quality control and quality assurance of pharmaceuticals, thus contributing to the safety and efficacy of drugs.

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