WHO Drug Information

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Consultation documents

ATC/DDD classification

International Nonproprietary Names (INN)

Abbreviations and web sites

CHMP	Committee for Medicinal Products for Human Use (EMA)
EMA	European Medicines Agency (www.ema.europa.eu)
EU	European Union
FDA	U.S. Food and Drug Administration (www.fda.gov)
Health Canada	Federal department responsible for health product regulation in Canada (www.hc-sc.gc.ca)
MHLW	Ministry of Health, Labour and Welfare, Japan
MHRA	Medicines and Healthcare Products Regulatory Agency, United Kingdom (www.mhra.gov.uk)
Medsafe	New Zealand Medicines and Medical Devices Safety Authority (www.medsafe.govt.nz)
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
PMDA	Pharmaceuticals and Medical Devices Agency, Japan (www.pmda.go.jp/english/index.htm)
Swissmedic	Swiss Agency for Therapeutic Products (www.swissmedic.ch)
TGA	Therapeutic Goods Administration, Australia (www.tga.gov.au)
U.S.	United States of America

Note:
The online version of this issue (available at www.who.int/medicines/publications/druginformation) has direct clickable hyperlinks to the documents and web pages referenced.

Regulatory collaboration

The African Vaccine Regulatory Forum (AVAREF): A platform for collaboration in a public health emergency

The Ebola virus disease outbreak in West Africa has been followed by a global multi-stakeholder response, led by WHO, to make medical products available to treat and prevent the disease. The swift pace of product development has challenged regulatory systems globally, and especially those of resource-constrained sub-Saharan African countries.

To address the challenge of authorizing clinical trials of Ebola candidate vaccines with limited available data, the WHO African Vaccine Regulatory Forum (AVAREF) was used as a collaboration platform enabling regulators, ethics committees and sponsors to reach consensus on key ethical and regulatory questions. Given AVAREF's crucial role in speeding up product development through coordinated regulatory efforts to combat Ebola it is essential that necessary resources are allocated to further strengthen its capacity.

Challenges of product development during public health emergencies

Medical products are complex, and high levels of scientific expertise are needed to ascertain their quality, safety and efficacy. Traditionally, product development and approvals take years, with carefully planned, robust and systematically executed, large clinical trials serving as basis for safety and efficacy data to inform regulatory decision-making.

While developed countries have adequate regulatory systems and capacity in place to assess and authorize clinical trials in order to ensure their scientific integrity, most African regulatory authorities have severe resource constraints and therefore lack the capacity to adequately review and authorize clinical trials and to ensure the safety of trial subjects during the clinical development of products *(1)*.

Public health emergencies impose on African regulators the additional pressure of having to accelerate access to needed products for the public good by approving clinical trial applications and products within much shorter timelines than usual. The fundamental question regulators have to grapple with is: How to authorize a promising product with very limited evidence of safety and efficacy in instances where large clinical trials are not possible?

This is the scenario created by the largest-ever outbreak of Ebola Virus disease, which started in Guinea, Liberia and Sierra Leone with a few cases in other

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West African countries, Europe and North America *(2)*.

As part of the global response to this public health emergency, WHO convened several consultations on different aspects of product development with a view to accelerate development and access to promising products including vaccines. One of the outcomes of these consultations was the decision to use existing regulatory networks as platforms to support accelerated product development and approvals.

The African Vaccine Regulatory Forum (AVAREF)

AVAREF is a regional regulatory network founded by WHO in 2006, at a time when the focus on clinical trials of vaccines began to shift from developed countries to developing countries, including those in sub-Saharan Africa. The network brings together national regulatory authorities (NRAs) and ethics committees of the countries in the WHO African Region. It currently has 23 members[1].

AVAREF aims to support NRAs in regulatory decision-making. It provides information to countries on vaccine candidates and timelines for clinical trials, and promotes communication and collaboration between African NRAs and ethics committees. It also provides opportunities to bring in the expertise and advice of regulators from Europe and North America – including Health Canada, the European Medicines Agency (EMA) and the United States' Food and Drug Administration (FDA)'s Center for Biologics Evaluation and Research (CBER) – for the benefit of their African counterparts. At the same time AVAREF promotes convergence towards harmonization of regulatory practices and processes to ensure timely regulatory evaluations and approvals of clinical trial applications and products.

Key among AVAREF's achievements has been firstly the establishment of innovative regulatory pathways for clinical trials, secondly the development and use of common guidelines for submission of clinical trial applications, and thirdly the use of joint reviews of multicountry clinical trial applications and joint good clinical practice (GCP) inspections. These strategic forms of collaboration can significantly improve timelines for product development *(3, 4)*.

Joint reviews and GCP inspections have played a key role in ensuring timely regulatory authorization and approvals of MenAfriVac®, the meningococcal A conjugate vaccine whose rollout in the meningitis belt of Africa has eliminated epidemic meningitis due to Group A *Neisseria meningitidis* as a public health problem *(5)*. A joint review approach was also used to coordinate and expedite the review of the multicountry Phase III clinical trial for the lead malaria candidate vaccine, RTS,S/AS01, which is about to conclude in seven African countries.

WHO's use of the AVAREF platform in responding to the Ebola emergency

The Ebola outbreak created a global urgency and a need for accelerated development of vaccines and treatments. In the wake of the outbreak, prompt authorization of clinical trial applications and overall regulatory oversight of

[1] Botswana, Burundi, Cameroun, Central African Republic, Ethiopia, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Kenya, Malawi, Mali, Mozambique, Nigeria, Rwanda, Senegal, Sierra Leone, South Africa, United Republic of Tanzania, Uganda, Zambia and Zimbabwe

products that could help to prevent or treat Ebola are particularly challenging: The design of clinical trials is becoming more difficult due to very specific features of the disease, and the capacity constraints are greater than ever in affected countries.

In response to this situation, the annual meeting of AVAREF, held in Pretoria, South Africa on 3–7 November 2014, devoted two days to discussions addressing the key regulatory questions around the Ebola outbreak. Participants discussed ways to put into place mechanisms for the review and authorization of clinical trials while planning for the approval of products for emergency use.

The meeting enabled regulators and manufacturers to achieve progress in three principal areas: firstly, pre-submission discussions with sponsors and manufacturers, secondly the general principles and mechanisms for the authorization of clinical trials and products, and thirdly the organization of joint reviews to facilitate timely approvals of clinical trials.

Pre-submission discussions

Pre-submission meetings with regulators in Africa can be very challenging for manufacturers, especially when they are dealing with several countries with different requirements. The AVAREF meeting provided a unique opportunity for sponsors and manufacturers to present and discuss the characteristics of their products, preclinical data available from non-human primate studies and from first in-human studies where available. All known and potential target countries for clinical trials were represented in one place for discussions on the products and the designs and timelines of clinical trials. In addition, the African regulators as well as ethics committee members and regulators from Europe, the U.S. and Canada – where some first trials for some of the products in humans have been approved – were able to make suggestions to sponsors about clinical trial designs and data to submit for approval of trial applications.

Clinical trial and product approvals

The AVAREF meeting opened discussions on how regulatory authorizations of clinical trials and approvals of products for emergency use can be addressed in the current Ebola outbreak without compromising the safety of populations. These discussions were based on available regulatory experience and expertise of the U.S. FDA, Health Canada and EMA. Most African countries lack specific regulatory pathways and mechanisms and could therefore adopt or adapt some of the mechanisms used in other countries. The session also highlighted the need for a global regulatory mechanism to be put into place for product development in emergencies such as the Ebola outbreak and the earlier pandemic influenza.

The meeting participants reached consensus around the use of AVAREF as a collaborative platform, and the value of joint reviews as a useful means of ensuring that clinical trial applications for products against Ebola are reviewed adequately and that shorter timelines consistent with accelerated product development and manufacturer timelines are met.

Joint reviews

WHO convened three joint reviews of clinical trial applications utilizing the

AVAREF platform. To date, ethical and regulatory approval has been secured within 90 days from the completion of the joint review. WHO played a convening and supportive role in the joint review sessions by:

- facilitating agreement on the format for the clinical trial applications;
- ensuring the participation of supporting agencies (the regulatory authorities of Ghana, the United States, Europe, the United Kingdom, Canada and Switzerland);
- liaising with sponsors regarding information-sharing among supporting agencies about products under review;
- setting up an electronic platform to manage the review process and to make necessary documents available to regulators and ethics committee members; and
- facilitating the finalization of a summary report stating agreed-upon actions and timelines following the review.

Recommendations

The meeting recommendations were circulated among all stakeholders, NRAs, ethics committees, manufacturers, sponsors and partners. The agreed recommendations are presented in *Annex 1*.

Support and funding

The ninth annual plenary meeting of AVAREF was organized with support from the Bill & Melinda Gates Foundation and the Programme for Appropriate Technologies in Health/Malaria Vaccines Initiative (PATH/MVI). In addition, the Center for Biologics Evaluation and Research of the U.S. FDA (CBER FDA), the Health Products and Food Branch of Health Canada and the EMA contributed through the participation of their experts. The joint reviews were supported by WHO.

Conclusion

To ensure that health products are safe, effective and of good quality, regulatory oversight of product development in countries should be consistent with ICH and other relevant international guidelines. Regulatory agencies of developing countries which lack the full capacity to meet these requirements should be supported to build or strengthen their capacities in line with international regulatory standards. WHO fully recognizes this and is actively supporting Member States to strengthen their regulatory systems through regular assessments, capacity-building in a variety of ways and by promoting regional harmonization efforts.

AVAREF is a WHO-supported platform that has proven to be instrumental in providing regulatory support to accelerate product development during public health emergencies, as exemplified with products in development against Ebola. Going forward, these achievements will also support the work of African regulators on vaccines for diseases such as HIV, tuberculosis and malaria, which are affecting many millions of people in the African region. Lastly, AVAREF may serve as an important regional platform linked with international networks such as the Developing Countries Vaccine Regulatory Network (DCVRN) to promote the increasing number of multi-regional or global trials.

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Annex 1: 9th AVAREF meeting recommendations

Sponsors/ manufacturers:	Regulatory authorities (RAs):	WHO:
Ebola		
1. To immediately release the planned time lines for submission of clinical trial applications indicating specific trial sites. 2. To hold pre-submission meetings with each participating NRAs and EC, and to attend 3. Manufacturers to attend the joint review sessions with their appropriate staff; 4. Manufacturers to file clinical trial applications through the focal persons identified by Heads of NRAs 5. To use the AVAREF clinical trials format (African Common Clinical Trial Document) for the submissions of clinical trial applications. 6. To include in their submissions all pertinent data that is available at the time of submission 7. To respond swiftly to any query from NRAs or EC/IRB	**National RAs and ethics committees (ECs) / institutional review boards (IRBs):** 1. To prioritize assessment of clinical trial applications in parallel (regulatory/ethics) to minimize delays and to apply fast-track procedures 2. To immediately release all national/regional provisions governing the area of clinical trials and highlight aspects favourable to fast track procedures 3. To accept to review all clinical trials submitted by manufacturers/sponsors **Supporting RAs (EMA, USFDA, Health Canada):** 1. In collaboration with WHO, do everything in their power to share data relevant to clinical trials with the NRAs of participating countries 2. To provide expertise to support NRAs in the joint reviews when requested	1. To request Heads of RAs to: a. Identify and named senior regulators staff as the agency entry focal points for Ebola b. Designate named reviewer(s) to participate in a joint review process with the mandate to take regulatory/ ethics decisions (reviewers are empowered to take decisions during the joint review meeting). 2. To facilitate a joint review session of the clinical trial applications with a target date of 15 December 2014 3. To involve the NRAs of the Ebola-affected countries in the joint review process 4. To provide expertise and develop briefing materials for ethics committees 5. To develop additional briefing materials on the vaccines, and novel clinical trial designs, to assist the national/regional reviews 6. To proactively play the needed broker role in facilitating the interaction between manufacturers and countries 7. To engage with heads of Institutions and research institutions and provide necessary support to countries to develop procedures for accelerated review of Ebola related research. 8. To ensure that ethics committees have the necessary support to follow up approved trials and research studies through site monitoring and having mechanisms to rapidly review amendments etc.
Tuberculosis, HIV/AIDS and malaria vaccines	1. To gradually strengthen regional harmonization of technical processes and procedures 2. To emphasize utilization of joint process implementation 3. To establish mechanisms for strengthening Transparency on processes/procedures and on country/regional performance (including adapting indicators for research ethics systems) 4. To interact actively with the African Medicines Registration Harmonization Initiative (AMRH)	1. To support and strengthen collaborative mechanisms among NRAs and ethics committees including capacity building through regular trainings 2. To encourage multiplication of joint implementation of regulatory activities including joint reviews and joint inspections 3. To host and manage the AVAREF virtual community platform developed by Health Canada, the secretariat to implement the transition by end January 2015 4. WHO to provide specific guidelines for evaluation of clinical trial applications for vaccines against TB and HIV, build capacity to efficiently address other anticipated products in the pipeline

WHO prequalification

Update on prequalification of diagnostics and medicines

In addressing shortcomings in manufacture, regulation and supply that exist across multiple diseases and product types, WHO prequalification is probably the single, most effective source of hands-on regulatory capacity building. And by serving as a single entry point to donor funding for manufacturers who are willing to offer quality products, it greatly facilitates international procurement and distribution.

In 2014, the prequalification programme both consolidated its processes for the different product categories and continued to broaden its achievements. This article provides an overview of those achievements.

Norms and standards

Established on the basis of the norms and standards adopted by the WHO Expert Committee for Specifications on Pharmaceutical Preparations, the Prequalification Team has become an important source of feedback to the standard-setting process for medicines. In 2014 it contributed to a wide range of pharmaceutical quality guidelines and proposed a concept paper for new guidance on good data management.

The Prequalification Team also provided significant input into discussions to align international quality assurance requirements for diagnostic products based on stringent regulatory principles and emerging global consensus. It further issued draft guidance on post-market surveillance of in vitro diagnostics (IVDs) for comment *(1)*.

Integration of workstreams

The year 2014 saw the merger of the independent prequalification streams for diagnostics, medical devices, medicines and vaccines and the creation of the Prequalification Team. This generated greater synergy, but also demanded considerable time and effort for reorganization and establishment of a quality management system. For diagnostics, significant resources were dedicated to streamlining processes, in particular to improve communication and enhance transparency.

Funding

In the absence of WHO budgetary allocations, prequalification is currently largely funded by just two donors: UNITAID and the Bill & Melinda Gates Foundation.

User fees were introduced for prequalification of medicines in 2014, fees had already been introduced previously for diagnostics and vaccines. A review of 2014 applications showed that the number of submissions for medicines did not appear to have been affected negatively by the introduction of user fees.

A financing model aimed at creating a sustainable source of funding was developed and made available for comment (see also page *164*).

Results

An overview of 2014 results for diagnostics and medicines is presented on the next pages.

WHO prequalification in numbers: **2014 results for diagnostics and medicines**

A participatory approach

Rotational posts:
Future partners in Member States

3	Rotational assessors for medicines completed a 3-month fellowship *(2)* From: Botswana, D.R. Congo, Uganda
2	Rotational inspectors completed a 4-month fellowship in the Prequalification Team – a "first" From: China, Uganda
12	Former rotational staff from eight countries were involved in collaborative registration (→page *136*)

Eligible products

Invitations for Expression of Interest (EoI) for prequalification of medicines:
Adapting to changing needs

6	Updated EoIs issued in 2014 *(3)* i.e. for: HIV-related products 2 Antimalarials 1 Reproductive health products 1 Active pharmaceutical ingredients (APIs) 2
32	HIV-related formulations added including 12 medicines to treat hepatitis B and C
7	Antimalarials for children re-specified according to input from the WHO malaria programme
3	Reproductive health products added: • Levonorgestrel intrauterine system for five years continuous use • Misoprostol 25 mcg tablet • Magnesium sulfate injection
8	APIs added: dolutegravir, clofazimine, linezolid, ribavirin, rifabutin, simeprevir, sofosbuvir, valgancyclovir Two APIs removed: didanosine, ofloxacin

Assessment

Diagnostics:
Building streamlined procedures

54	Technologies under assessment as at December 2014 (38 through the full procedure, 16 through the abbreviated procedure): HIV-related: 31 Hepatitis C-related: 11 Hepatitis B-related: 5 Malaria-related: 7
24	Inspections performed in 2014 with regulatory staff participation
20	Submissions under screening (as at December 2014)

Medicines:
A tried and tested approach

81	Dossiers for finished products under assessment (as at December 2014)
6	Joint assessment sessions ("Copenhagen sessions") held in 2014 Participation from regulatory authorities, including staff involved in collaborative registration
94	Inspections conducted in 2014 with participation of regulatory staff: Of finished product sites: 39 Of API sites: 32 Of contract research organizations: 11 Of quality control (QC) laboratories: 12
105	Invitations to submit an application for requalification sent to manufacturers, leading to: 73 submissions being assessed 29 products withdrawn by manufacturers 1 product cancelled by WHO. (2 invitations were awaiting a response.)

WHO prequalification in numbers: 2014 results for diagnostics and medicines (continued)

Lists of products and services

Prequalified medicines:
More choices for procurement

416	Medicines listed on WHO website *(4)* (as at 31 March 2015)
53	Medicines prequalified in 2014 "Firsts:" • Dexamethasone injection • Generic capreomycin injection • Azithromycin 250 mg tablets, • Dolutegravir tablets • Mifepristone tablets • Sulfadoxine/pyrimethamine + amodiaquine • Generic morphine tablets • First products manufactured in Egypt • First four Nigerian manufacturers comply with WHO-GMP "Firsts", 2015: Buprenorphine, oxytocine

Prequalified APIs:
More choices for manufacturers

78	APIs listed on WHO website *(5)* (as at 12 March 2015)
22	APIs prequalified in 2014 "Firsts": • Efavirenz • Levofloxacin • Pyronaridine • Zinc

Prequalified quality control laboratories:
Trusted partners in QC testing

38	Laboratories listed on WHO website *(6)* (as at 22 January 2015) WHO African Region: 8 WHO Region of the Americas: 7 WHO South-East Asia Region: 4 WHO European Region: 13 WHO Eastern Mediterranean Region: 2 WHO Western Pacific Region: 4
7	Laboratories prequalified in 2014

Prequalified IVDs:
Safe, well-performing diagnostics to guide prevention and treatment decisions

38	IVDs listed on WHO website *(7)* (as at 31 March 2015)
9	IVDs prequalified in 2014 HIV assays 6 Malaria rapid diagnostic tests 2 Hepatitis B (HbsAg) assay 1
3	"Firsts": • An IVD manufactured in India • An IVD manufactured in China • First product prequalified under the new streamlined process (a CD4 technology; assessment time: 81 days)
51	Clearing the backlog: Non-progressing applications closed or withdrawn in 2014

Bridging the gaps

Expert Review Panel (ERP):
Risk assessment for needed products that are not yet available as stringently assessed versions

Diagnostics: Pilot and Round 1 *(8)*

0	Technologies found acceptable in pilot (of 2 point-of-care HIV early infant diagnosis technologies assessed)
5	Technologies found acceptable for time-limited procurement in Round 1 (of 12 accepted for review) For any international procurement: 2 On a case-by-case basis: 3

Medicines *(9)*: Rounds 11 and 12

12	Products found acceptable for time-limited procurement including newer ARVs, paediatric anti-malarials, 2nd line tuberculosis products (of 64 products accepted for review)

WHO prequalification in numbers: 2014 results for medicines and diagnostics (continued)

Training and advocacy

Events for manufacturers and regulators:
Building capacity and awareness

>350	Participants attended the joint UNICEF/UNFPA/WHO meeting for manufacturers and suppliers *(10)* – record participation

Diagnostics, 2014:

19	IVD manufacturers incentivized to submit applications
6	IVD manufacturers reached in one-on-one meetings on their research and development activities
1	Training session held on diagnostics dossier screening and assessment

Medicines, 2014:

33	Events organized or co-organized
27	Technical assistance missions Manufacturers supported: 20 Countries of manufacture: 5 (China, India, Kenya, Nigeria, Pakistan)
1	Technical assistance project for Nigerian manufacturers *(11)*
6	National QC laboratories supported with technical assistance

Use of prequalified products in WHO Member States

Pharmacovigilance:
Monitoring medicines safety

10	Countries participated in inter-regional active surveillance training workshop
3	Gap assessments for tuberculosis-related products completed (D R Congo, Swaziland, Zanzibar)
5	National cohort event monitoring (CEM) databases set up

Use of prequalified products in WHO Member States (continued)

Collaborative registration of medicines:
Putting countries in the driving seat

23	Participating countries 19 African, 4 Eastern European
62	Marketing authorizations approved, listed on WHO website *(12)* + 55 submissions under review (as at 6 May 2015)
36	Marketing authorizations approved in 2014
93 days	Median time from information-sharing to registration (2014)

International procurement:
Rewarding investments in quality

US$ 399 million	Global Fund-financed prequalified medicines delivered in 2014 By category, million US$ (PQ only*) Antiretrovirals: 301 (43%) Antimalarials: 67 (100%) Anti-tuberculosis products 1st line: 11 (100%) 2nd line: 19 (82%) *PQ-only = not approved by a stringent regulatory authority
US$ 55.6 million	Global Fund-financed prequalified IVDs delivered in 2014 By category million US$: HIV RDT& EIA: 30.5 Malaria RDT: 12.5 HIV CD4 technologies: 7.1 HIV virological technologies: 5.6

Source: Global Fund Price and Quality Reporting (PQR) database. Global Fund-financed procurement represents a significant portion of internationally-funded procurement.

Conclusions

Driven by the stringent quality requirements of donors, WHO prequalification offers manufacturers a means of accessing markets for products that meet international quality norms and standards.

In 2014, prequalification of medicines succeeded in making efficient use of its tried and tested "generic" approach to assess the quality of a wide range of chemical medicines, building on the safety and efficacy assessment of innovator products carried out by stringent regulatory authorities. Through its highly participatory and collaborative activities WHO leveraged these well-established processes to increase the capacity of manufacturers and regulators to implement stringent quality standards for pharmaceutical products.

Quality assurance of diagnostic technologies presents more complex challenges. This product category is diverse and rapidly evolving, yet in many parts of the world, regulatory mechanisms for assessing diagnostics are very limited. WHO prequalification is playing a key role in international efforts to understand the markets and regulatory landscapes of needed diagnostic technologies for priority diseases, and to define stringent standards for their assessment and post-market surveillance in those countries where they are needed most.

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Norms and standards

Biotherapeutics and biosimilars

Advances in biotechnology have enabled scientists to produce biological medicinal products that provide new treatment options for a wide range of diseases, including life-threatening ones. However, these complex medicines are expensive to develop and produce, and their high cost potentially affects equitable access to them.

Biosimilars – products that are very similar to already approved biotherapeutic products – could make this new generation of medicines available more widely at a more affordable cost to health systems. This article describes some recent developments in global efforts to create regulatory pathways and naming systems for biotherapeutics, including biosimilars.

Biotherapeutic products

New technologies have made it possible to produce large quantities of medicines that are derived from living systems. Biotherapeutic medicines can now be produced in large quantities in bacteria, yeast, transformed cell lines of mammalian origin (including human origin), insect and plant cells, as well as transgenic animals and plants. In most cases this is done by using genetically modified cells, which are engineered to produce the desired proteins.

Some biotherapeutics are proteins that are naturally present in the human body, such as growth hormones, insulin, erythropoietins, enzymes or antibodies. Others are biologically active proteins that do not exist in nature and are produced by techniques such as recombinant deoxyribonucleic acid (rDNA) technology. Examples include chimeric, humanized or fully human monoclonal antibodies, antibody-related proteins or fusion proteins. These substances can treat a wide range of diseases, including various forms of cancer, heart attacks, stroke, diabetes, rheumatoid arthritis, multiple sclerosis, hepatitis C, chronic renal failure, anaemia, low white blood cell counts, inflammatory bowel disease and others.

Biotherapeutics are more complex than chemical medicines and are therefore more challenging and more expensive to develop and produce. Often they are initially approved for an indication while they are being studied further, and the licence is subsequently modified to approve additional uses as new clinical data become available. Biotherapeutics also present special safety challenges because they are immunogenic, meaning that they are recognized as foreign proteins in the body and can trigger unwanted immune reactions.

Medicines of the future

Recognizing that biotherapeutics provide new treatment options to save lives and restore health, the 67th World Health Assembly adopted a resolution on access to biotherapeutics *(1)*, calling for effective regulation and equitable access. This is a timely call, considering the speed at

which the markets for new generation of medicines are evolving. According to a recent report *(2)* biologic medicines accounted for 27% of pharmaceutical sales in Europe at the end of 2013, with a year-on-year growth almost three times that of the pharmaceutical sales value as a whole, and with patents for many top-selling biologicals expiring or due to expire by 2020.

Biosimilars

The expiry of patents and/or data protection for the first major group of originator's biotherapeutics has ushered in an era of products that are designed to be "similar" to a licensed originator product. These products rely for their licensing partly on existing information regarding safety and efficacy obtained with the originator products. Biosimilars – also called "similar biotherapeutic products", "follow-on biological products" or "subsequent entry biologics" in different regulatory systems – can bring down the cost of medicines by increasing competition and can thus increase patient access. A similar development was seen in recent decades with generic versions of chemical medicines.

Biosimilars are not generics

Although the market aspects appear similar, there are important differences between generics and biosimilars. While generics are exact copies of the chemical structures of their reference products, biosimilars are highly complex molecules produced in living systems with inherent variability. By definition they will not be identical to their biotherapeutic reference products. This has implications for regulatory assessment.

For generics, regulatory safety and efficacy assessment relies on a relatively simple premise: If a generic is shown to be bioequivalent (distributed in the body at the same rate as the reference product) then it can be assumed to be equally safe and effective as the reference product, and it will be interchangeable with the latter, meaning that it can be substituted or switched without consulting the prescriber.

For biosimilars – which are not identical to the biotherapeutic reference product – the 'generic' approach by demonstration of bioequivalence is not sufficient to ensure adequate development, regulatory assessment and licensing. More sophisticated scientific approaches are required to compare a biosimilar with its reference product based on both non-clinical and clinical data. Tailor-made studies are needed for each biosimilar to define the degree of difference from its reference product, and to determine whether it is interchangeable with the reference product and whether its efficacy, safety, immunogenicity and interchangeability can be assumed ("extrapolated") for a different indication or in a different population than that studied.

Regulation of biosimilars

WHO guidance

WHO provided guidance on biosimilars in 2009 *(3)*. The guidance text is a "living document" to be developed further in line with advances in scientific knowledge and experience.

WHA Resolution 67.21 calls for an update of the WHO guidance text, taking into account the technological advances for the characterization of biotherapeutics and considering national regulatory needs and capacities. The 2014 International Conference of Drug Regulatory Authorities (ICDRA) adopted a number of recommendations on biotherapeutics

and biosimilars *(4)*, identifying some areas to develop further in the WHO guidance. These include: extrapolation of indication, special considerations for evaluation of monoclonal antibodies, acceptance criteria and evaluation of reference biotherapeutic products including the reliance on reference agencies, and the design, conduct and interpretation of studies to evaluate comparability.

At its 65th meeting the WHO Expert Committee on Biological Standardization decided to initiate an update of the WHO biosimilars guidance and to implement recommendations from the 16th ICDRA meeting on biotherapeutics including biosimilars *(5)*.

National requirements

While WHO provides norms and standards, national regulatory oversight is what ensures the quality, safety and efficacy of biotherapeutic products. Countries need efficient pathways to approve clinical trials and biotherapeutic products. Once products are on the market, effective pharmacovigilance systems are needed to track adverse events, including unwanted immune reactions.

National regulations on biosimilars have evolved in the last decade. The European Medicines Agency (EMA) published its first regulations for biosimilars in 2005, and on 1st June 2015 there were 19 biosimilars listed on the EMA website[1]. Biosimilars regulations based on EMA and/or WHO guidelines have been introduced in a number of countries, with some adaptations to suit the national context, for example to lower the barriers of clinical trial requirements or to accept reference products that are not licenced domestically.

In the United States a pathway for approval of biosimilars was put into place after the signing of the Biologics Price Competition and Innovation Act on 23 March 2010 by President Barack Obama. The FDA's biosimilars regulation guideline came into force in 2014, and in March 2015 the first biosimilar was approved under the new guidance *(6)*. In September 2014 the FDA published the first edition of its "Purple Book", a set of lists of licensed biological products.

Going forward, WHO guidelines will provide a valuable reference for establishing new national regulatory requirements or updating existing ones, and for promoting convergence at the global level to enable regulatory cooperation.

Naming of biosimilars

Naming of biotherapeutics and biosimilars has important implications for a range of stakeholders including regulators, the pharmaceutical industry, health systems, health professionals and patients.

Different naming systems for biosimilars are currently in use in countries. Some regulatory authorities have been using the International Nonproprietary Name (INN), while others have added a qualifier which in some cases incorporates the company name. To complicate matters further, a product may be viewed as a biosimilar to a given reference product in some jurisdictions but not others.

Various arguments have been voiced for and against giving distinct names to biosimilars. Those in favour argue that each biosimilar differs from its reference product and from other biosimilars, and that distinct names will make it easier to know which product a patient is receiving, to ensure correct use and to track adverse events. Those against reason that by

[1] www.ema.europa.eu – Find medicine – Human Medicine – (browse by type): Biosimilars

definition biosimilars are highly similar to the reference product with no clinically meaningful differences, and that a common name is therefore sufficient and will help to limit marketing costs, making products more affordable for health systems.

Following requests from several drug regulatory authorities the WHO INN Programme has proposed a Biological Qualifier scheme *(7)*, which is currently under discussion. Recognizing the value of regulatory convergence as a tool to increase global access to safe, effective, quality biosimilars, participants to the 16th ICDRA recommended that a clear terminology should be defined for naming these products, enabling a clear identification of the evaluation pathway *(4)*.

Systems in countries are meanwhile evolving. A placeholder non-proprietary name was assigned to the first biosimilar approved in the United States through the new abbreviated regulatory pathway for biosimilars *(6)*, and in Australia an interim system for naming of biosimilars has been proposed given that the WHO proposal has superseded the previous position on which the national naming policy was based *(8)*.

Conclusion

Ensuring regulation of biotherapeutic products in WHO Member States along globally consistent principles is an urgent matter with significant public health impact. Information and education of all stakeholders will also be crucial, as doctors' and patients' perceptions of biosimilar medicines, local pricing and reimbursement regulations and procurement policies and terms will all influence equitable access to biotherapeutics.

Implementation of WHO standards for biologicals is recognized as having a great value from a stakeholders' perspective. WHO envisages a comprehensive review of the current concept of biological standards and their use, starting with standards for biotherapeutic products, including biosimilars, in 2015. However, the scope of work and required resources to cover the continuously growing expectations exceed the current capacity of the Organization's Secretariat. Discussions will continue at WHO to plan this work and to identify a new funding strategy.

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4 16th International Conference of Drug Regulatory Authorities (ICDRA). WHO Drug Information. 2014; 28(3): 297-306.

5 WHO Expert Committee on Biological Standardization. Main outcomes of the meeting held from 13–17 October 2014.

6 U.S. Food and Drug Administration. FDA approves first biosimilar product Zarxio. [News release]. 6 March 2015. (See also page *157*.)

7 WHO Programme on International Nonproprietary Names (INN). Biological Qualifier. An INN Proposal. INN Working Doc. 14.342. Revised draft July 2014.

8 Therapeutic Goods Administration. Evaluation of biosimilars. [Web page]. 20 April 2015. (See also page *153*.)

Safety news

Restrictions

Bromhexine: not to be used in children under six in New Zealand

New Zealand – Following international reports of rare but serious allergic reactions (including anaphylaxis and severe skin reactions) associated with the use of bromhexine, the regulatory authority of New Zealand, Medsafe, has recommended that bromhexine-containing medicines to treat cough and cold symptoms should only be used in adults and children six years of age and over as there is not enough evidence to support their use in younger age groups.

In February 2015, the EMA had warned about these risks and had recommended that they should be included in product information of bromhexine and ambroxol (the active metabolite of bromhexine).

► Medsafe Safety information, 29 April 2015.

Codeine for cough and cold: not to be used in children under 12

European Union – The European Medicines Agency (EMA) has concluded its review of codeine-containing cough and cold medicines in children and has recommended further restrictions to minimize the risk of morphine-induced side effects, such as breathing problems, that occur due to the conversion of codeine into morphine in the body.

Codeine should never be used in children below 12 years. Its use to relieve cough and cold is not recommended in children and adolescents between 12 and 18 years who have problems with breathing. All liquid codeine medicines should be available in child-resistant containers to avoid accidental ingestion.

In 2013 the EMA had reviewed the risks and benefits of using codeine for pain relief in children, and had recommended similar restrictions. *(1)*

New Zealand – Medsafe has warned about the above-mentioned risks and has recommended to restrict the use of codeine-containing products for cough and cold symptoms to adults and children 12 years of age and over. *(2)*

► *(1)* EMA Press release, 24 April 2015.
(2) Medsafe Safety information, 29 April 2015.

Safety warnings

Sitagliptin: thrombocytopenia

Japan – The Pharmaceuticals and Medical Devices Agency (PMDA) has warned about cases of thrombocytopenia reported in patients treated with the anti-diabetic medicine sitagliptin hydrate (Glactiv®, Januvia®) in Japan, and has recommended to update the product information for these medicines. Patients should be monitored, and in case of abnormalities the drug should be discontinued and appropriate measures should be taken.

► PMDA Summary of investigation results and Revisions of precautions, 24 March 2015.

SGLT2 inhibitor diabetes medicines: ketoacidosis

United States of America – The U.S. Food and Drug Administration (FDA) has warned that serious cases of ketoacidosis have been reported in the United States in patients treated with the sodium-glucose cotransporter-2 (SGLT2) inhibitors canagliflozin, dapagliflozin, and empagliflozin. These medicines are approved to treat type-2 diabetes and are available as single-ingredient products and in combination with other diabetes medicines such as metformin. The FDA is investigating whether changes are needed in the prescribing information for these products.

Patients taking SGLT2 inhibitors who have symptoms of ketoacidosis (difficulty breathing, nausea, vomiting, abdominal pain, confusion, unusual fatigue or sleepiness) should be evaluated. If ketoacidosis is confirmed, health professionals should discontinue the SGLT2 inhibitors and take appropriate measures to correct the acidosis and monitor blood sugar levels.

► FDA Safety announcement, 5 May 2015.

Hepatitis C drugs and amiodarone: symptomatic bradycardia

United States of America – Following reports of symptomatic bradycardia in patients taking hepatitis C medicines and the antiarrhythmic drug amiodarone, the FDA has warned that serious slowing of the heart rate can occur when amiodarone is taken together with either ledipasvir/sofosbuvir (Harvoni®) or with sofosbuvir (Sovaldi®) and another direct acting antiviral, such as the investigational drug daclatasvir or simeprevir (Olysio®). Where alternative treatment options are unavailable, the FDA recommends heart rate monitoring in an inpatient hospital setting for the first 48 hours, followed by daily monitoring by a doctor or the patient during at least the first two weeks of treatment.

Warnings have been added to the product information and patient leaflet for ledipasvir/sofosbuvir and for simeprevir. The FDA will continue to monitor the risk and investigate the reason for the adverse events. *(1)*

Canada – Health Canada has warned that postmarketing cases of symptomatic bradycardia, including two cases that occurred in Canada, have been reported in patients taking amiodarone with the above-mentioned hepatitis C products. Co-administration of amiodarone with Harvoni™ or Sovaldi® in combination with another direct-acting antiviral is not recommended.

The regulatory authority is working with the manufacturer to update the product monographs for Harvoni™ and Sovaldi® to reflect this new information. *(2)*

European Union – An EMA review conducted as a result of a safety signal has confirmed a risk of severe bradycardia or heart block when sofosbuvir with ledipasvir (Harvoni®) or a combination of sofosbuvir (Sovaldi®) and daclatasvir (Daklinza®) are used in patients who are also taking amiodarone.

To manage this risk the EMA recommends that in patients taking these hepatitis C medicines amiodarone should only be used if other antiarrhythmics cannot be given, and only with close monitoring. Due to the long half-life of amiodarone monitoring is also needed in patients starting such hepatitis C

treatments within a few months of stopping amiodarone. *(3)*

► *(1)* FDA Safety Announcement, 24 March 2015.

(2) Health Canada Advisory, 2 April 2015.

(3) EMA Press release, 24 April 2015.

Asunaprevir and daclatasvir: erythema multiforme

Japan – The PMDA has warned that cases of erythema multiforme have been reported in patients treated concomitantly with daclatasvir (Daklinza®) and asunaprevir (Sunvepra®) in Japan. The two products are approved in Japan for improvement of viraemia in patients with serogroup 1 (genotype I) chronic hepatitis C or compensated cirrhosis type C. Product information for both products will be updated to include this information.

► PMDA Summary of investigation results and Revisions of precautions, 23 April 2015.

Fingolimod: progressive multifocal leukoencephalopathy

United Kingdom – The marketing authorization holder, in agreement with the EMA and Medicines and Healthcare Products Regulatory Agency (MHRA), has warned health professionals to be vigilant for the risk of progressive multifocal leukoencephalopathy (PML) in patients treated with fingolimod. The medicine should be permanently discontinued if PML is confirmed.

This follows the first reported case, in February 2015, of PML in a multiple sclerosis patient taking fingolimod (Gilenya®) without previous treatment with natalizumab or other immunosuppressive medicines. PML was suspected on a routine brain MRI scan and confirmed by positive JC virus DNA in cerebrospinal fluid using quantitative PCR. Fingolimod was stopped immediately upon confirmation of PML, and no signs or symptoms of PML had appeared at the time of communication.

PML is a rare and serious brain disease caused by reactivation of the JC virus in patients with a weakened immune system. The risk of PML with fingolimod is being evaluated further.

► Drug Safety Update volume 8 issue 10 May 2015: 4.

Letter to health professionals, 29 April 2015.

Pomalidomide: risks of cardiac failure, interstitial lung disease and hepatotoxicity

United Kingdom – The MHRA has issued new monitoring instructions for pomalidomide (Imnovid®), used to treat relapsed and refractory multiple myeloma. This follows an EMA review which identified cardiac failure and interstitial lung disease as common side effects of this medicine (affecting up to one in 10 patients), while serious liver damage was found to be uncommon (affecting up to one in 100 patients).

Cardiac failure occurred mostly in patients with cardiac disease or cardiac risk factors. Pomalidomide should be used with caution in these patients, and they should be monitored for signs and symptoms of heart failure.

Interstitial lung disease typically started within six months of starting treatment, but took as long as 18 months to appear in some cases. Health professionals should carefully assess patients with any new or worsening respiratory symptoms and stop pomalidomide during assessment. If interstitial lung disease is confirmed, it should be treated appropriately and pomalidomide should only be resumed

after a thorough evaluation of the benefits and risks.

Serious hepatotoxicity manifested mainly as acute hepatitis. Regular liver function monitoring is recommended during the first six months of treatment, when this risk appears to be highest. Insufficient data are available to support specific guidance on monitoring frequency.

► MHRA Drug safety update, 20 May 2015.

High-dose ibuprofen and dexibuprofen: cardiovascular risks

European Union – The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has completed a review confirming a small increase in the risk of cardiovascular problems, such as heart attacks and strokes, in patients taking high doses of ibuprofen (2400 mg or more per day). No increase in cardiovascular risk is seen with ibuprofen at doses up to 1200 mg per day.

The PRAC recommends to avoid doses of 2400 mg of ibuprofen per day or higher in patients with serious underlying heart or circulatory conditions and in those who have previously had a heart attack or stroke, and to assess a patient's cardiovascular risk factors before initiating long-term treatment with ibuprofen, particularly at high doses.

Data from laboratory studies further indicate that ibuprofen reduces the anti-clotting effects of aspirin. In clinical practice, occasional use of ibuprofen should not be a problem; however its long-term use may affect the benefits of low-dose aspirin in preventing heart attacks and strokes.

The above findings and recommendations also apply to dexibuprofen, with 1200 mg or more per day being considered a high dose. Updated information will be included in product information for both medicines. *(1)*

Canada – A Health Canada safety review found that oral ibuprofen taken at doses of 2400 mg per day or more increases the risk of heart attack and stroke to levels similar to those seen with COX-2 inhibitors and diclofenac.

Prescription oral ibuprofen products in Canada have a maximum recommended daily dose of 2400 mg and are authorized to relieve the pain and inflammation of rheumatoid arthritis and osteoarthritis. The prescribing information will be updated to warn that doses of 2400 mg per day should not be used in patients who have a history of heart disease and stroke, or who have cardiovascular risk factors such as smoking, diabetes, high blood pressure, high blood cholesterol or a strong family history of cardiovascular disease.

The review found no evidence of an increased cardiovascular risk with over-the-counter ibuprofen products if they are used as directed, i.e. at a maximum daily dose of 1200 mg for no more than seven days. *(2)*

► *(1)* EMA Press release, 13 April 2015.

(2) Health Canada Information update, 23 April 2015.

ADHD medicines: risk of suicidal thoughts in certain patients

Canada – Following reports of suicide-related events in patients treated with Attention Deficit Hyperactivity Disorder (ADHD) medicines, Health Canada has revised the prescribing information for methylphenidate, amphetamines and guanfacin-containing ADHD products available on the Canadian market. For the ADHD drug atomoxetin (Strattera®)

the risk was already known and communicated in 2005.

Health Canada considers that although these medicines may contribute to suicidal thoughts in certain patients, the benefits of treatment continue to outweigh the risks. Health professionals should take psychiatric disorders into account when prescribing these medicines and should monitor each patient's psychological state during treatment.

► Health Canada Information update, 30 March 2015.

Varenicline: potential alcohol interaction and other effects

United States of America – The FDA is warning that the smoking cessation medicine varenicline (Chantix®) can change the way in which people react to alcohol. In addition, rare accounts of seizures in patients treated with varenicline have been reported. The FDA has approved changes to the product information to warn about these risks. Until patients know how varenicline affects their ability to tolerate alcohol, they should decrease the amount of alcohol they drink. Patients taking varenicline who have a seizure should stop the medicine and seek medical attention immediately.

Studies have been undertaken to investigate the risk of serious neuropsychiatric side effects of varenicline. The FDA will update the public when the outcomes become available.

► FDA Drug safety communication, 9 March 2015.

Rebamipide: adverse effects on the eye

Japan – The PMDA has reported that lacrimal duct obstruction and dacryocystitis have been observed in Japan in patients treated with rebamipide (Mucosta®), an ophthalmic solution used to treat dry eyes. Product information will be updated to recommend patient monitoring, with discontinuation of the medicine and appropriate measures in case of any abnormalities.

► PMDA Summary of investigation results and Revisions of precautions, 24 March 2015.

Known risks

Ferumoxytol: strengthened warnings

United States of America – The FDA has strengthened an existing warning that serious, potentially fatal allergic reactions can occur with the intravenous iron replacement product ferumoxytol (Feraheme®). The product now carries a Boxed Warning about these serious risks, and is contraindicated in patients with a history of hypersensitivity to any intravenous iron product. In other patients it should only be used if the benefits outweigh the risks, and should be administered by infusion over at least 15 minutes with appropriate dilution. *(1)*

In July 2014 an EMA review of ferumoxytol had come to similar conclusions. *(2)*

► *(1)* FDA Drug safety communication, 30 March 2015.

(2) EMA News, 11 July 2014.

Triamcinolone acetonide: tendon rupture

Japan –The PMDA has reported that cases of tendon rupture have observed in patients treated with injectable triamcinolone acetonide (Kenacort-A®) in

Japan. Product information in Japan will be updated to reflect this risk. *(1)*

These observations confirm the risk reflected in approved product information in Europe *(2)*, which carry a warning that repeated injection of this medicine into inflamed tendons should be avoided as it has been shown to cause tendon rupture.

► *(1)* PMDA Summary of investigation results and Revisions of precautions, 24 March 2015.

(2) Example: www.medicines.org.uk/emc/medicine/6392

Cyclophosphamide: rhabdomyolysis

Japan – Following reports of rhabdomyolysis in patients treated with the antineoplastic agent cyclophosphamide hydrate (Endoxan®) in Japan, the PMDA has recommended to update the product information for oral and injectable products. Signs of rhabdomyolysis include myalgia, feelings of weakness, increased creatine kinase (creatine phosphokinase), increased blood myoglobin, and increased urine myoglobin. If rhabdomyolysis occurs, the medicine should be stopped and appropriate measures taken. *(1)*

Approved product information for cyclophosphamide in the United Kingdom *(2)* includes rhabdomyolysis as a very rare adverse event.

► *(1)* PMDA Summary of investigation results and Revisions of precautions, 24 March 2015.

(2) Example: www.medicines.org.uk/emc/medicine/29592

Panitumumab: Stevens-Johnson syndrome

Japan – Following reports of adverse events suggestive of Stevens–Johnson syndrome in patients treated with panitumumab (Vectibix®) in Japan and elsewhere, approved product information in Japan has been revised to include this risk. *(1)*

EMA-approved product information for panitumumab *(2)* lists Stevens-Johnson syndrome and toxic epidermal necrolysis rare adverse events, occurring in one of 1001-10000 patients treated.

► *(1)* PMDA Summary of investigation results and Revisions of precautions, 24 March 2015.

(2) EMA. Vectibix : EPAR - Product Information. Last updated 2 March 2015.

Pazopanib: retinal detachment

Japan – Following reports of retinal detachment in patients treated with the antineoplastic agent pazopanib (Votrient®) in Japan and elsewhere, the PMDA has recommended to add information about this adverse event to product information approved in Japan. If possible signs such as eye floaters, photopsia, visual field defect or reduced visual acuity are observed, ophthalmologic examination should be performed and appropriate measures taken. *(1)*

EMA-approved product information for pazopanib *(2)* includes this adverse effect as uncommon, occurring in one of 101-1000 patients treated.

► *(1)* PMDA Summary of investigation results and Revisions of precautions, 24 March 2015.

(2) EMA. Votrient : EPAR - Product Information. Last updated 9 February 2015.

Zoledronic acid: further measures to minimize risk of osteonecrosis of the jaw

European Union – The EMA has completed a periodic review of zoledronic acid (Aclasta®), one of the bisphosphonate medicines with a known risk of osteonecrosis of the jaw. Although the risk is very low, the EMA has recommended to update the product information and to introduce a patient reminder card to minimize this risk.

Patients should highlight any dental problems to their doctor before starting treatment, ensure good dental hygiene during treatment, inform their dentist that they are being treated with zoledronic acid, and contact the doctor and dentist if any problems with the mouth or teeth occur during treatment.

The risk also exists with other medicines used for osteoporosis and other conditions that affect the bones, such as other bisphosphonates and denosumab. Similar revisions will be considered as part of periodic reviews during 2015 and 2016.

► EMA Press release, 27 March 2015.

Duloxetine: neuroleptic malignant syndrome

Japan – The PMDA has warned about neuroleptic malignant syndrome having occurred in patients treated with duloxetine (Cymbalta®) in Japan, and has recommended to update the product information.

In 2006 the FDA had warned about the risk of a potentially life-threatening serotonin syndrome with serotonin noradrenaline reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs), particularly with concomitant use of certain other nervous system drugs.

► *(1)* PMDA Summary of investigation results and Revisions of precautions, 23 April 2015.

(2) FDA Alert [7/2006]: Potentially Life-Threatening Serotonin Syndrome with Combined Use of SSRIs or SNRIs and Triptan Medications. Web page last updated 14 July 2013.

Unchanged recommendations

Rotavirus vaccine: benefits outweigh risks

Geneva – The Global Advisory Committee on Vaccine Safety has issued a statement to affirm that the safety profile of current rotavirus vaccines is acceptable, with the benefits of vaccination greatly exceeding risks.

This follows reported cases of intussusception in multiple countries for the two most widely used vaccines to prevent rotavirus gastroenteritis in young infants globally. The findings underscore the importance of close monitoring of infants and prompt medical care after vaccination. If recognized and treated early, intussusception generally has a good outcome and is rarely fatal.

The benefits of rotavirus vaccination are particularly important in resource-poor countries where rotavirus disease remains an important cause of mortality among young children.

► WHO Essential medicines and health products. News, 11 May 2015.

Natalizumab: no definite link with melanoma

Australia – The Therapeutic Goods Administration (TGA) has concluded its review of the immunosuppressant

medicine natalizumab (Tysabri®), and has found insufficient evidence of a definite link between this medicine and melanoma.

Natalizumab is used to treat patients with relapsing-remitting multiple sclerosis. Given the high incidence of melanoma in Australia, the TGA will continue to monitor this issue. Health professionals should ensure that any new or changed suspicious skin lesions in patients treated with natalizumab are promptly detected and investigated.

► TGA Monitoring communication, 21 May 2015.

Olanzapine: inconclusive findings after two deaths in 2013

United States of America – Following the deaths of two patients in 2013 after injection of appropriate doses of olanzapine pamoate (Zyprexa Relprevv®), the FDA's study to determine the causes has ended with inconclusive results. It is possible that the deaths were caused by rapid but delayed entry of the drug into the bloodstream following intramuscular injection, and that the high drug levels found in the two patients' blood occurred after death.

On the basis of all of the information reviewed, the FDA is not recommending any changes to the prescribing or use of olanzapine. Health care professionals are reminded to follow the requirements of the Risk Evaluation and Mitigation Strategy (REMS) for the product.

► FDA Safety announcement, 23 March 2015.

Safety reviews started

Medicine	Use	Concerns	Reviewing authority reference
Natalizumab (Tysabri®)	Treatment of multiple sclerosis	Possible need to revise advice on managing the risk of progressive multifocal leukoencephalopathy	► EMA News, 8 May 2015.
Inhaled corticosteroids	Treatment of chronic obstructive pulmonary disease (COPD)	Need to evaluate the known risk of pneumonia when these medicines are used for COPD	as above
Crizotinib (Xalkori®)	Treatment of certain types of lung cancer	Possible risk of cardiac failure	► PMDA risk communication, 8 May 2015.
Technetium (^{99}m Tc) injection (Clearbone®)	Scintigraphy	Possible risk of shock and anaphylaxis	as above

Data integrity concerns

GVK Biosciences: EMA confirms suspension of products over flawed studies

European Union – The EMA has confirmed its January 2015 recommendation to suspend a number of medicines for which authorization in the EU was primarily based on clinical studies conducted at GVK Biosciences in Hyderabad, India. This is the outcome of a re-examination requested by marketing authorization holders for seven of the medicines concerned.

Around 700 pharmaceutical forms and strengths of medicines studied at the Hyderabad site remain recommended for suspension, while for around 300 others, including one included in the re-examination, sufficient supporting data from other sources had been provided. An updated list of medicines recommended for suspension is available on the EMA website. Some of these may remain on the market in countries where they are of critical importance to meet patients' needs; as decided by the national authorities of the respective EU Member State. For medicines that are considered critical, companies are given 12 months to submit additional data.

► EMA Press release, 22 May 2015.

Hospira S.P.A: Health Canada restrict imports

Canada – Health Canada has restricted the importation of medicines from Hospira S.P.A. in Liscate, Italy, due to data integrity concerns raised by a trusted regulatory partner about the reliability of the laboratory data generated at this site.

The Canadian import licences for medicines from this facility are being amended to require independent third-party testing against the approved Canadian specifications prior to release of any medically necessary products. Products that are not on the medically necessary list will not be imported or released to the Canadian market until Health Canada is satisfied that the data integrity issues have been addressed. A list of affected products is available on the authority's web site, and updates will be provided through the online Inspection Tracker.

► Health Canada Advisory information update, 12 June 2015 (with subsequent updates).

Zhejiang Hisun Pharma, Polydrug Laboratories: Health Canada recommends voluntary quarantine

Canada – Health Canada has requested that Canadian importers voluntarily quarantine drug products with active pharmaceutical ingredients (APIs) manufactured or tested by Zhejiang Hisun Pharma Company Ltd., in Zhejiang, China *(1)* as well as those manufactured or tested by Polydrug Laboratories, in Ambarnath, Maharashtra, India *(2)*, due to data integrity concerns.

No risk to health has been identified, and Health Canada is not requesting a recall of any products. The authority is providing updates on the situation through its Inspection Tracker.

► *(1)* Health Canada Advisory information, 16 June 2015.

(2) Health Canada Advisory information, 24 June 2015.

Falsified product alert

Falsified meningitis vaccines circulating in West Africa

WHO has published a medical product alert relating to the confirmed circulation of falsified versions of meningitis vaccines in Niger. Following a report submitted to the WHO Surveillance and monitoring system for substandard and falsified medical products by the focal point within the Niger Regulatory Authority, increased vigilance is requested for the following lots/batches of vaccines and solvents.

- Product: **Mencevax ACW**
  Batch number: AMENA020AA; manufacturing date: 12-2014, expiry date: 11-2017
  The batch number is genuine but the manufacturing and expiry dates are false. The genuine version of this batch expired in 2011. The product contains 50 doses per vial.
- Product: **Mencevax ACWY**
  Batch number: AMEHA020AA; manufacturing date: 12-2013, expiry date: 11-2016
  The batch number, manufacturing date and expiry date for this product are false. This falsified product contains 50 doses per vial.
- Product: **Diluent for Mencevax**
  Batch number: A003B128AA; manufacturing date: 02-2013, expiry date: 01-2019
  The batch number, manufacturing date and expiry date for this diluent are false. This falsified product contains 50 doses of diluent.
- Product: **Menomune ACY-W135**; batch number: UH 301AA; expiry date: 29 APR 17
  The batch number is genuine but the expiry date is false. The genuine version of this batch of vaccine expired in 2014. This falsified product contains 10 doses per vial.
- Product: **Menomune ACYW-135**; batch number: UH 301AA; expiry date: 28 FEB 16
  The batch number is genuine but the expiry date is false. The genuine version of this batch of vaccine expired in 2014. This falsified product contains 10 doses per vial.
- Product: **Menomune ACYW-135**; batch number: UH299AA; expiry date: 28 FEB 16
  The batch number is genuine but the expiry date false. The genuine version of this batch of vaccine expired in 2014. This falsified product contains 10 doses per vial.
- Product: **Diluant for Menomune**; batch number: UH 262 AA; expiry date: 25 OCT 16
  The batch number is genuine but the expiry date false. The genuine version of this batch of diluant expires on 25 OCT 15. This falsified product contains sufficient solvent to reconstitute 10 doses of vaccine.
- Product: **Diluant for Menomune**; batch number: D0953-1; expiry date: 20-2017
  This is not a genuine batch number for a diluent for Menomune Vaccine. This falsified product contains sufficient solvent to reconstitute 10 doses of vaccine.

No serious adverse reactions linked to these batches of falsified vaccines have been reported at this stage. Genuine Mencevax is manufactured by GlaxoSmithKline (GSK), and genuine Menomune is manufactured by Sanofi Pasteur.

These falsified products have not yet been subject to laboratory analysis. The alert was issued on the basis of inconsistencies in the packaging material and confirmation from GSK and from Sanofi Pasteur that the batch numbers, manufacturing dates and expiry dates are inconsistent with the genuine product.

WHO advises increased vigilance within the supply chains of countries likely to be affected by these falsified products. It is necessary to ensure that vaccines are obtained from authentic and reliable sources. Ministry of Public Health / National medicines regulatory authorities are asked to immediately notify WHO via rapidalert@who.int if the above-mentioned batches are discovered in their countries.

▶ WHO Medical Product Alerts No. 2/2015, 22 May 2015 and 3/2015, 27 May 2015. (With photographs.)

WHO recognises the seriousness of the current meningitis outbreak in West Africa and the additional demand for meningitis vaccines. Further information concerning this outbreak is available at www.who.int/mediacentre/news/situation-assessments/meningitis-niger/en/.

Regulatory news

Assessment

Final FDA guidance on opioids with abuse-deterrent properties

United States of America – The FDA has issued its final guidance to assist industry in developing opioid drug products with potentially abuse-deterrent properties. The document explains the FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties. It makes recommendations about how such studies should be performed and evaluated, and discusses what labelling claims may be approved based on the study results.

This guidance does not address generic opioid products. The FDA is working on draft guidance in this area.

► FDA News release, 1 April 2015.

EMA scientific advice on clinical trials leads to faster approvals

European Union – An EMA analysis of marketing authorization application outcomes between 2008 and 2012 has found that companies that changed their clinical development plans in accordance with EMA recommendations were more likely to be granted a marketing authorization.

EMA, through its Scientific Advice Working Party (SAWP), provides scientific advice to applicants in designing clinical trials that are scientifically sound and generate adequate data for regulatory benefit-risk assessment. The analysis found that two out of three clinical trial designs submitted were inadequate, and that the success rate of applications with inadequate trials was half as high (41%) than that of applications with adequate trial designs (84%) or those changed according to SAWP recommendations (86%). The scientific advice thus leads to stronger applications from industry, and protects patients from participating in clinical trials that are unlikely to lead to the approval of new medicines.

► EMA News, 17 April 2015.

Generics information-sharing pilot extended

European Union – The EMA has informed applicants that the deadline for participation in the information-sharing pilot project for generics has been extended. Companies are encouraged to submit expressions of interest.

The European Medicines Agency (EMA) launched this project in January 2015 for centrally approved products as part of the International Generic Drug Regulators Pilot (IGDRP) programme. The pilot allows EMA to share its assessments of applications for generic medicines in real time with collaborating regulatory agencies in order to facilitate the timely authorization and availability of safe, effective and high quality generic medicines worldwide.

► EMA News, 21 April 2015.

Swissmedic News, 4 May 2015.

More information about IGDRP: The International Generic Drug Regulators Pilot. WHO Drug Information 28(1); 2014:3-10.

TGA reviews its guidance on evaluation of biosimilars

Australia – The Therapeutics Goods Administration (TGA) is reviewing its guidance on evaluation of biosimilars in light of a globally evolving understanding of biotherapeutics. In particular, an interim system for naming of biosimilars has been proposed, given that the WHO draft policy *Biological Qualifier - An INN Proposal*, published in July 2014, has superseded the previous position on which the TGA policy was based. The interim system will use the Australian biological name without a specific biosimilar identifier suffix. For example a biosimilar to the reference product Neupogen filgrastim would be named 'Tradename' filgrastim.

► TGA News, 20 April 2015.

Updated risk management plan format in Australia

Australia – The TGA has published its updated guideline on submission of risk management plans (RMPs) by companies, including a template for an Australian-specific Annex to RMPs.

An RMP outlines how safety concerns will be identified and mitigated once a pharmaceutical product is on the market to help ensure that the benefit-risk balance remains favourable. Submission of RMPs has been required in Australia since 2009 for all new chemical entities, as well as for already registered products when there is a major change in the way in which the product is used or if a new safety concern is identified.

► TGA News, 4 May 2015.

Transparency

WHO calls for disclosure of clinical trial results

Geneva – WHO has issued a public statement calling for the disclosure of results from clinical trials for medical products, whatever the result, to help all actors to set priorities for research and development as well as public health interventions. The call for disclosure includes older unreported clinical trials, the results of which may still have an important bearing on scientific research today.

WHO also reaffirms the need for all clinical trials to be registered on a WHO primary clinical trial registry so that they can be accessible through the International Clinical Trials Registry platform. This platform was established in response to a 2005 call by WHO. It regularly imports trial records from major national and regional clinical trial registries.

► WHO Note for the media, 14 April 2015.

Australia adopts new regulator performance framework

Australia – The Australian Government has developed a regulator performance framework comprising six outcomes-based key performance indicators (KPIs). The KPIs are supported by a series of qualitative and quantitative outputs and evidence, as developed in consultation with the TGA Industry Consultative Committee and the Australian Therapeutic Goods Advisory Council, to assess the TGA's achievements in the different areas of good regulatory performance.

► TGA key performance indicators and measures: Regulator Performance Framework. Version 1.0, May 2015. [web page]. 10 June 2015.

Databases

Health Canada launches searchable inspection database

Canada – Health Canada has launched its Drug and Health Product Inspections Database, a searchable web tool providing information on foreign and domestic inspections of pharmaceutical manufacturing sites conducted by Health Canada and abroad since 2012. This publicly available database brings together key data about drug establishments and inspection results, including detailed inspections report cards.

The new tool is a milestone under Health Canada's Regulatory Transparency and Openness Framework. Another useful tool under this framework is Health Canada's Inspection Tracker, which provides a snapshot of emerging issues identified through the inspection programme and the actions that the authority is taking.

► Health Canada News release, 13 April 2015.

WHO launches open access to its global medicines safety database

WHO has launched an open access platform to its database of suspected adverse reaction reports maintained by the Uppsala Monitoring Centre in Sweden. The platform, named VigiAccess, is a new web application that will allow anyone to access information on reported cases of adverse events related to over 150 000 medicines and vaccines, with more than ten million cases reported from over 120 countries.

By providing open access to this database, WHO aims to improve patient safety, increase transparency and encourage the reporting of adverse effects from medicinal products. The platform can be accessed at www.vigiaccess.org.

► WHO Essential medicines and health products. Media advisory, 17 April 2015.

EMA to record adverse events from literature in EudraVigilance

European Union – A new service offered by EMA is expected to improve safety monitoring of medicines and simplify pharmacovigilance activities for companies. In accordance with the European Union's (EU) pharmacovigilance legislation, the Agency will screen medical literature for 400 active substance groups and will enter identified reports of suspected adverse reactions into the the EU adverse drug reaction collection and management system, EudraVigilance. A list of the substances and scientific journals covered is available on the EMA website. The service will start on 1 July 2015 and will be fully rolled out in September 2015.

This initiative will benefit over 4 000 companies that will no longer need to enter suspected adverse reactions into EudraVigilance for the active substances and literature covered.

► EMA News, 12 May 2015.

Approved

Cholic acid for rare bile acid synthesis disorders

Product name: Cholbam®
Dosage form: Capsules
Class: Bile acid preparation
ATC code: A05AA03
Approval: FDA (rare paediatric disease priority review)
Use: Treatment of patients with bile acid synthesis disorders due to single enzyme defects, and patients with peroxisomal disorders (including Zellweger spectrum disorders)
Benefits: First approved treatment option for patients lacking cholic acid due to rare, genetic metabolic disorders. In children, if these conditions are not treated they will impair growth and can lead to life-threatening liver injury.

► FDA News release, 17 March 2015.

Eluxadoline for irritable bowel disease

Product name: Viberzi®
Dosage form: Tablets
Class: Mu-opioid receptor agonist
Approval: FDA
Use: Treatment of irritable bowel disease with diarrhoea in adults
Benefits: Additional treatment option for irritable bowel disease with diarrhoea
Safety information: Eluxadoline can cause spasm in the sphincter of Oddi, which can result in pancreatitis. Eluxadoline should not be used in patients with a history of bile duct obstruction, pancreatitis, severe liver impairment, or severe constipation, nor in patients who drink more than three alcoholic beverages per day.
Note: The FDA has also approved an extension of indications for rifaximin (Xifaxan®) to include treatment of irritable bowel disease in adults. Rifaximin, an antibiotic derived from rifampicin, was previously approved as treatment for travellers' diarrhoea caused by *E. coli* and for reduction of the risk in adult patients of recurring overt hepatic encephalopathy.

► FDA News release, 27 May 2015.

Empaglifozin & metformin for diabetes

Product name: Synjardy®
Dosage form: Film-coated tablets
Class: Fixed-dose combination of oral blood glucose lowering agents
ATC code: A10BD20
Approval: EMA
Use: Treatment of adults with type 2 diabetes mellitus as an adjunct to diet and exercise in patients inadequately controlled on other treatments.
Benefits: Clinically relevant improvement in glycaemic control compared with metformin on its own.

► EMA Summary of opinion, 26 March 2015.

Evolocumab to lower cholesterol

Product name: Repatha®
Dosage form: Solution for injection in a pre-filled syringe or in a pre-filled pen
Class: Lipid-lowering agent, monoclonal antibody, PCSK9 protein-blocker (first-in-class treatment)
ATC code: C10AX13
Approval: EMA
Use: Treatment of hypercholesterolaemia or mixed dyslipidaemia in adults, and treatment of homozygous familial hypercholesterolaemia in adults and adolescents. The effect of evolocumab on cardiovascular morbidity and mortality has not yet been determined.
Benefits: Reduces serum LDL-cholesterol levels in.patients who are unable to control their cholesterol with statins.
Safety information: The use of evolocumab may lead to very low cholesterol levels where safety has not yet been established.

► EMA Press release, 22 May 2015.

Approved

Isavuconazonium sulfate for certain invasive fungal infections

Product name: Cresemba®
Dosage form: Available in oral and intravenous formulations
Class: Azole antifungal agent
Approval: FDA (Qualified Infectious Disease Product designation)
Use: Treatment of invasive aspergillosis and invasive mucormycosis.
Benefits: Treatment option for two rare but serious fungal infections.
Safety information: Serious potential side effects include liver problems, infusion reactions and severe allergic and skin reactions.

▶ FDA News release, 6 March 2015.

Atazanavir & cobicistat for treatment of HIV-1 infection

Product name: Evotaz®
Dosage form: Fixed-dose combination tablets
Class: Antiretroviral
ATC code: J05AR15
Approval: EMA
Use: Treatment of HIV-1 infection in adults without known mutations associated with resistance to atazanavir
Benefits: sustainable virological suppression if given in combination with other antiretrovirals.

▶ EMA Summary of opinion, 21 May 2015.

Anthrax immunoglobulin (human)

Product name: Anthrasil®
Dosage form: Solution for intravenous injection
Class: Specific immunoglobulin
Approval: FDA
Use: Treatment of patients with inhalational anthrax in combination with appropriate antibacterial drugs
Benefits: The results of studies in research animals provided sufficient evidence that the product is reasonably likely to benefit humans with inhalational anthrax.
Note: Inhalational anthrax is a rare disease that can occur after exposure to infected animals or contaminated animal products, or as a result of an intentional release of anthrax spores. The product has been purchased for the U.S. Strategic National Stockpile. Its approval makes it available in an emergency without a prior emergency use authorization from the FDA.

▶ FDA News release, 25 March 2015.

Dinutuximab to prolong survival in children with high-risk neuroblastoma

Product name: Unituxin®
Dosage form: Injection
Class: Antineoplastic agent, monoclonal antibody; *ATC code:* L01XC16
Approval: FDA (priority review and orphan product designation); EMA (orphan designation)
Use: In combination with other drugs, first-line therapy for paediatric patients with high-risk neuroblastoma, a type of cancer that most often occurs in young children.
Benefits: First specific approved treatment to prolong survival in children with high-risk neuroblastoma
Safety information: Dinutuximab irritates nerve cells, causing severe pain that requires treatment with intravenous narcotics. Despite prophylaxis, two thirds of children experience pain and about 40% experience severe pain. The medicine can also cause nerve damage and life-threatening infusion reactions, and has some other serious side effects.

▶ FDA News release, 10 March 2015.
EMA Press release, 22 May 2015.

Filgrastim-sndz, first biosimilar in the U.S.

Placeholder nonproprietary name*: Filgrastim-sndz
Product name: Zarxio®
Dosage form: Solution for injection or infusion
Class: Immunostimulant, colony stimulating factor; *ATC code:* L03AA02
Reference product: Filgrastim (Neupogen®)
Approval: FDA
Use: To reduce the effects of neutropenia in patients with cancer receiving various types of chemotherapy or undergoing bone marrow transplantation and in patients with severe chronic neutropenia; to mobilize blood progenitor cells into the peripheral blood for collection and autologous therapy.
Benefits: Reduction of neutropenia
Note: This is the first biosimilar product approved in the U.S. through the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), which created an abbreviated regulatory pathway for biosimilars. Biosimilar filgrastim products have been marketed in various countries outside the U.S.

*A comprehensive naming policy for biosimilar and other biological products remains to be adopted. The FDA intends to issue draft guidance in the near future on how current and future biological products marketed in the U.S. should be named.

► FDA News release, 6 March 2015.

Tasimelteon to regulate sleep patterns in blind adults

Product name: Hetlioz®
Dosage form: Hard capsules
Class: Psycholeptic, melatonin receptor agonist; *ATC code:* N05CH03
Approval: EMA (orphan designation)
Use: Treatment of non-24-hour sleep-wake disorder in totally blind adults.
Benefits: Ability to entrain the master body clock in people who do not perceive light, and whose sleep-wake pattern is not synchronized with the 24-hour clock.

► EMA Press release, 24 April 2015.

Extensions of indications

Moxifloxacin for treatment of plague

Product name: (Avelox®)
Dosage form: Tablets
Class: Antibacterial, fluoroquinolone; *ATC code:* J01MA14
Approval: FDA
Newly approved use: Treatment of pneumonic plague and septicemic plague; prevention of plague in adult patients
Note: The approval was granted based on an animal study, as it would not have been feasible or ethical to conduct trials in humans.

► FDA News Release, 8 May 2015

Sirolimus for very rare lung disease

Product name: Rapamune®
Dosage forms: Tablet, oral solution
Class: Selective immunosuppressant; *ATC code:* L04AA10
Approval: FDA (breakthrough therapy, priority review; orphan product designation)
Newly approved use: Treatment of lymphangioleiomyomatosis (LAM), a rare, progressive lung disease that primarily affects women of childbearing age.
Safety information: Serious side effects including hypersensitivity and swelling (edema) have been observed in renal transplant patients.
Note: This is the first medicine approved in the U.S. to treat LAM.

► FDA News release, 28 May 2015.

Approved

Generic

Glatiramer acetate
A complex active ingredient

Reference product: Copaxone®
Dosage form: Injection
Class: Immunostimulant; *ATC code:* L03AX13
Approval: FDA
Use: Treatment of relapsing forms of multiple sclerosis
Note: The reference product is a copolymer mixture with inherent batch-to-batch variability. For this approval, FDA scientists therefore established a scientific approach for demonstrating that the active ingredient of the generic is the same as that of the reference product.

▶ FDA News release, 16 April 2015.

Early access

Pembrolizumab
Early access in the United Kingdom

Product name: Keytruda®
Dosage form: Powder for concentrate for solution for infusion
Class: antineoplastic; monoclonal PD-1 antibody. ATC code (temporary): L01XC18
Approval: EMA (previously approved in the U.S. in September 2014)
Use: Treatment of unresectable or metastatic melanoma
Benefits: Can slow the progression of cancer in a condition where other treatments currently have poor results.
Safety information: Pembrolizumab may be associated with side effects resulting from excessive activity of the immune system. Most will resolve following appropriate treatment or on stopping pembrolizumab.
Note: Pembrolizumab is the first medicine to be approved in the United Kingdom under the MHRA's Early Access to Medicines Scheme (EAMS), ahead of receiving a positive recommendation from EMA. The EAMS was introduced in 2014 to provide early access to new medicines in the United Kingdom for patients that have a high unmet clinical need. The scientific opinions issued under this Scheme describe the risks and benefits of the medicine and the context for its use, supporting the prescriber and the patient to make a decision on whether to use the medicine before its licence is approved.

▶ MHRA Announcement, 11 March 2015.
EMA Press release, 22 May 2015. ⬢

Publications and events

Global health

WHO publishes 2015 World Health Statistics

Geneva – WHO has published its 2015 *World Health Statistics*, assessing progress made in Member States towards health-related goals.

2015 is the final year for the United Nations' Millennium Development Goals (MDGs), which were set by governments in the year 2000. By the end of this year, if current trends continue, the world will have met global targets for turning around the epidemics of HIV, malaria and tuberculosis, and will have made substantial progress in reducing maternal and child deaths. However wide gaps persist between and within countries.

With regard to essential medicines the report shows that access is still limited, especially where drugs are not available in the public sector and where prices have increased as a result of increases in countries' wealth. [According to World Bank data, 73% of the world's poor today live in middle-income countries – Ed.]

Countries will decide on new global goals for 2030 at the UN General Assembly in September. Additional emerging challenges to tackle in the post-2015 agenda include the growing impact of noncommunicable diseases and the changing social and environmental determinants that affect health.

► WHO News, 13 May 2015.

Sixty-eighth World Health Assembly closes

Geneva – The Sixty-Eighth World Health Assembly, held on 18–26 May 2015 in Geneva, adopted a number of landmark resolutions and decisions, including an historic resolution on air pollution, the first global plan of action on antimicrobial resistance, a new global malaria strategy and decisions on the International Health Regulations.

In decisions stemming from the 2014 Ebola outbreak, the Assembly gave the go-ahead for structural reforms intended to enable WHO to respond effectively to future emergencies. A US$ 100-million contingency fund will be set up for in-field operations. Delegates appreciated Organization's key coordination role in supporting development of Ebola vaccines, diagnostics and medicines (see also pages *161*–*162*). They further requested WHO to continue helping countries to strengthen national health systems.

In other decisions related to medical products the Assembly agreed to improve access to sustainable supplies of affordable vaccines, to prepare the phased withdrawal of oral polio vaccines, to strengthen emergency and essential surgical care including access to safe anaesthetics such as ketamine (see also page *160*), and to postpone the review of the Member State mechanism to combat substandard, spurious, falsely labelled, falsified and counterfeit medical products until 2017.

► WHO Media centre. Sixty-eighth World Health Assembly [web page].

Access to medical products

WHO updates essential medicines lists

Geneva – WHO has published the 2015 editions of its *Model List of Essential Medicines* and its *Model List of Essential Medicines in Children*. Among the medicines that have been added are five new direct-acting oral antivirals to treat hepatitis C, 16 anti-cancer medicines and five anti-tuberculosis medicines, four of which – including bedaquiline and delamanide – target multi-drug resistant tuberculosis.

The essential medicines lists are updated every two years by a WHO Expert Committee, based on evaluations of the efficacy, safety and cost-effectiveness of the proposed medicines. As governments and institutions around the world are increasingly using the WHO list to guide the development of their own essential medicines lists, the changes could have enormous public health impact globally. This year, the Committee underscored the urgent need to take action to promote equitable access to several new highly effective medicines, some of which are currently too costly even for high-income countries.

► WHO News release, 8 May 2015.

Access to new medicines in Europe

Copenhagen – The WHO Regional Office for Europe has released a report on access to new medicines in Europe. The study features findings from 27 countries and explores different approaches that health authorities in European countries are using to deal with high spending on new medicines.

As the number of new medicines introduced in Europe rises, governments need novel policy approaches to evaluate the cost–effectiveness of new drugs and make informed public health choices. The report outlines possible policy directions and choices that may help governments to reduce high prices when introducing new drugs. The findings suggest that cooperation and transparency are the best tools to ensure equitable pricing and access.

► WHO Regional Office for Europe. Press release, 26 March 2015.

Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research. Copenhagen, WHO Regional Office for Europe, 2015.

Ketamine not to be placed under international control

Vienna – During its 58th Session held on 9–17 March 2015 in Vienna, the United Nations Commission on Narcotic Drugs (CND) deferred action on the scheduling of ketamine as an internationally controlled substance.

Ketamine is a widely used anaesthetic included in the WHO essential medicines list. The Government of China postponed its proposal to include ketamine in a Schedule under the 1971 Convention on Psychotropic Substances and suggested that more information should be gathered. WHO and a number of governments welcomed China's decision, seeing that international controls would limit access to a needed medicine especially in the developing world, and that countries can impose national controls to minimize abuse and trafficking.

► Live reporting from the 58th Session of the Commission on Narcotic Drugs and its Special Segment on the 2016 UNGASS. 13 March 2015.

Medicines quality

Falsified antimalarials less common than previously thought

Two studies of antimalarial drug quality conducted in Cambodia and Tanzania found no evidence of falsified medicines in either country. Previous reports had suggested that up to one third of antimalarials could be falsified. However, substandard drugs were found in 31% of samples in Cambodia and in 12% of samples in Tanzania. The results highlight the need to strengthen regulatory systems, enabling them to carry out effective routine surveillance.

In Tanzania, one fourth of 1 737 samples analyzed were WHO-prequalified, and these were less likely to be of poor quality than those not prequalified.

These are the first published results from the ACT Consortium's drug quality programme, which analyzed over 10 000 samples from malaria-endemic countries over five years. The studies were funded by the Bill & Melinda Gates Foundation; the Cambodia study also received support from the UK Department for International Development. Results from Nigeria, Equatorial Guinea, Ghana and Rwanda will be published in the next few months.

► London School of Hygiene and Tropical Medicine, News. 20 April 2015.

Ebola

Focus on vaccination and malaria in Ebola-affected countries

Geneva – WHO has called for intensification of routine immunization services in all areas of Ebola-affected countries, and for mass measles vaccination campaigns in areas that are free of Ebola transmission. The Ebola outbreak, which has infected some 24 000 people and killed around 10 000 of them, has also reduced vaccination coverage in Guinea, Liberia and Sierra Leone as health facilities and staff have focused on halting the outbreak.

The malaria burden has also increased as patients have been unable or afraid to seek treatment during the Ebola outbreak. To reduce the number of febrile people with malaria presenting at Ebola evaluation facilities, WHO recommended mass drug administration of anti-malarial medicines to all eligible people in areas heavily affected by Ebola. An estimated 3 million people have been reached in Sierra Leone and Liberia from October 2014 to January 2015 through door-to-door distribution.

The focus on vaccinations and malaria is part of WHO's efforts to support countries in early recovery on their way to rebuilding their health systems.

► WHO News, 20 March 2015.

First Ebola vaccine efficacy trial launched in Guinea

Conakry – The Guinean Government with the World Health Organization (WHO) has initiated the first efficacy trial of an Ebola vaccine. Ring vaccination tests of VSV-EBOV, a lead Ebola vaccine developed by the Public Health Agency of Canada, are to be conducted in one of the areas in Guinea where most Ebola cases occurred. The concept of the trial is based on vaccinating the "rings" – the group of contacts of a newly diagnosed Ebola "index case" – either immediately after confirmed diagnosis of the index case, or three weeks later. This strategy allows all known contacts to be vaccinated within a short period of time and constitutes an alternative to the use of a placebo.

The Guinea Ebola vaccine trial is a coordinated effort among numerous international partners. A total of around 10 000 people in 190 rings are planned to be vaccinated. Results could be available as early as July 2015.

► WHO News, 20 March 2015.

WHO proposes emergency use assessment procedures

Geneva – WHO has proposed a set of Emergency Use Assessment and Listing (EUAL) procedures for in vitro diagnostic products, medicines and vaccines intended to address a public health emergency caused by a disease. It applies when the community may be willing to tolerate less certainty about the safety and efficacy of a product (or its safety and performance in the case of a diagnostic), given the high morbidity and/or mortality of the disease and the shortfall of options to diagnose, prevent and/or treat it.

An EUAL is granted on a defined minimum level of information, making a product available for a time-limited period in an emergency while further data are being gathered and evaluated. It is important to note that the procedures are not the same as WHO prequalification and should not be thought of as such.

► WHO Essential Medicines and Health Products. News, 10 March 2015.

WHO lists Ebola diagnostic tests for emergency use in West Africa

Geneva – WHO has listed four diagnostic tests as being eligible for UN procurement in Ebola affected countries, after successful assessment through the EUAL procedure. As the Ebola outbreak is winding down, sensitive, effective diagnostic tests are important to identify any remaining infections and keep them from spreading.

The EUAL evaluation for diagnostics comprises three key components: (1) a review of technical documentation relating to safety and performance; (2) a review of documentation about the manufacture of the product and the manufacturer's quality management system (QMS); and (3) an independent laboratory evaluation coordinated by WHO to determine the product's performance and operational characteristics.

► WHO Essential Medicines and Health Products. News, 8 May 2015.

WHO In vitro diagnostics and laboratory technology. Emergency Use Assessment and Listing (EUAL) Procedure for Ebola Virus Disease (IVDs) [web page].

Hepatitis

WHO publishes first hepatitis B treatment guidelines

Geneva – WHO has issued its first-ever guidance for the treatment of chronic hepatitis B. This disease has a huge health impact as it can lead to cirrhosis and liver cancer, and the medicines that can prevent the development of these conditions are currently out of reach for many patients.

The *WHO guidelines for the prevention, care and treatment of persons living with chronic hepatitis B infection* cover the full spectrum of care, with a focus on settings with limited resources, and taking into account special populations such as people co-infected with HIV, children and adolescents, and pregnant women.

Key recommendations include the use of simple tests to assess the stage of liver disease, prioritizing treatment for those with cirrhosis, the use of tenofovir or entecavir to treat chronic hepatitis B, and

regular monitoring to assess treatment outcomes and detect liver cancer at an early stage. To prevent new hepatitis B infections. WHO recommends to vaccinate all children with a first dose given at birth. WHO's recently launched policy on injection safety, calling for the worldwide use of "smart" syringes to prevent the re-use of syringes or needles, will also help prevent new hepatitis B infections.

In 2014 WHO published its first guidelines on treating hepatitis C.

► WHO News release, 12 March 2015.

Patent landscapes of hepatitis C medicines

Geneva –WHO has analyzed the patent situation for new hepatitis treatments to provide clarity on whether or not the medicines are patent-protected in individual countries. Updated information has been published for sofosbuvir in about 20 countries, as well as on ledipasvir and daclatasvir, the latter with a complete data set for the primary patent.

Hepatitis C Virus infection is a chronic disease that often leads to severe liver disease and kills between 350 000 and 500 000 people annually. The World Health Assembly, in its Resolution WHA67.6, requests WHO to assist Member States in ensuring equitable access to quality, effective, affordable and safe hepatitis treatments.

► WHO Essential medicines and health products. News, 24 March 2015.

Hepatitis C diagnostics needed

An article in *The Lancet Global Health* emphasizes the importance and economic impact of reliable diagnostics in the fight against hepatitis C. This disease is severely underdiagnosed, especially in limited-resource settings. The authors advocate for a concerted effort to develop and fund appropriate diagnostic tests, which will maximize the effect of treatment programmes and thereby reduce the overall cost to health systems.

► Denkinger CM, Kessel M. Diagnostics for hepatitis C: an urgent need for action. The Lancet Global Health 2015;3(4), e195, April 2015. DOI: http://dx.doi.org/10.1016/S2214-109X(15)70092-6.

Note: Hepatitis C diagnostics are among the priority products assessed by the WHO prequalification team in view of procurement by international organizations. At the end of 2014 four products were under full assessment, seven were under abbreviated assessment in recognition of stringent regulatory approval, and for 17 products completion of dossiers was ongoing.
For more information on WHO prequalification of in vitro diagnostics see WHO Drug Information 28(3):2014: 312-316, and the article starting on page *133* of this issue.

Dementia

Advancing research and care

Geneva – At the First Ministerial Conference on Global Action Against Dementia, hosted by WHO on 16–17 March 2015, the Government of the United Kingdom announced that over US$ 100 million will be invested in a pioneering new global Dementia Discovery Fund. Major pharmaceutical companies have committed in principle to investing in promising research efforts for dementia that could bring about a breakthrough in treatment.

An estimated 47 million people are living with dementia worldwide. This number is expected to triple by 2050, with enormous personal, social and economic consequences that could affect low- and middle-income

countries disproportionately. The conference participants – which included representatives of 80 WHO Member States, 80 philantropic foundations, 45 on-governmental organization and four United Nations agencies – adopted a call for action on dementia at the global level. *(1)*

London – On the first day of the WHO conference the MHRA published the conclusions of a workshop held with representatives of ten regulatory authorities in November 2014. The participants identified six areas to work towards addressing the scientific gaps in the understanding of dementia, enabling regulators to contribute to strategies to bring innovative therapies to the market. *(2)*

► *(1)* WHO News release, 17 March 2015.
(2) MHRA News, 16 March 2015.

WHO matters

WHO prequalification programme proposes new financing model

Geneva – The WHO prequalification programme for in-vitro diagnostics, medical devices, medicines and vaccines has called for comments on its new financing model for its services and support to normative and regulatory functions, which are increasingly considered to be a global public health good.

In the last two decades, prequalification has helped to greatly increase access to affordable, quality-assured medical technologies in low- and middle-income countries. Its standards and processes are now being leveraged in collaborative procedures and regional regulatory networks, enabling regulators to speed up product assessments in countries, organize joint reviews and develop and introduce standard regulatory dossier formats.

While no major changes will be made to the fees currently charged for initial assessment and major variations, an annual financial contribution from manufacturers is proposed to be introduced. The model aims to generate at least 50% of the funds required to operate the prequalification programme, which is currently funded entirely by international donors through short-term grants.

The new model was designed following discussions with representatives of prequalification stakeholders and a review of a range of alternative options. WHO then sought additional input — via questionnaire — in order to assess whether any of the parameters of the model required adjustment. The input received is now under review.

► WHO Essential medicines and health products. Call for public comments on the new financing model for WHO Prequalification and supporting regulatory functions [webpage].

WHO officials meet with CFDA Vice Minister

On March 27, 2015, the Vice Minister of the China Food and Drug Administration (CFDA), met with a WHO delegation to exchange opinions on various medicines-related topics including drug prequalification, general assessment of drug regulatory systems, the reform of drug evaluation and approval systems, and poliomyelitis vaccines. The main directors of CFDA's Department of Drug and Cosmetics Supervision and relevant directors of Department of International Cooperation attended the meeting.

► CFDA Press release, 31 March 2015.

Upcoming events

3rd International PPRI Conference on medicines pricing and reimbursement

The 3rd Pharmaceutical Pricing and Reimbursement Information (PPRI) conference will be held on **12-13 October** 2015 in Vienna, Austria. Registration will close on 30 September.

The event will be organized by the WHO Collaborating Centre on Pharmaceutical Pricing and Reimbursement Policies. Titled "Challenges Beyond the Financial Crisis" it will take a critical look at recent developments, policy reforms and initiatives taken to maintain access to medicines in a context of financial crisis.

Visit the conference website at http://whocc.goeg.at/Conference2015 for more information.

2015 WHO-UNICEF-UNFPA meeting with manufacturers

The 2015 joint WHO-UNICEF-UNFPA meeting with pharmaceutical and diagnostics manufacturers and suppliers will be held in Copenhagen during the week of **23-27 November**.

More information will be published on the three organizations' websites closer to the event.

Consultation documents

To receive draft monographs by email please contact Mrs Wendy Bonny (bonnyw@who.int), specifying that you wish to be added to the electronic mailing list.

The International Pharmacopoeia

Draft note for guidance on organic impurities in active pharmaceutical ingredients and finished pharmaceutical products

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.606, May 2015).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/**.**
Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

*[**Note from the Secretariat.** Considering current practices in use for* The International Pharmacopoeia *and available guidance on how to establish limits for impurities, the following note for guidance on organic impurities in active pharmaceutical substances and finished pharmaceutical products was drafted. It is intended to replace the text on* Related substances in finished pharmaceutical product monographs *in the folder Notes for guidance, Supplementary Information section with the following chapter.]*

1. Scope

Impurities are critical quality attributes of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs), which potentially affect their safety and efficacy. Therefore, all applicable monographs in *The International Pharmacopoeia* (Ph. Int.) shall contain requirements for the control of impurities.

Impurities in APIs and FPPs may include starting materials, by-products, intermediates, degradation products, reagents, ligands, catalysts and organic solvents. They can be classified as either organic or inorganic.

This note for guidance covers requirements for controlling organic process impurities and degradation products in APIs and FPPs, and provides guidance on how to assess compliance with Ph.Int. requirements.

Several statements in this document refer in particular to the future, i.e. they are applicable to monographs included in the Ph.Int. after the publication of this note of

guidance.[1] Compliance with previous monographs has to be evaluated using the replaced text *Related substances in finished pharmaceutical product monographs*[2] or on a case-by-case basis.

Excluded from this note for guidance are biological/ biotechnological products, peptides, oligonucleotides, radiopharmaceuticals, herbal products and crude products of animal and plant origin. These types of substances require specific considerations.

Further excluded are the following substances:

- extraneous contaminants that should not occur in APIs and FPPs and are more appropriately addressed as good manufacturing practices (GMP) issues;
- enantiomeric impurities;
- crystallographic modifications ("polymorphic forms");
- residual solvents resulting from API or FPP manufacture;
- impurities that arise from printing inks, container-closure systems or excipients (not excluded, however, are reaction products between excipients and APIs);
- organic impurities that are leached from container-closure systems.

2. Defining the purity of APIs and FPPs

To control relevant organic impurities specific monographs usually contain a discriminative, stability-indicating test entitled "Related substances". This test may be supplemented by a specific test where a given impurity is not adequately controlled by the related substances test or where there are particular reasons (for example, safety reasons) for requiring specific control.

Monographs on APIs shall include specifications for process-related impurities that result from the manufacturing process and degradation products observed during manufacture and stability studies, while monographs on FPPs shall include tests and limits for degradation products. If appropriate, tests for impurities in dosage forms may also limit impurities arising during the synthesis of APIs. This approach provides, in conjunction with the monograph on the API, the means for an independent control laboratory (e.g. a small regulatory laboratory) without access to manufacturer's data, to establish whether or not an API of pharmacopoeial quality has been used to manufacture the FPP under examination.[3]

Instruction for control of impurities may also be included in the manufacture section of a monograph, for example, where the only analytical method appropriate for the control of a given impurity is to be performed by the manufacturer since the method is too technically complex for general use. The production process (including the purification steps) needs to be validated to give sufficient control so that the product, if tested, would comply with the specified limits using a suitable analytical method.

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[1] Since the publication of the Fourth Supplement of the Fourth Edition, the year of publication (together with a two digit number) is added below the title of each text (monograph, general chapter or text for the supplementary information).

[2] Once this new note for guidance is adopted by the Expert Committee on Specifications for Pharmaceutical Substances, the replaced text can be found in *The International Pharmacopoeia* under "Omitted texts".

[3] It is recognized that limits for degradation impurities given in FPP monographs may need to be higher than the limits for the same impurities that appear in the monograph for the corresponding API.

Under the section on “impurities” in the monographs for pharmaceutical substances and dosage forms, substances are listed (transparency list) that are known to be limited by the described test method(s). In dosage form monographs reference may also be made to the list in the monograph of the corresponding API. Whenever possible the impurities are identified as degradants and/or synthesis impurities.

Tests for related substances are intended to provide appropriate limitation of known potential or actual impurities rather than to protect against all possible impurities. The tests are not necessarily designed to detect any adventitious contaminants or adulteration. Material or products found to contain an impurity not detectable by means of the prescribed tests is not of pharmaceutical quality if the nature or amount of the impurity found is incompatible with good pharmaceutical practices (GPP) or applicable regulatory standards.

3. Setting acceptance criteria for organic impurities

Limits in the Ph.Int. are usually set based on:

- the evaluation of information, provided by manufacturers, concerning the nature of impurities, the reason for their presence, the concentrations that may be encountered in material prepared under conditions of good pharmaceutical manufacturing practices and the manner in which the API or FPP may change during storage and when subjected to stress conditions (e.g. light, heat, moisture, acid, base or oxygen), together with an indication of the toxicity of any impurity in relation to that of the substance itself;
- justified limits accepted by regulatory authorities or by the WHO Prequalification Team after a full consideration of the toxicity studies and clinical trials carried out before granting a marketing authorization or before inclusion of the product in the WHO list of prequalified medicinal products or the WHO list of prequalified APIs. The limits may be amended in the event that new safety data become available following regulatory evaluation;
- limits published by other pharmacopoeias applying good pharmacopoeial practices (GPhP);[4]
- principles published in current regulatory guidance documents, such as those published by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Comments received during the public consultation of the draft monographs are evaluated and taken into consideration if relevant.

Acceptance criteria for impurities focus in particular on safety considerations. They should not be solely based on process capabilities. The historical safety record, the route of administration, the type of dosage form, the maximum daily dose, the duration of treatment, the need for and the availability of the medicine can also be taken into consideration when setting limits for impurities.

Highly toxic (e.g. genotoxic) impurities or degradation products are addressed using applicable guidance.

[4] At the time this note for guidance was drafted the draft proposal for good pharmacopoeial practices (GPhP) (QAS/13.526/Rev.5) was sent out for public consultation (see http://www.who.int/medicines/areas/quality_safety/quality_assurance/GPhP-Rev5-QAS13-526.pdf?ua=1). The statement made thus refers to the future, i.e. to a time when good pharmacopoeial practices have been implemented and put into practice by pharmacopoeias.

4. Compliance with the requirements

Where a monograph has no related substances test (or equivalent) or where the existing test does not comply with the requirements of the applicable regulatory standards the user of a monograph must nevertheless ensure that there is suitable control of organic impurities.

Where a pharmaceutical substance may contain impurities other than those mentioned in the Impurities section (for example, because it was manufactured using a new method of synthesis) it is necessary to verify that these impurities are detectable by the method(s) described in the monograph; otherwise a new method should be developed and a revision of the monograph should be requested.

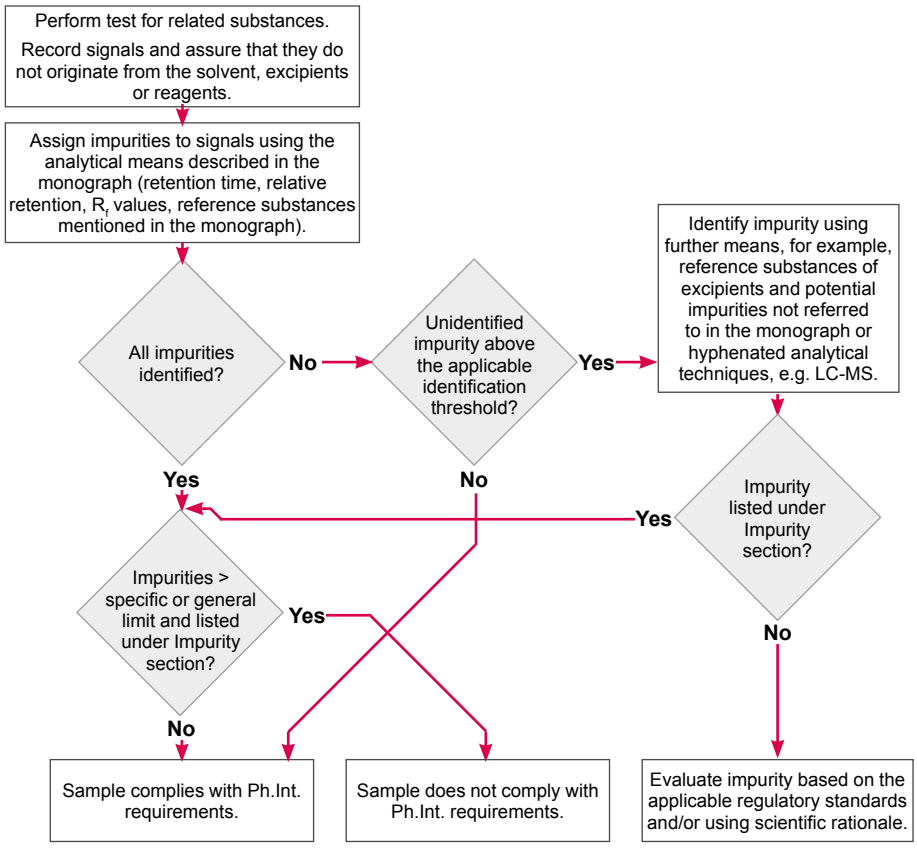
Where a peak or a spot cannot be assigned unambiguously to a listed impurity using the means described in the monograph (retention times, relative retentions, Rf values or comparison to reference substances mentioned in the monograph) the user has to apply additional measures in order to identify the impurities conclusively. These means may include, for example, the analysis of reference substances of excipients, potential impurities not referred to in the monograph or the use of additional analytical techniques, e.g. so-called hyphenated analytical techniques, e.g. GC- or LC-mass spectroscopic methods.

Where an impurity other than those listed under the Impurities section is found in an API or in a dosage form it is the responsibility of the user of a monograph to check whether it has to be identified/qualified, depending on its content, nature and safety, on the maximum daily dose of the API and relevant identification/qualification thresholds for the impurity, etc., in accordance with the applicable regulatory standards and sound scientific principles to control impurities.

The general acceptance criterion for impurities (“any other impurity”, “other impurity”, “any impurity”) equivalent to a nominal content greater than the applicable identification threshold is valid only for those impurities identified in the transparency list, except those that have their own specific acceptance criterion in the monograph. It is thus the responsibility of the user to determine the validity of the acceptance criteria (i.e. to qualify the limit) for impurities not mentioned in the Impurity section.

See *Figure 1* for guidance on how to assess compliance with the acceptance criteria of the tests for related substances in the Ph.Int.

Figure 1. **Decision tree for assessing compliance with the acceptance criteria of the test for related substances in the *International Pharmacopoeia***



Glossary

degradation product.
An impurity resulting from a chemical change in the active pharmaceutical ingredient (API) brought about during manufacture and/or storage of the API or the dosage form by the effect of, for example, light, oxygen, temperature, pH, water or by reaction with an excipient and/or the immediate container closure system.

extraneous contaminant.
An impurity arising from any source extraneous to the manufacturing process.

identification threshold.
A limit above (>) which an impurity should be identified, based on the applicable regulatory standards.

identified impurity.
An impurity for which a structural characterization has been achieved.

impurity (pharmaceutical substance).
Any component of a pharmaceutical substance that is not the chemical entity defined as the pharmaceutical substance.

impurity (dosage form).
Any component of the dosage form that is not the pharmaceutical substance or an excipient in the dosage form.

intermediate.
A material produced during steps of the synthesis of an active pharmaceutical ingredient that undergoes further chemical transformation before it becomes an active pharmaceutical ingredient.

ligand.
An agent with a strong affinity to a metal ion.

polymorphic forms.
Different crystalline forms of the active pharmaceutical ingredient. These can include solvation or hydration products (also known as pseudo-polymorphs) and amorphous forms.

qualification threshold.
A limit above (>) which an impurity should be qualified.

specified impurity.
An impurity that is individually listed and limited with a specific acceptance criterion in the monograph. A specific impurity can be either identified or unidentified.

starting material.
A material used in the synthesis of an active pharmaceutical ingredient (API) that is incorporated as an element into the structure of an intermediate and/or of the API. Starting materials are normally commercially available and of defined chemical and physical properties and structure.

unidentified impurity.
An impurity for which a structural characterization has not been achieved and that is defined solely by qualitative analytical properties (e.g. chromatographic retention time).

unspecified impurity.
An impurity that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion (e.g. relative retention time).

***

Draft revision of the chapter on reference substances and reference spectra

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.607, May 2015).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/**.**
Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

*[**Note from the Secretariat.** Following up on a recommendation of the forty-ninth meeting of the Expert Committee on Specifications for Pharmaceutical Preparations to use in The International Pharmacopoeia, where appropriate, ultraviolet (UV) absorptivity values for assays and other quantification purposes with a view to limit reference to International Chemical Reference Substances (ICRS), it is proposed to revise the chapter on reference substances and reference spectra.*
Additional changes are proposed to reflect recent discussions within the ICRS Board.

*[**Note from the editor.** In accordance with WHO editorial policy the text reproduced below does not include tracked changes. Changes from the current monograph are indicated by insert and ~~delete~~ in the working document available at the above-mentioned web address.]*

1. International Chemical Reference Substances

1.1 Introduction

International Chemical Reference Substances (ICRS) are primary chemical reference substances for use in physical and chemical tests and assays described in *The International Pharmacopoeia* or in other World Health Organization (WHO) quality assurance documents adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. ICRS are used to identify, determine the purity or assay of pharmaceutical substances and preparations or to verify the performance of test methods.

This chapter describes principles to be applied during the establishment and use of ICRS, which guarantee that the reference substances are suitable for their intended purpose.

This chapter is not applicable to WHO International Biological Reference Preparations.

1.2 Terminology

Chemical reference substance
The term chemical reference substance, as used in this text, refers to an authenticated, uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination and which possesses a degree of purity adequate for its intended use.

Primary chemical reference substance
A designated primary chemical reference substance is one that is widely acknowledged to have the appropriate qualities within a specified context and whose assigned content

when used as an assay standard is accepted without requiring comparison with another chemical substance.

Secondary chemical reference substance
A secondary chemical reference substance is a substance whose characteristics are assigned and/or calibrated by comparison with a primary chemical reference substance.

1.3 Purpose of ICRS

The purpose of establishing ICRS is to provide users of *The International Pharmacopoeia* or other WHO quality assurance documents adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations with authenticated substances for reference. Many analytical tests and assays are based on comparison of physical or chemical attributes of a sample with those of the reference substance. ICRS serve as such reference substances and thus enable the analyst to achieve accurate and traceable results. Furthermore ICRS may be used to assess system suitability during analyses and to calibrate analytical instruments.

ICRS may also be employed to establish secondary reference substances for routine analysis according to the WHO *General guidelines for the establishment, maintenance and distribution of chemical reference substances*.[1] In cases of doubtful results or dispute, however, the tests performed using ICRS are the only authoritative ones.

1.4 Production of ICRS

All operations related to the establishment and distribution of ICRS should be carried out according to the relevant guidelines. Among these, the WHO *General guidelines for the establishment, maintenance and distribution of chemical reference substances*[1] and International Organization for Standardization (ISO) Guide 34 – *General requirements for the competence of reference material producers* (including related guides) take precedence.

Manufacture

WHO encourages pharmaceutical manufacturers to donate suitable candidate materials and thus to contribute to the availability of ICRS.

Candidate material for the establishment of ICRS may be synthesized and purified for this purpose or may be selected from the pharmaceutical production provided that the purity and homogeneity are suitable. In some cases, for example, in order to improve the stability of the reference substance it may be useful to process the reference substance (e.g. by freeze drying) or to select an alternative salt (or salt vs base), solvate or hydrate. The content assigned to the standard takes into account which substance is selected.

Compliance with the relevant tests of the corresponding monograph as published in *The International Pharmacopoeia* is required where applicable.

Reference substances are dispensed into suitable containers under appropriate filling and closure conditions, to ensure the integrity of the reference material. The containers employed are preferably single-use in order to minimize the risk of decomposition, contamination and moisture uptake. Where multiple-use containers are employed

[1] WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report. Geneva, World Health Organization. WHO Technical Report Series, No. 943, 2007, Annex 3.

appropriate use and handling controls should be implemented by the user to assure their suitability.

Analytical characterization

The candidate material should be tested with suitable analytical techniques aiming to characterize all relevant quality attributes. The identity is confirmed and the purity is determined, usually based on results obtained with the validated methods of the respective monographs. However, the use of further analytical techniques may be appropriate in order to fully characterize the candidate material. Absolute methods (for example, volumetric titrations, differential scanning calorimetry) should be employed to complement and verify the results of relative methods where the properties of a sample are compared with those of a reference substance (for example, chromatographic methods). The extent of testing and the number of laboratories involved in characterizing the material depends on the intended use of the reference substance to be established. If required, assay standards are characterized in interlaboratory trials to increase the accuracy of the assigned value.

A thorough purity investigation of the candidate material is performed to verify the identity of all relevant components (i.e. main component, organic and inorganic impurities, water and residual solvents) and to quantify them. The cumulative percentage of all components should yield 100% (mass balance approach).

The purity of a candidate material is calculated on the “as is” basis, so that the analyst can use the substance without pretreatment, for example, drying.

Provided that all components themselves are expressed as a percentage of the weight of sample taken the “as is” content can be calculated as follows:

Purity = 100 – organic impurities [%] – inorganic impurities [%] – water [%] – residual solvents [%]

Formula 1. Formula to calculate the purity of ICRS on an “as is” basis.

When chromatographic methods are used to test for related substances impurity concentrations are often determined in relation to the principal compound. The “as is” content of organic impurities, to be substituted in formula 1, can be calculated as follows:

Organic impurities = chromatographic result x (100 [%] – water [%] – residual solvents [%] – inorganic impurities [%]) / 100

Formula 2. Formula to calculate the percentage of organic impurities, determined by a chromatographic method, on an “as is” basis.

The content assigned to a quantitative ICRS depends on the purity of the candidate material and is specific to the method for which the substance will serve as a reference. If the reference substance is intended to be used with a method that has the same selectivity as the method used to determine its purity the calculated purity will be assigned as the content of the ICRS. However, if the intended method is less discriminative it may be necessary to add to the purity the content of impurities that cannot be discriminated from the response of the parent compound. The following example illustrates this:

A candidate material is analysed with different analytical methods to identify and quantify all relevant components. The results reveal that, besides the labelled substance, the following components are present: 2.0% water (analysed by Karl Fischer titration, calculated on an "as is" basis); 1.0% enantiomer of the labelled substance (analysed by chiral high-performance liquid chromatography (HPLC), calculated in relation to the sum of the peak areas of both enantiomers); and two organic impurities, each 0.75% (analysed by an achiral HPLC method, calculated in relation to the sum of the peak area of all peaks, ignoring solvent and injection peaks). The purity of the standard is calculated to 95.55% (purity = 100% – (2.5% x 0.98) – 2%). The candidate material is intended to be used as a reference in an assay test, which stipulates the use of the same HPLC method as already applied to determine the organic impurities in the characterization of the candidate material. A content of 96.53% is assigned to the reference substance (assigned content = 100% – (1.5% x 0.98) – 2%). The concentration of the enantiomer is not taken into consideration as the method, for which the reference substance is intended, is not selective for the enantiomer.

Labelling

The labelling should provide all the necessary information to use the reference substance as intended, i.e. the name of the reference substance, the batch number, storage conditions, etc. If intended for quantification the assigned content or potency (for microbiological assays) is also given. The accompanying leaflet is considered to be part of the labelling.

Release and adoption

ICRS are established and released under the authority of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The Committee adopts new ICRS and new lots as being suitable for use as described in *The International Pharmacopoeia* or in other WHO quality assurance documents.

Stability monitoring and distribution

At the WHO custodian centre for ICRS the established reference substances are stored and distributed under conditions suitable to ensure their stability.

The fitness-for-purpose of ICRS is monitored by regular re-examinations. Their frequency and extent is based on:

- the stability of the ICRS;
- the container and closure systems;
- the storage conditions;
- the hygroscopicity;
- the physical form;
- the intended use.

The analytical methods employed to verify the stability are chosen among those used during the establishment of the reference standard. The maximum permitted deviation from the assigned value should be predefined and, if exceeded, the batch should be re-established or replaced.

1.5 Use and storage of ICRS by the user

The letters RS after the name of a substance in a test or assay described in *The International Pharmacopoeia* or in other WHO quality assurance documents adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations indicate the use of the respective ICRS.

ICRS are suitable for the analytical purpose described in *The International Pharmacopoeia* or other WHO quality assurance documents adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The analytical specifications and test methods in these documents are being revised to stay abreast of advances in analytical science and regulatory. Along with these changes the intended use of already established ICRS often needs to be adjusted, for example, because an ICRS previously used for identification only shall newly also be employed in quantitative tests. Information on the actually established intended uses of an ICRS can be found in the leaflet enclosed with the substance when distributed or accessible via the ICRS online database (see http://www.edqm.eu). The information found in the current leaflets is applicable to all standards of the respective batch number.

If used for other purposes the responsibility of assessing the suitability rests with the user or the authority that prescribes or authorizes this use. If reference substances other than ICRS are used for purposes described in *The International Pharmacopoeia* or in other WHO quality assurance documents adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations the suitability of these substances has to be demonstrated by the user.

The user has to apply an assigned content in assay determinations or when it is indicated in the method description.

ICRS are supplied in adequate quantities for immediate use after opening of the container. Users should purchase only sufficient units for short-term use.

It is generally recommended that the user stores ICRS protected from light and moisture and preferably at a temperature of about 5 ± 3 °C. When special storage conditions are required this is stated on the label or in the accompanying leaflet.

If an unopened container is stored under the recommended conditions it remains suitable for use as long as the respective batch is valid. Information on current batch numbers is provided on the website of the WHO custodian centre for ICRS (see under Ordering information).

Reference standards that are normally stored at 5 ± 3 °C are dispatched at ambient temperature since short-term excursions from the storage recommendations are not considered to be deleterious to the reference substance. Reference substances stored at -20 °C are packed on ice or dry ice and dispatched by courier. Reference substances stored at -80 °C or stored under liquid nitrogen are packed on dry ice and dispatched by courier.

1.6 Rational use of ICRS

Specifications and test procedures of *The International Pharmacopoeia* are intended to be applicable in all WHO Member States wishing to implement them. Procuring reference substances may, however, be difficult in certain areas of the world due to delays in their delivery and the cost of purchase. *The International Pharmacopoeia* therefore endeavours to reduce the number of reference substances required to

perform the included tests and assays. For this purpose the following strategies and practices may be applied during the elaboration of monographs:

- in situ preparation of impurities for identification purposes;
- quantification of impurities by comparing their responses with the response of the parent compound in a diluted sample solution along with the establishment of correction factors to compensate for differences in the responses of the impurity and the parent compound;
- provision of International Infrared Reference Spectra (IIRS) for use in identification tests;
- provision of assay methods not requiring reference substances, like titrations and UV spectrophotometry using absorptivity values. These methods shall be provided as alternatives in particular to chromatographic assays in monographs for pharmaceutical substances.

These strategies, however, shall only be applied when, during the elaboration of the methods, evidence could be obtained that the intended measures do not compromise the quality of the analytical results and are equally satisfying to conclusively demonstrate conformance to the applicable standards.

1.7 Analytical data provided in the leaflet of the ICRS

The leaflets of the ICRS may provide analytical information, including, but not limited to:

- the IR spectrum of the substance (together with a description of the sample preparation);
- additional analytical information at the time of establishment;
- the assigned content.

The section “Additional analytical information at the time of establishment” provides data about the purity of the reference substance and the methods used to determine it. The information was valid at the time of the establishment of the standard and will not be monitored or adjusted. The information may help the user to understand the calculation of the content that has been assigned to a standard for quantification. It may further be of value to assess risks or uncertainties associated with an unintended use of an ICRS. This information, however, is not given to authorize such an unintended use. As laid down under section 1.5, ICRS are adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations for their intended uses only; the responsibility for an unintended use of an ICRS rests with the user or the authority that prescribes or authorizes this use.

1.8 Ordering information

Since April 2010 the European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe, is responsible for the establishment, preparation, storage and distribution of ICRS for *The International Pharmacopoeia*. A list of currently available ICRS can be found on its website (see http://www.edqm.eu).

Orders for ICRS should be sent to:

European Directorate for the Quality of Medicines & HealthCare
7 allée Kastner
CS 30026
F-67081 Strasbourg, France
Fax: +33 (0)3 88 41 27 71 - to the attention of EDQM Sales Section
Email: orders@edqm.eu

The current price for ICRS per package, as well as the cost for the delivery is available on the above-mentioned website.

2. International Infrared Reference Spectra

International infrared reference spectra are provided for use in identification tests as described in monographs of *The International Pharmacopoeia* or other WHO quality assurance documents adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

The reference spectra are produced from authenticated material using an appropriate sample preparation technique. They are recorded with a Fourier transform infrared spectrophotometer (FTIR). Instructions for the preparation of spectra are given in 1.7 Spectrophotometry in the infrared region; Identification by reference spectrum.

A spectrum of the test substance is considered to be concordant with a reference spectrum if the transmission minima (absorption maxima) of the principal bands in the test spectrum correspond in position, relative intensities and shape to those in the reference spectrum.

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Levonorgestrelum
Levonorgestrel

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.614, May 2015).

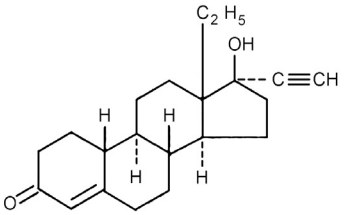
The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/**.**
Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

*[**Note from the Secretariat.** It is proposed to revise the monograph on Levonorgestrel. Comments are particularly sought on whether the monograph should include a limit test for dextronorgestrel.]*
*[**Note from the editor.** In accordance with WHO editorial policy the text reproduced below does not include tracked changes. Changes from the current monograph are indicated by insert and ~~delete~~ in the working document available at the above-mentioned web address.]*

Molecular formula. $C_{21}H_{28}O_2$

Relative molecular mass. 312.5

Graphic formula



Chemical name. (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one; CAS Reg. No. 797-63-7.

Description. A white or almost white, crystalline powder.

Solubility. Practically insoluble in water; sparingly soluble in dichloromethane R, slightly soluble in ethanol (~750 g/L) TS and ether R.

Category. Contraceptive.

Storage. Levonorgestrel should be kept in a well-closed container, protected from light.

Requirements

Definition. Levonorgestrel contains not less than 98.0% and not more than 102.0% of $C_{21}H_{28}O_2$, calculated with reference to the dried substance.

Identity tests

- Either tests A and C or tests B and C may be applied.

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from levonorgestrel RS or with the reference spectrum of levonorgestrel.

B. Carry out the examination as described under 1.14.4 High-performance liquid chromatography using the conditions described under "Related substances", Method A. Prepare the following solutions. For solution (1) dissolve 10 mg of the test substance in 7 mL of acetonitrile R using sonication and dilute to 10 mL with water R. Dilute 1 volume to 100 volumes with a solvent mixture consisting of 30 volumes of water R and 70 volumes of acetonitrile R. For solution (2) use a solution containing 0.01 mg levonorgestrel RS per mL of the same solvent mixture. Inject 50 µL of solution (1) and (2). The retention time of the principal peak in the chromatogram obtained from solution (1) is similar to the principal peak in the chromatogram obtained from solution (2).

C. Determine the specific optical rotation (1.4) using a 10 mg per mL solution of the test substance in dichloromethane R. Calculate with reference to the anhydrous substance; the specific optical rotation is between -35° to -30°.

Sulfated ash (2.3). Not more than 1.0 mg/g, determined on 1.0 g.

Loss on drying. Dry to constant weight at 105 °C; it loses not more than 5.0 mg/g.

Related substances.

- Perform test A and B.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octylsilyl gel groups (5 µm). The material contains embedded polar groups.[1]

Use the following conditions for gradient elution:

Mobile phase A: Mix 400 volumes of acetonitrile R with 600 volumes of water R.

Mobile phase B: Use acetonitrile R.

Time (min)	Mobile phase A (%v/v)	Mobile phase B (%v/v)	Comments
0–50	100 to 20	0 to 80	Linear gradient
50–51	20 to 100	80 to 0	Return to initial composition
51–65	100	0	Re-equilibration

Operate with a flow of 0.7 mL/min. As a detector use an ultraviolet spectrophotometer set at a wavelength of 215 nm and, for impurity O, at 200 nm. Maintain the column at 30°C.

Prepare as a solvent solution a mixture of 30 volumes of water R and 70 volumes of acetonitrile R.

Prepare the following solutions. For solution (1) dissolve about 10 mg of the test substance in 7 mL of acetonitrile R using sonication and dilute to 10 mL with water R.

[1] A Symmetry Shield RP8 column was found suitable.

For solution (2) dilute 1 volume of solution (1) to 1000 volumes with the solvent solution. For solution (3) dissolve 5.0 mg of norethisterone RS in 35 mL of acetonitrile R and dilute to 50.0 mL with water R. Dilute 1.0 mL of this solution to 100 mL with solution (2).

Inject solution 50 µL of solution (3). The assay is not valid unless the resolution factor between the two principal peaks due to levonorgestrel (retention time about 20 minutes) and the peak due to norethisterone (impurity U) (with a relative retention of about 0.8) is at least 3.0.

Inject alternately 50 µL each of solutions (1) and (2). The chromatogram obtained with solution (1) may show the following impurities at the following relative retention with reference to levonorgestrel (retention time about 20 minutes): impurity H: about 0.5; impurity U: about 0.8; impurity K: about 0.85; impurity A: about 0.91; impurity M: about 0.95; impurity O: about 1.16; impurity B: about 1.26; impurity S: about 1.9. Use also the chromatogram obtained with solution (3) to identify impurity U.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 0.4, is not greater than 3 times the area of the principal peak obtained with solution (2) (0.3%);
- the area of any peak corresponding to either impurity B or K is not greater than 3 times the area of the principal peak obtained with solution (2) (0.3%);
- the area of any peak corresponding to impurity M, when multiplied by a correction factor of 3.1, is not greater than 2 times the area of the principal peak obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity O (recorded at 200 nm), when multiplied by a correction factor of 2.6, is not greater than 3 times the area of the principal peak obtained with solution (2) (0.3%);
- the area of any peak corresponding to either impurity S or U is not greater than 2 times the area of the principal peak obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity H is not greater than 1.5 times the area of the principal peak obtained with solution (2) (0.15%);
- the area of any other peak, other than the principal peak due to levonorgestrel, is not greater than the area of the principal peak obtained with solution (2) (0.10%);
- the sum of the corrected areas of any peak corresponding to impurity A and M and the areas of all other peaks, other than the principal peak or any peak corresponding to impurity O, is not greater than 10 times the area of the principal peak obtained with the solution (2) (1.0 %). Disregard any peak with an area less than 0.05 times the area of the principal peak obtained with solution (2) (0.05%).

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (15 cm × 4.6 mm) packed with base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl gel groups (3 µm).[2]

Use the following conditions for gradient elution:

Mobile phase A: Mix 400 volumes of acetonitrile R with 600 volumes of water R.

Mobile phase B: Mix 100 volumes of water R with 900 volumes of acetonitrile R.

[2] A Pack ODS-AQ (YMC) column was found suitable.

Time (min)	Mobile phase A (%v/v)	Mobile phase B (%v/v)	Comments
0–1	92	8	Isocratic
1–3	92 to 82	8 to 18	Linear gradient
3–6	82	18	Isocratic
6–16	82 to 60	18 to 40	Linear gradient
16–21	60 to 0	40 to 100	Linear gradient
21–32	0	100	Isocratic
32–33	0 to 92	100 to 8	Return to initial composition
33–50	92	8	Re-equilibration

Operate with a flow of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 200 nm.

Prepare as a solvent solution a mixture of 30 volumes of water R and 70 volumes of acetonitrile R.

Prepare the following solutions. For solution (1) dissolve 10.0 mg of the test substance in 7 mL of acetonitrile R using sonication and dilute to 10.0 mL with water R. For solution (2) dissolve 5.0 mg of ethinylestradiol RS in 35 mL of acetonitrile R using sonication and dilute to 50.0 mL with water R. Dilute 3.0 mL of the solution to 100.0 mL with the solvent mixture. For solution (3) dilute 1.0 mL of solution (1) to 100.0 mL with solution (2).

Inject solution 50 µL of solution (3). The assay is not valid unless the resolution factor between the two principal peaks due to levonorgestrel (retention time about 12 minutes) and the peak due to ethinylestradiol (with a relative retention of about x) is at least x.x. ***[Note from the Secretariat.*** *The missing figures will be added at a later stage.]*

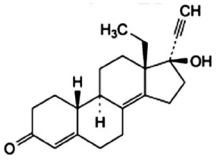
Inject alternately 50 µL each of solutions (1) and (2). The chromatogram obtained with solution (1) may show the following impurities at the following relative retention with reference to levonorgestrel (retention time about 12 minutes): impurity W: about 0.9; impurity V: about 1.9.

In the chromatogram obtained with solution (1):

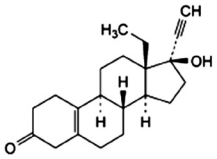
- the area of any peak corresponding to impurity W is not greater than the area of the principal peak obtained with solution (2) (0.3%);
- the area of any peak corresponding to impurity V is not greater than 0.5 times the area of the principal peak obtained with solution (2) (0.15%).

Assay. Dissolve 0.200 g in 45 mL of tetrahydrofuran R. Add 10 mL of silver nitrate (100 g/L) TS. After 1 minute titrate with sodium hydroxide (0.1 mol/L) VS, determining the end-point potentiometrically. Carry out a blank titration. 1 mL of sodium hydroxide (0.1 mol/L) VS, is equivalent to 31.25 mg of $C_{21}H_{28}O_2$.

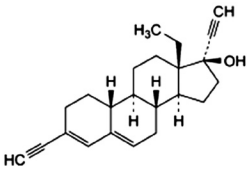
Impurities



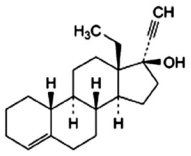
A. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-4,8(14)-dien-20-yn-3-one,



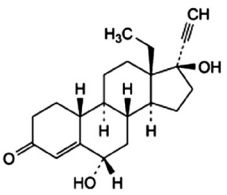
B. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-5(10)-en-20-yn-3-one,



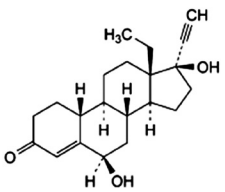
C. 13-ethyl-3-ethynyl-18,19-dinor-17α-pregna-3,5-dien-20-yn-17-ol,



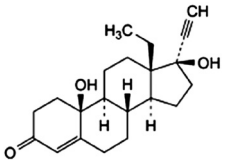
D. 13-ethyl-18,19-dinor-17α-pregn-4-en-20-yn-17-ol (3-deoxolevonorgestrel),



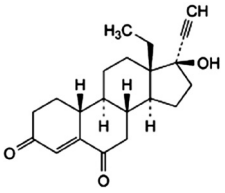
G. 13-ethyl-6α,17-dihydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one (6α-hydroxylevonorgestrel),



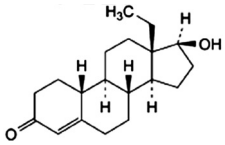
H. 13-ethyl-6β,17-dihydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one (6β-hydroxylevonorgestrel),



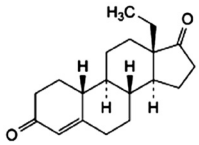
I. 13-ethyl-10,17-dihydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one (10-hydroxylevonorgestrel),



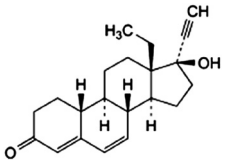
J. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yne-3,6-dione (6-oxolevonorgestrel),



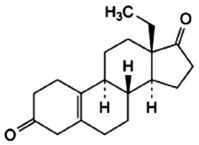
K. 13-ethyl-17β-hydroxygon-4-en-3-one (18-methylnandrolone),



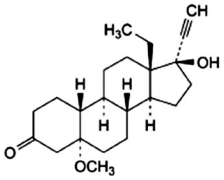
L. 13-ethylgon-4-ene-3,17-dione (levodione),



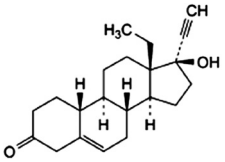
M. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-4,6-dien-20-yn-3-one (Δ6-levonorgestrel),



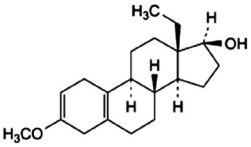
N. 13-ethylgon-5(10)-ene-3,17-dione (Δ5(10)-levodione),



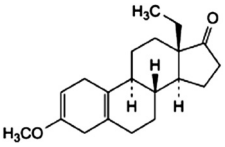
O. 13-ethyl-17-hydroxy-5α-methoxy-18,19-dinor-17α-pregn-20-yn-3-one (4,5-dihydro-5α-methoxylevonorgestrel),



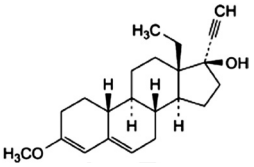
P. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-5-en-20-yn-3-one (Δ5-levonorgestrel),



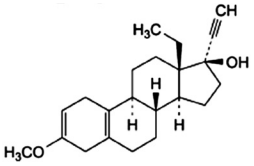
Q. 13-ethyl-3-methoxygona-2,5(10)-dien-17β-ol,



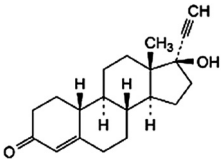
R. 13-ethyl-3-methoxygona-2,5(10)-dien-17-one,



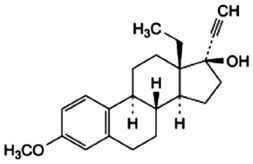
S. 13-ethyl-3-methoxy-18,19-dinor-17α-pregna-3,5-dien-20-yn-17-ol,



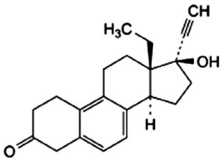
T. 13-ethyl-3-methoxy-18,19-dinor-17α-pregna-2,5(10)-dien-20-yn-17-ol,



U. 17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one (norethisterone),



V. 13-ethyl-3-methoxy-18,19-dinor-17α-pregna-1,3,5(10)-trien-20-yn-17-ol,



W. 13-ethyl-17-hydroxy-18,19-dinor-17α-pregna-5,7,9-trien-20-yn-3-one.

***

Estradioli cypionas
Estradiol cypionate

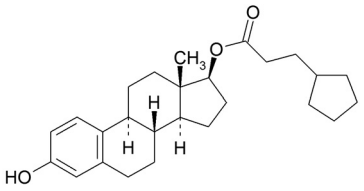
This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.618, May 2015).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/**.**
Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

Molecular formula. $C_{26}H_{36}O_3$

Relative molecular mass. 396.56

Graphic formula



Chemical name. Estra–1,3,5(10)–triene–3,17–diol, (17*β*)–, 17–cyclopentanepropanoate; estradiol 17–cyclopentanepropionate; CAS Reg. No. 313–06–4.

Description. A white to almost white, crystalline powder.

Solubility. Soluble in alcohol, acetone and dioxane; sparingly soluble in vegetable oils; insoluble in water.

Category. Contraceptive.

Storage. Estradiol cypionate should be kept in tightly closed containers, protected from light.

Requirements

Definition. Estradiol cypionate contains not less than 97.0% and not more than 102.0% (“Assay”, Method A) or not less than 98.0% and not more than 102.0% (“Assay”, Method B) of $C_{26}H_{36}O_3$, calculated with reference to the dried substance.

Identity tests

- Either test A alone or tests B and C may be applied.

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from estradiol cypionate RS or with the reference spectrum of estradiol cypionate.

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”, Method A. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to estradiol in the chromatogram obtained with solution (2).

C. Melting range, 149°C–153°C.

Specific optical rotation (1.4). Use a 20 mg/mL solution in dioxane R; $[\alpha]_D^{20°C}$ = +39° to +44°.

Loss on drying. Dry at 105°C for 4 hours; it loses not more than 10 mg/g.

Sulfated ash (2.3). Not more than 1.0 mg/g.

Heavy metals. Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 3; determine the heavy metals content according to Method A; not more than 10 µg/g.

Related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given below under "Assay", Method A.

Prepare the following solutions in acetonitrile R. For solution (1) transfer 50 mg of the test substance to a 50 mL volumetric flask and dilute to volume. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. For solution (3) use a solution containing 0.5 mg of estradiol cypionate RS and 0.5 mg of estradiol cypionate impurity B RS per mL.

Inject 25 µL of solution (3). The test is not valid unless the resolution between the peak due to impurity B (with a relative retention of about 0.91) and the peak due to estradiol cypionate (retention time about 15 minutes) is at least 1.5.

Inject alternately 25 µL each of solution (1) and (2).

In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to estradiol cypionate: impurity A about 0.17; impurity E about 0.76; impurity B about 0.91; impurity C about 1.44; and impurity D about 2.22.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, impurity C or impurity D is not greater than 0.15 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);
- the area of any peak corresponding to impurity B, when multiplied by a correction factor of 0.4, is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity E is not greater than 0.15 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);
- the area of any other peak, other than the principal peak, is not greater than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.10%);
- the sum of the area of any peak corresponding to impurity A, C, D, E, the corrected area of any peak corresponding to impurity B and the areas of all other peaks, other than the principal peak, is not greater than the area of the principal peak obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Assay

- Either test A or test B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with base-deactivated

particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).[1]

Use the following conditions for gradient elution:

Mobile phase A: Water R

Mobile phase B: Acetonitrile R

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–25	20	80	Isocratic
25–30	20 to 0	80 to 100	Linear gradient
30–40	0	100	Isocratic
40–41	0 to 20	100 to 80	Return to initial composition
41–50	20	80	Re-equilibration

Operate with a flow rate of 1.2 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 280 nm.

Prepare the following solutions in acetonitrile R. For solution (1) use 1.0 mg solution of the test substance per mL. For solution (2) use 1.0 mg of estradiol cypionate RS per mL. For solution (3) use a solution containing 0.5 mg of estradiol cypionate RS and 0.5 mg of estradiol cypionate impurity B RS per mL.

Inject 25 µL of solution (3). The test is not valid unless the resolution between the peak due to impurity B (with a relative retention of about 0.91) and the peak due to estradiol cypionate (retention time about 15 minutes) is at least 1.5.

Inject alternately 25 µL each of solution (1) and (2). Measure the areas of the peaks corresponding to estradiol cypionate obtained in the chromatograms, and calculate the percentage content of estradiol cypionate ($C_{26}H_{36}O_3$), using the declared content of $C_{26}H_{36}O_3$ in estradiol cypionate RS.

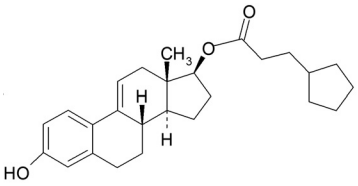
B. Dissolve about 0.05 g, accurately weighed, in sufficient methanol R to produce 100 mL; dilute 2.0 mL of this solution to 100 mL with the same solvent. Measure the absorbance (1.6) of a 1 cm layer of the diluted solution at the maximum at about 280 nm and calculate the percentage content of estradiol cypionate ($C_{26}H_{36}O_3$) using the absorptivity value of estradiol cypionate.

***[Note from the Secretariat.** It is intended to determine the absorptivity value of estradiol cypionate during the establishment of estradiol cypionate RS. The value will then be included in the test description.]*

[1] An Agilent ZORBAX SB-C_{18} column has been found suitable.

Impurities

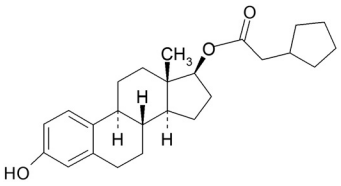
A. Estradiol



B. 3–Hydroxyestra–1,3,5(10),9(11)-tetraene-17*β*–yl cyclopentanepropanoate

C. 3–Hydroxy–4-methylestra–1,3,5(10)-trien–17*β*–yl cyclopentanepropanoate; 4-Methylestradiol cypionate

D. Estra–1,3,5(10)-trien–3,17 *β*–diyl di(cyclopentanepropanoate); Estradiol dicypionate



E. Estra–1,3,5(10)–triene–3,17–diol,(17*β*)–,17-cyclopentaneacetate

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ATC/DDD classification

The Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) as a measuring unit are tools for exchanging and comparing data on drug use at international, national or local levels. The ATC/DDD system has become the gold standard for international drug utilization research. It is maintained by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway.
Visit www.whocc.no/ for more information.

ATC/DDD classification (temporary)

The following ATC codes and DDDs were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in March 2015. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology (whocc@fhi.no) before 1 September 2015. If no objections are received before this date, the new ATC codes and DDDs will be considered final and will be included in the January 2016 version of the ATC/DDD Index.

New ATC 5th level codes:

ATC level name/INN	ATC code
anthrax immunoglobulin	J06BB19
armodafinil	N06BA13
atorvastatin, amlodipine and perindopril	C10BX11
begelomab	L04AA35
brexpiprazole	N05AX16
brodalumab	L04AC12
cediranib	L01XE32
ceftazidime, combinations	J01DD52
conjugated estrogens and bazedoxifene	G03CC07
drisapersen	M09AX04
droxidopa	C01CA27
dulaglutide	A10BX14
emtricitabine, tenofovir alafenamide and rilpivirine	J05AR19
ibuprofen	R02AX02
idarucizumab	V03AB37
ivacaftor and lumacaftor	R07AX30
ixazomib	L01XX50
lesinurad	M04AB05
necitumumab	L01XC22
palbociclib	L01XE33

Continued/

Temporary

New ATC 5th level codes, continued:

ATC level name/INN	ATC code
pantoprazole, amoxicillin, clarithromycin and metronidazole	A02BD11
perindopril and bisoprolol	C09BX02
ramucirumab	L01XC21
reslizumab	R03DX08
salmeterol and budesonide	R03AK12
saxagliptin and dapagliflozin	A10BD21
selexipag	B01AC27
sodium benzoate	A16AX11
tivozanib	L01XE34
valsartan and lercanidipine	C09DB08
valsartan and sacubitril	C09DX04
zoledronic acid, calcium and colecalciferol, sequential	M05BB08

Change of ATC codes:

ATC level name/INN	Previous ATC code	New ATC code
calcium acetate[1)]	A12AA12	V03AE07
ferric citrate	B03AB06	V03AE08

[1)] Previous ATC level name: calcium acetate anhydrous

New DDDs:

ATC level name/INN	DDD	unit	Adm.R*	ATC code
alogliptin	25	mg	O	A10BH04
armodafinil	0.15	g	O	N06BA13
artesunate	0.28	g	P	P01BE03
clenbuterol	40	mcg	O	R03CC13
colistin	3	MU	Inhal. powder	J01XB01
dasabuvir	0.5	g	O	J05AX16
dulaglutide	0.16	mg	P	A10BX14
eliglustat	0.168	g	O	A16AX10
empagliflozin	17.5	mg	O	A10BX12
teduglutide	5	mg	P	A16AX08
tofacitinib	10	mg	O	L04AA29
umeclidinium bromide	55	mcg[2)]	Inhal. powder	R03BB07

** Administration Route: O=oral; P=parenteral*

[2)] Refers to umeclidinium, delivered dose

Change of DDDs:

ATC level name/INN	Previous DDD			New temporary DDD			ATC code
	DDD	unit	Adm.R*	DDD	unit	Adm.R*	
apixaban	5	mg	O	10	mg	O	B01AF02
dabigatran etexilate	0.22	g	O	0.3	g	O	B01AE07
human menopausal gonadotrophin	30	U	P	75	U	P	G03GA02
rivaroxaban	10	mg	O	20	mg	O	B01AF01

** Administration Route: O=oral; P=parenteral*

ATC/DDD classification (final)

The following ATC codes, DDDs and alterations were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in October 2014. These are considered as final and will be included in the January 2016 version of the ATC/DDD Index.

New ATC 5th level codes:

ATC level name/INN	ATC code
asfotase alfa	A16AB13
ataluren	M09AX03
atazanavir and cobicistat	J05AR15
belinostat	L01XX49
benzyl alcohol	P03AX06
blinatumomab	L01XC19
brivaracetam	N03AX23
bupropion and naltrexone	A08AA62
ceftolozane and enzyme inhibitor	J01DI54
dasabuvir	J05AX16
dasabuvir, ombitasvir, paritaprevir and ritonavir	J05AX66
drospirenone	G03AC10
efinaconazole	D01AC19
emtricitabine and tenofovir alafenamide	J05AR17
emtricitabine, tenofovir alafenamide, elvitegravir and cobicistat	J05AR18
insulin degludec and liraglutide	A10AE56
isavuconazole	J02AC05
lamivudine and raltegravir	J05AR16
lenvatinib	L01XE29
luliconazole	D01AC18
nemonoxacin	J01MB08
nintedanib	L01XE31
nivolumab	L01XC17
obeticholic acid	A05AA04
octenidine	R02AA21
olodaterol and tiotropium bromide	R03AL06
ombitasvir, paritaprevir and ritonavir	J05AX67
papillomavirus (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)	J07BM03
pembrolizumab	L01XC18
pitolisant	N07XX11
rosuvastatin and valsartan	C10BX10
sebelipase alfa	A16AB14
sirolimus	S01XA23
smallpox, live attenuated	J07BX01
sofosbuvir and ledipasvir	J05AX65
sonidegib	L01XX48
tasimelteon	N05CH03

Final

New DDDs:

ATC level name/INN	DDD	unit	Adm. R.*	ATC code
abarelix	3.6	mg	P	L02BX01
albiglutide	5.7	mg	P	A10BX13
aripiprazole	13.3	mg	P depot	N05AX12
azilsartan medoxomil	40	mg	O	C09CA09
canagliflozin	0.2	g	O	A10BX11
cobicistat	0.15	g	O	V03AX03
daclatasvir	60	mg	O	J05AX14
dexmethylphenidate	15	mg	O	N06BA11
lomitapide	40	mg	O	C10AX12
loxapine	9.1	mg[1)]	Inhal. powder	N05AH01
misoprostol	0.2	mg	V[2)]	G02AD06
olodaterol	5	mcg	Inhal. sol	R03AC19
peginterferon beta-1a	8.9	mcg	P	L03AB13
riociguat	4.5	mg	O	C02KX05
siltuximab	37	mg	P	L04AC11
simeprevir	0.15	g	O	J05AE14
sucroferric oxyhydroxide	1.5	g	O	V03AE05
vedolizumab	5.4	mg	P	L04AA33

** Route of administration (Adm.R): O=oral; P=parenteral; V=vaginal; Inhal=inhalation*

1) delivered dose

2) vaginal insert, refers to the content of one vaginal insert