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Radiopharmaceuticals: General monograph

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Iobenguane (¹³¹I) injection

Fluconazole capsules

Fluconazole injection

Levamisole hydrochloride

Dextromethorphan hydrobromide

Publications and events

Public health topics

WHO hepatitis C guidelines published

WHO report reveals worldwide antibiotic resistance

EU and US continue joint battle against antimicrobial resistance

WHO core functions need reliable funding

WHO and Global Fund strengthen partnership

WHO report reveals worldwide antibiotic resistance

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ViiV and MPP sign licence agreement for dolutegravir

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First WHO GMP-compliant Nigerian manufacturer

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WHO Drug Information Vol. 28, No. 2, 2014
Regulatory harmonization

WHO collaboration with world pharmacopoeias

The International Pharmacopoeia is a result of WHO’s focus on quality medicines. It provides publicly available standards for quality control testing of pharmaceuticals. With the advent of globalization the need for harmonized pharmaceutical standards has become increasingly urgent. In recent years, WHO has supported regulatory convergence among Member States in various ways. The Organization has taken the lead in bringing together all active pharmacopoeias to work towards convergence of their standards and practices. This initiative is starting to deliver.

The use of pharmacopoeial standards

A pharmacopoeia is an official publication that lays down quality standards for pharmaceutical products in a country or region. It contains quality specifications for active pharmaceutical ingredients and finished dosage forms. A quality specification, as described in a monograph, is composed of a set of appropriate tests which will confirm the identity and purity of the substance or product, the amount of certain known impurities contained in it, as well as other characteristics such as its dissolution or disintegration properties.

Pharmacopoeial standards enable independent testing to verify that pharmaceutical products conform to official specifications. Pharmacopoeial testing is used in regulatory assessment of quality specifications, bioequivalence data, stability data and labelling information provided by the manufacturer. Testing of products circulating on the market can help to detect products that do not meet approved specifications, including illicit products that may have infiltrated the supply chains.

It should be emphasized that pharmacopoeial testing cannot replace regulatory assessment of product data to ensure that medicines are consistently produced and controlled according to internationally accepted quality standards.

Pharmacopoeias around the world

National and regional pharmacopoeias form part of the legislation that governs the production and testing of medicinal substances, including all starting materials, including active and inactive substances, and finished products. According to the information available to WHO (1), there are 46 national pharmacopoeias around the world, some of them dating back to the 18th and 19th centuries. Regional pharmacopoeias include the European Pharmacopoeia, first published in 1967, as well as the African Pharmacopoeia and the recently launched Mercosur pharmacopoeia developed by Argentina, Brazil, Paraguay, Uruguay and Venezuela.

Three major pharmacopoeias, namely those of Japan, Europe and the United States, came together in 1989 in the Pharmacopoeial Discussion Group (PDG) to discuss harmonization topics. WHO subsequently joined the PDG as an observer.
**The International Pharmacopoeia**

Efforts to establish a unified pharmacopoeia have been pursued for over a century. WHO was mandated to coordinate this work in 1948 through the WHO Expert Committee on Unification of Pharmacopoeia – today named WHO Expert Committee on Specifications for Pharmaceutical Preparations. The first volume of *The International Pharmacopoeia* was published in 1951.

WHO provides *The International Pharmacopoeia* (2) free of charge, with quality specifications that are ready for use by Member States. The focus is on essential medicines, i.e. those products that satisfy the health care needs of the majority of the population.

Many of the medicines included in *The International Pharmacopoeia* are not found in any other pharmacopoeia because they are not being used in the respective countries or regions, and/or their quality control is not considered a priority by the local authorities. By making technical information available for these medicines, WHO promotes access to quality medicines for all.

In 2003 WHO proposed future directions for *The International Pharmacopoeia*. Beyond essential medicines, priority would be given to new therapeutic agents and new combinations of medicines used to treat diseases most prevalent in low- and middle-income countries, notably HIV/AIDS, malaria and tuberculosis (3). More recently, the planning for updating of monographs has been aligned with the needs of the WHO Prequalification Programme.

Monographs for *The International Pharmacopoeia* are developed through a clear stepwise process described on the WHO web site (4). This process provides a unique global forum for consultation among experts and stakeholders.

**Continued need for global harmonization**

With the advent of globalization, export and import of pharmaceutical substances and finished medicinal products have increased. However, national and regional pharmacopoeias have evolved separately from each other and differences in pharmacopoeial standards therefore persist. For medicines that are manufactured for international trade and placed on the market in various countries, a multitude of different requirements may apply, resulting in costs and delays that can compromise access to needed medicines.

**Recent harmonization efforts**

The discussion on global harmonization of pharmacopoeias was reopened during the 2002 International Conference of Drug Regulatory Authorities (ICDRA). The recommendations of the 2002 and 2004 ICDRA meetings led to renewed global harmonization efforts. A number of international events followed, enabling strategic discussions and networking.

In 2012 WHO convened the First International Meeting of World Pharmacopoeias, bringing together representatives of 23 pharmacopoeias around the world. This has become an important recurring event which is co-organized by WHO and the relevant authorities of the host country or region, i.e.:

- Second International Meeting of World Pharmacopoeias, 2013 – India;
- Third meeting, 2014 – United Kingdom;
- Fourth meeting, October 2014 – Council of Europe;
- Fifth meeting, June 2015 – United States; and
- Sixth meeting, autumn 2015 – China.
Good pharmacopoeial practices

One of the salient recommendations of the 2012 meeting of world pharmacopoeias was to develop a guidance text on good pharmacopoeial practices. It was agreed that this should be done under the auspices of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, benefiting from its well-established, transparent, consultative approach to international standard-setting.

The primary objective of the WHO Good Pharmacopoeial Practices (GPhP) guidance is to harmonize approaches and policies in establishing pharmacopoeial standards. The implementation of GPhP by national and regional pharmacopoeial authorities is voluntary.

It is envisaged that adherence to GPhP will:

• strengthen global pharmacopoeial cooperation;
• increase transparency on how pharmacopoeial standards are developed and maintained; and
• improve cooperation between pharmacopoeial authorities and stakeholders (e.g. regulators, industry).

Adherence to GPhP can foster exchanges, work sharing and acceptance of monographs among pharmacopoeias. This will make it easier for pharmacopoeial authorities, regulators and manufacturers to ensure that medicines moving on the global market comply with stringent standards and meet the local requirements.

Progress to date

A comprehensive draft guidance text on GPhP was circulated for comment in October 2012 and subsequently developed further by an initial drafting group. In addition, a shorter concept paper describing the purpose and benefits of good pharmacopoeial practice was drafted and published for comment (5).

As a next step the world pharmacopoeias will continue to work jointly on the GPhP guidance text. The draft is expected to be shared in 2015 with regulators, laboratory specialists, manufacturers and other stakeholders for their input.

Challenges

It has been recognized that retrospective harmonization of existing pharmacopoeial standards is difficult to achieve. Ongoing efforts therefore aim at prospective harmonization of new monographs. This endeavour is facing two main challenges.

Firstly, pharmacopoeias are embedded in national or regional regulatory systems with different public health priorities, business models and capacities. Regulatory systems themselves need to converge to make pharmacopoeial harmonization possible.

Secondly, developments in science and medical practice, globalization and the presence of adulterated products require pharmacopoeias to evolve constantly. While these adjustments present opportunities for prospective harmonization, it also means that a coordinated maintenance process is required to preserve harmonization over time. The process must also extend to related logistics, such as the establishment and maintenance of reference standards.

Future perspectives

The renewed, global effort towards pharmacopoeial harmonization has led to stepwise progress being achieved. Bilateral agreements are being concluded for example on sharing of monographs for medicines used to treat diseases which are not of major public health importance.
in industrialized countries, such as malaria and tuberculosis.

Good pharmacopoeial practice is a promising new approach to support convergence of global initiatives in this important area through a single forum. The higher the level of participation, the greater will be the benefits to the stakeholders and ultimately to patients in WHO Member States.

References

Technologies, standards and norms

Quality standards for pharmaceutical products

The WHO Expert Committee on Specifications for Pharmaceutical Preparations advises the WHO Director-General and Member States on pharmaceutical quality issues. The heightened interest in quality of medicines became apparent in the request expressed by Member States during the 2013 meeting of the World Health Assembly to hold an open session on this topic in conjunction with the 48th Expert Committee meeting. This article gives an overview of guidance adopted by the Committee at its 48th meeting, held in Geneva on 14-18 October 2013.

The WHO Expert Committee on Specifications for Pharmaceutical Preparations

The WHO Expert Committee on Specifications for Pharmaceutical Preparations provides guidelines on a wide range of medicines quality assurance issues. This work is linked to WHO’s mandate to set necessary standards (both written and physical) that complement and improve current regulatory requirements created and applied in WHO Member States, including those developed by regional and inter-regional regulatory fora. Input from a wide range of experts from different settings, together with a global stakeholder consultation process, ensures that the guidelines are scientifically well-founded, meaningful and implementable.

In line with current regulatory concepts, the guidance aims to ensure that quality is built into a pharmaceutical product at each step of its life cycle and checked by measures such as testing to verify that all batches of finished product on the market conform to approved specifications. Accordingly the guidelines cover all areas of pharmaceutical quality assurance, from medicines design and production throughout distribution until they reach the end user.

The International Pharmacopoeia

The development of a unified pharmacopoeia was the initial scope of work of the Expert Committee when it was created at the very first World Health Assembly in 1948. The maintenance of The International Pharmacopoeia remains an important area of its work. In recent years, discussions in this area have provided a platform for renewed global efforts to harmonize the official quality specifications and test methods for pharmaceuticals across countries and regions1.

At its 48th meeting the Committee adopted 16 specific monographs for inclusion in The International Pharmacopoeia, including 5 for medicines to treat neglected tropical diseases, 3 for antimalarial medicines, 3 for antiviral medicines, 2 for maternal, newborn, child and adolescent health medicines, 1 for an antituberculosis medicine, and 2 for other medicines. In addition, it adopted four general texts relating respectively to melting temperature and melting range, strengths of medicines in alignment with

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1 See also the article on page 127 of this issue.
the most recent essential medicines list, dissolution testing of tablets and capsules, and reference substances and spectra.

Furthermore, the Committee endorsed the proposals made on International Chemical Reference Substances (ICRS) by the ICRS Board. It agreed to the adoption of 11 new ICRS and considered the withdrawal of 13 ICRS that no longer had a pertinent monograph in *The International Pharmacopoeia*.

In the area of radiopharmaceuticals WHO collaborates with the International Atomic Energy Agency (IAEA) to ensure that *The International Pharmacopoeia* is up to date. At its meeting the Committee discussed a workplan for adding and updating priority monographs. It also adopted a 13-step procedure for the ongoing development and revision of specifications for radiopharmaceuticals (1), ensuring that the monographs undergo thorough review and consultation as is the case for other content of *The International Pharmacopoeia*.

**Good manufacturing practice (GMP)**

Compliance with GMP is a fundamental requirement that must be met in any pharmaceutical quality assessment process. GMP applies to the entire manufacturing chain of innovator and generic products.

The Expert Committee adopted an update of the main principles of the WHO good manufacturing practices for pharmaceutical products (2). The revised text has considered all current concepts and inputs from different WHO regions and countries, including the concepts of quality-by-design, risk management and pharmaceutical quality management throughout a product’s life cycle. Together, these concepts provide for a tailored, science-based, systematic approach to pharmaceutical manufacturing and development, taking into account the critical attributes and risk factors identified for each specific product with a focus on patient safety. The revised GMP guidelines call for implementation of a Pharmaceutical Quality System (PQS) that extends to all life-cycle stages of a product, with a strong link between pharmaceutical development and manufacturing activities to facilitate innovation and continual improvement.

Furthermore, given the importance of outsourcing in the context of today’s globalized production, the revised guideline includes strengthened recommendations on the control of activities conducted by contractors and sub-contractors.

Ongoing revisions of supplementary GMP and related guidelines on non-sterile process validation and on hold-time studies were also discussed.

**Model quality assurance system for procurement agencies**

Humanitarian organizations provide significant amounts of medicines for use in resource-constrained countries. Given that most of the recipient countries have limited medicines regulatory capacity, these organizations have developed their own quality assurance systems for the pharmaceuticals that they procure or fund.

At the request of international organizations WHO had developed a model quality assurance system (MQAS) for procurement agencies, which was adopted by the Expert Committee in 2006. The MQAS has become one of the pillars of medicines quality assurance by international donors and humanitarian organizations. Additional requirements are in place for antiretrovirals, anti-tuberculosis medicines and antimalarials, which must be WHO-prequalified or approved by a stringent regulatory authority.

As international organizations harmonized and strengthened their quality
assurance policies over the years, they were looking for a more standardized way to implement the MQAS principles. The guidance document was revised by a working group with representatives of 13 organizations involved in international procurement and funding of medicines. The revised MQAS guidance document (3) – including an updated model inspection report and a newly revised inter-agency product questionnaire – was approved by the Committee at its 48th meeting, together with a standardized assessment tool (4) enabling procurement agencies to assess their own systems and those of their intermediary suppliers. The revised MQAS has been described in more detail in an earlier issue of this journal.

A common interpretation of MQAS requirements will form a basis for partner organizations to share the outcomes of their assessments, thus saving resources. It will also help to entrench uniform quality requirements for donor-funded medicines. This is especially important for products such as life-saving antibiotics, which are not subject to additional quality requirements by donors but nonetheless critically important for public health.

**WHO prequalification of stringently assessed products**
The WHO Prequalification Team assesses priority essential medicines belonging to selected key therapeutic areas to establish whether they are acceptable, in principle, for procurement by international organizations. For products that are already approved by a stringent regulatory authority WHO will recognize that authority’s scientific evaluation, provided that both the manufacturer and the authority agree to share with WHO certain specific information.

At its 48th meeting the Committee adopted a revised guideline on prequalification of stringently approved products. The revised text includes the requirements for both multisource (generic) and innovator products – previously described in two separate guidelines – with a number of updates for the latter product type (5).

The principles of this guideline can be applied to other initiatives for unilateral or mutual recognition of product approval between authorities.

**Product dossier assessment: quality part**
To harmonize the format of product dossiers in submissions for marketing authorization of pharmaceuticals, ICH member countries had introduced the Common Technical Document (CTD) format in 2003. The CTD is today the required format for submissions in many WHO Member States. The Association of Southeast Asian Nations (ASEAN) has developed and implemented the ASEAN Common Technical Dossier (ACTD) format with a view to arriving at mutual recognition arrangements on product approval. The CTD is also the required format for WHO prequalification dossiers.

The “quality part” (Module 3) of the CTD is concerned with technical specifications and manufacturing processes of the active ingredients and the finished product. It is applicable both to innovator and generic products. The information provided in this part of the dossier is critical for pre-approval assessment and post-marketing control.

The WHO Prequalification Team had developed detailed guidance for applicants on how to submit quality data in prequalification dossiers in line with Module 3 of the CTD format. This guidance has been adapted further to make it suitable for wider use. A document was adopted by the Committee that describes
harmonized, efficient processes for the development of product dossiers by manufacturers and for their assessment by NMRAs (6).

Although the guidelines reflect stringent regulatory principles they are not intended to be prescriptive. Alternative, scientifically justified approaches are acceptable, and regulatory authorities may have requirements not specifically described in this guidance.

By promoting the wide implementation of the CTD format in WHO Member States the guidance will contribute to regulatory convergence. For manufacturers it can save resources in dossier development, as they will be able to submit the same dossier to multiple regulatory authorities. For regulators it will facilitate collaboration and exchange of information, enabling them to pool their resources to control the quality of pharmaceutical products circulating in the global markets.

References


The draft versions of the revised guidelines (1-6) as posted for public comment are available at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/.
Essential medicines

Intensified efforts required to withdraw oral artemisinin-based monotherapies

The emergence and spread of artemisinin resistance calls for intensified efforts to withdraw oral artemisinin-based monotherapy (oAMT) from the markets. Despite substantial progress, oAMTs are still available in many countries.

Intensified action is needed to protect the therapeutic life of artemisinin-based combination therapy (ACT), the mainstay of treatment for malaria caused by Plasmodium falciparum. No alternative medicine is ready to enter the market in the next few years to replace ACTs. The loss of this lifesaving class of medicines would have devastating consequences.

Background

Most malaria deaths occur as a result of infection with the P. falciparum parasite (1). P. falciparum has thus far developed resistance to all classes of medicines used in its treatment. The emergence of resistance took several decades for quinine, 12 years for chloroquine, 5 years for mefloquine and approximately 1 year for proguanil, sulfadoxine-pyrimethamine and atovaquone (2).

Artemisinins constitute the only class of medicines that are still widely effective against P. falciparum. However, they must be combined with a longer-acting partner medicine to ensure that no parasites survive the 3-day treatment course and become resistant. WHO recommends five artemisinin-based combination therapies (ACTs) as the mainstay of treatment for uncomplicated P. falciparum malaria (3).

In 2008, scientists confirmed the first cases of P. falciparum resistance to artemisinin derivatives in the western Cambodian province of Pailin (4), which in the past has already been the focus area for the initial development of resistance to other antimalarial compounds. In this particular province, artemisinins were extensively used as monotherapy during the past decade, and this – together with other, so far unidentified factors (5, 6) – contributed to the development of resistance.

WHO recommendations on phasing out oAMT

Based on observations of the biological mechanisms of resistance to other
antimalarial compounds, it is expected that the removal of oAMT products will help slow down the spread of *P. falciparum* resistance to artemisinins and that the prevalence of newly emerged resistant strains might decline over time. Both mechanisms will extend the time during which ACTs remain an effective weapon in the fight against malaria.

WHO therefore urges Member States to cease the marketing and use of oAMT products (see definition in Box 1) in the public and private sectors and to promote the rational use of ACTs. This recommendation was endorsed by all WHO Member States at the Sixtieth World Health Assembly in May 2007 (Resolution WHA60.18) (7), and reaffirmed in 2011 (Resolution WHA64.17) (8).

**Box 1: Oral artemisinin-based monotherapy**

- The recommendation to phase out artemisinin-based monotherapy refers only to oral formulations.
- Rectal and injectable formulations (e.g. artemesunate suppositories and artesunate injectables) are still required for pre-referral treatment and for the treatment of severe malaria, respectively (3).
- In very few and exceptional cases, oral formulations of artesunate or other artemisinin-derivatives might still be manufactured for co-packaging with a partner medicine in ACT products that are not yet available as fixed-dose combinations.

**Latest evidence on artemisinin resistance**

In January 2014, the WHO Global Malaria Programme published the latest status report on artemisinin resistance (9). Foci of artemisinin resistance have meanwhile been identified in five countries in the Greater Mekong sub-region, mainly along international borders: Cambodia, the Lao People’s Democratic Republic, Myanmar, Thailand and Viet Nam. Additional foci of resistance are suspected in Suriname, Guyana and French Guiana (France); the initial findings are pending confirmation by in-depth studies in these three areas.

There is cause for great concern that artemisinin resistance may spread beyond the Greater Mekong sub-region or emerge independently on other continents. The spread of artemisinin resistance would threaten people’s health and lives in malaria-endemic countries, and would reverse the recent progress in malaria control achieved in many countries.

**Web-based WHO monitoring system**

In order to track compliance with resolution WHA60.18, the WHO Global Malaria Programme has established a web-based monitoring system that contains regularly updated information on:

- **Regulatory actions** undertaken by national medicines regulatory authorities, available at [www.who.int/malaria/monotherapy_NDRAs.pdf](http://www.who.int/malaria/monotherapy_NDRAs.pdf); and
- **Pharmaceutical companies** involved in the production and marketing of oAMTs, available at [www.who.int/malaria/monotherapy_manufacturers.pdf](http://www.who.int/malaria/monotherapy_manufacturers.pdf). Since 2005 – based on product catalogues published on the web, printed advertisements in English and French, and samples of finished pharmaceutical products available to WHO – the Global Malaria Programme has identified about 100 companies involved in the production and marketing of oAMTs. Most likely this is not the complete list of companies and the real number is probably far higher. Where product information was no longer available on companies’ websites, the companies were removed from the WHO monitoring web page, although it is not clear whether they are still involved in the production and marketing of oAMTs.
Progress in phasing out oAMT

Regulatory action. The setting of regulations by national medicines regulatory authorities is a major determinant of successfully phasing out oAMTs from the markets. As of May 2014, substantial progress has been achieved. However, nine of the 78 national medicines regulatory authorities of falciparum-endemic countries do not yet comply with WHO recommendations; most of them are located in Africa (Figure 1).

Pharmaceutical companies. Despite substantial progress on the regulatory side and good cooperation of a number of pharmaceutical manufacturers, 30 of the 86 manufacturing companies currently listed in the WHO monitoring tool have not yet disclosed their intention to withdraw oAMTs from the market (Figure 2). WHO contacts companies regularly on the basis of the information collected to clarify their positions with regard to WHO recommendations.

Challenges

A number of challenges have been encountered in implementing regulatory actions at country level, particularly in countries with a federal state structure: while appropriate regulatory decisions were endorsed at the federal level, an adequate enforcement mechanism was required at the state level to adopt and implement the same regulations. India, for example, took regulatory steps to withdraw oAMTs from the market in 2008/9; however, regulatory action followed in only a few states, and the largest number of oAMTs manufacturers continues to be located in India (see Figure 2).

Another challenge is that in many malaria-endemic countries a flourishing informal private sector continues to sell oral monotherapy. This practice must be counteracted through a functional supply management system that can make effective and quality-assured medicines available at affordable prices.

The way forward

Success in removing oAMTs from the market depends ultimately on effective regulation of medicines at country level. Measures must be integrated with the complex domestic and international market dynamics and regulatory frameworks involved at each step in the production of artemisinin-based medicines: planting of seeds, extraction of raw material from the plant’s leaves, derivatization of active pharmaceutical ingredients and manufacture of the finished products.

Experience has shown that a variety of interventions can be used successfully to
interrupt the manufacture, export, import, sale and use of oAMTs. It is crucial to ensure at the same time that quality ACTs are widely available in both the public and private sectors.

- **Domestic markets.** To protect domestic markets, the most effective strategy is to refuse new and suspend existing marketing authorization and to stop issuing import licenses for such products. Domestic manufacturers should be regulated more stringently with regard to import licenses for APIs, for instance refusing API import licenses to companies that manufacture oAMTs only. In addition, FPP import licenses should be suspended for companies that market oAMTs only in order to prevent the re-packaging or re-branding of artemisinin-based FPPs produced in other countries.

- **Export markets.** Many countries have protected their domestic markets as described above; however, the manufacture and export of oAMTs have not been regulated with the same stringency. Consequently, oAMTs continue to be manufactured for export only and can easily enter malaria-endemic countries with weak regulatory systems. It is crucial, therefore, that countries protect not only their domestic markets but also the export markets by withdrawing manufacture and export licenses.

**Targets and timelines for regulatory action**

Derived from successful country experiences, Annex 1 proposes targets and timelines for the progressive removal of oAMTs from the market, which countries can adapt to their national context. Annex 2 is based on this generic guide and summarizes the minimum requirements for tracking progress in the form of a checklist.

Besides the widespread use of oAMTs, a number of other factors contribute to the emergence and spread of resistance. Annex 3 shows the main factors that should also be taken into consideration when regulating the market; potential solutions are described.

**Conclusion**

In view of the latest evidence on artemisinin resistance, and in the absence of safe, effective alternative medicines for the treatment of *P. falciparum* malaria, urgent action is required to protect this important class of life-saving medicines. Prevention of the development and spread of artemisinin resistance is crucially important, and oAMTs must therefore entirely be withdrawn from the markets.

Experience in a range of malaria-endemic countries has shown that phasing out oAMTs is possible. A number of critical steps should be considered to phase out oAMTs from the market. The synchronization of these steps with the large-scale deployment of quality ACTs is indispensable; enforcement mechanisms and the active recall of existing oAMTs stocks have proven to be very useful withdrawal tools. Reasonable timelines should be set that allow progressive adaptation and response of the private sector to new health directives. Government commitment and strong stewardship by national regulatory authorities are the crucial basis for achieving this.

Artemisinin resistance, which is being fuelled by the use of oral monotherapy products, is too serious a public health risk to allow their continued use.

**References**

Annex 1.
Generic guide with suggested timelines for phasing out oAMTs medicines from the market

<table>
<thead>
<tr>
<th>Action</th>
<th>Task</th>
<th>Suggested approximate timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Agreement on time frame for phasing out oAMTs in synchrony with wide-scale deployment of ACTs</td>
<td>Immediate</td>
</tr>
<tr>
<td>Step 2</td>
<td>Suspension of new approvals of marketing authorizations for oAMTs</td>
<td>Immediate</td>
</tr>
<tr>
<td>Step 3</td>
<td>Suspension of import licences for artemisinin or its derivatives (as API or FPP) to domestic companies that exclusively market oAMTs</td>
<td>3–4 months</td>
</tr>
<tr>
<td>Step 4</td>
<td>Wide-scale deployment of ACTs in the public sector and communication to prescribers and consumers to move away from monotherapy</td>
<td>Time X</td>
</tr>
<tr>
<td>Step 5</td>
<td>Widespread availability and affordability of ACTs in the private sector</td>
<td>Time Z</td>
</tr>
<tr>
<td>Step 6</td>
<td>Withdrawal of marketing authorization and of manufacturing licences for oAMTs as FPPs to protect domestic markets</td>
<td>6 months after Time X</td>
</tr>
<tr>
<td>Step 7</td>
<td>Suspension of export license for oAMTs as FPPs to protect export markets</td>
<td>6 months after Time X</td>
</tr>
<tr>
<td>Step 8</td>
<td>Active recall of oAMTs from the market</td>
<td>3 months after Time Z</td>
</tr>
<tr>
<td>Step 9</td>
<td>Enforcement activities (e.g. regular outlet inspections, confiscation and destruction of products, suspension of selling licenses, fines, prosecution)</td>
<td>Regular intervals after Step 8</td>
</tr>
<tr>
<td>Step 10</td>
<td>Monitoring to ensure complete elimination of oAMTs as FPPs from the market</td>
<td>10–12 months after Time X</td>
</tr>
</tbody>
</table>

oAMTs, oral artemisinin-based monotherapy; ACT, artemisinin-based combination therapy; API, active pharmaceutical ingredient; FPP, finished pharmaceutical product; Time X, time at which a country will deploy ACT in the public sector on a wide scale (All subsequent timelines are conditional on this.); Time Z, requires distribution of high-quality ACT at subsidized prices in the private sector.
### Annex 2. Checklist for monitoring regulatory action taken by national authorities to phase out oAMTs from domestic and export markets

<table>
<thead>
<tr>
<th>Regulatory action</th>
<th>Protection of domestic market</th>
<th>Protection of export market</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Marketing authorization</strong></td>
<td></td>
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</tr>
<tr>
<td>□ No more approvals of new marketing authorization for oAMTs FPPs</td>
<td></td>
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<tr>
<td>□ Suspension of existing marketing authorizations for oAMTs FPPs</td>
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<tr>
<td><strong>Manufacturing licenses</strong></td>
<td>□ Suspension of manufacturing licenses for oAMTs FPPs</td>
<td></td>
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<tr>
<td><strong>Import licenses</strong></td>
<td>□ Suspension of API and oAMTs FPP import licences for companies exclusively marketing oAMTs or exclusively involved in re-packaging or re-branding</td>
<td></td>
</tr>
<tr>
<td><strong>Export licenses</strong></td>
<td>□ Suspension of export licenses for APIs with clear documentation that they are exclusively used for the manufacture of oAMTs</td>
<td>□ Suspension of export licenses for oAMTs FPPs</td>
</tr>
<tr>
<td><strong>Wide-scale availability of affordable, quality ACTs products</strong></td>
<td>□ Public sector</td>
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<td>□ Private sector</td>
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<td></td>
<td>□ (informal private sector)</td>
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<tr>
<td><strong>Active recall and disposal of existing oAMTs stocks from all outlets</strong></td>
<td>□ Public sector</td>
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<td></td>
<td>□ Private sector</td>
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<td>□ (informal private sector)</td>
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<tr>
<td><strong>Regular inspection of outlet systems</strong></td>
<td>□ Public sector</td>
<td>□ Regular inspection of manufacturing sites</td>
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<td>□ Private sector</td>
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<td>□ (informal private sector)</td>
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<tr>
<td><strong>Harmonization of regulations at state and federal levels (where applicable)</strong></td>
<td>□ Public sector</td>
<td></td>
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<td></td>
<td>□ Private sector</td>
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<td></td>
<td>□ (Informal private sector)</td>
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</tbody>
</table>
## Annex 3. Main factors that contribute to the development and spread of artemisinin resistance and potential solutions

<table>
<thead>
<tr>
<th>Factor</th>
<th>Issue</th>
<th>Potential solution</th>
</tr>
</thead>
</table>
| **Patient compliance / adherence to treatment** | Artemisinin-based monotherapy would require a complete 7-day treatment course to fully clear parasitaemia (and is thus not recommended by WHO anymore; WHO recommends a three day treatment course with ACTs (3))  
⇒ Due to the rapid clearance of symptoms by the artemisinin derivative within 3 days, patients often discontinue treatment too early. Thus only sub-therapeutic levels of API are achieved which cannot fully clear parasitaemia. | ➤ Use ACT medicines that require a 3-day treatment regimen in line with WHO guidelines (3).  
➤ Provide comprehensive information resulting in patient compliance to the full treatment course – rational use.  
➤ Ensure widespread accessibility to affordable, quality, and ideally fixed-dose (co-formulated) ACTs.  
➤ Eliminate oAMTs from the market. |
| **Formulation of products (co-blistered versus co-formulated)** | Co-blistered packs of artemisinin derivative and their partner medicine.  
⇒ Rapid clearance of symptoms without complete parasite clearance by the artemisinin derivative and poor tolerability of the partner medicine result in patients often taking only the artemisinin component of the co-blistered product.  
⇒ Sub-therapeutic levels of API through only one instead of two modes of action cannot achieve full clearance of parasitaemia. | ➤ Use fixed-dose ACTs (co-formulated products containing both partner medicines in one tablet).  
➤ Ensure widespread accessibility to affordable, quality ACTs. |
| **Quality of medicines** | Products containing inadequate amounts of the API or degradation due to poor stability.  
⇒ Sub-therapeutic levels of API cannot fully clear parasitaemia. | ➤ Select antimalarial medicines from pre-qualified sources for procurement.  
➤ Ensure functioning quality assurance and quality control measures at country level. |
| **Migrating populations** | Artemisinin-resistant strains from other geographical areas are imported, which then recombine with local parasites to give rise to a pool of mutated and recombined parasites.  
⇒ Contribution to development and spread of resistance. | ➤ Increase monitoring and surveillance, with specific attention to mass population movements from areas with high levels of resistance.  
➤ Improve access to rational treatment with ACTs. |
| **Regulatory systems** | Lack of adequate mechanisms at country level to ensure that only high-quality medicines enter the market. | ➤ Strengthen national drug regulatory systems.  
➤ Build capacity and introduce structural reforms. |
| **Information** | Insufficient knowledge of both prescriber and patient. | ➤ Provide adequate training and communication to change prescribing habits.  
➤ Conduct information campaigns for patients. |
| **Availability of ACTs** | Insufficient amounts of quality ACTs at affordable prices. | ➤ Ensure wide-scale availability of affordable, quality ACTs and rapid diagnostic tests in both public and private sectors to crowd out oAMTs and promote rational use of ACTs. |
Safety and efficacy news

Substandard and falsified products

Falsified antimalarial medicines in West and Central Africa

World Health Organization – WHO warns about three separate falsified antimalarial medicines discovered in Cameroon, Ghana and Liberia. The medicines concerned are falsely labelled as Rivopharm Laboratories Sulfadoxine/Pyrimethamine BP 500mg + 25mg, Biochemie GmnH Quinine Sulfate 300mg B.P. and Weiders Farmasotiske Quinine Sulphate 300mg USP. They are circulating in packs of 1000 tablets with English and French labelling containing spelling mistakes and bearing a previous WHO Essential Drugs Programme logo, which is no longer in use by WHO.

National regulatory authorities are requested to increase vigilance within the formal and informal supply chains for these products as described in more detail in the WHO Drug Alert. If any other medicines are discovered bearing the discontinued WHO Essential Drugs Programme logo, steps should be taken to ensure that they meet full specifications.


Safety information

Diacerein-containing medicines: restricted use

European Union – The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) of the European Medicines Agency (EMA) has endorsed recommendations to restrict the use of diacerein-containing medicines in order to manage the risks of severe diarrhoea and effects on the liver. Diacerein-containing medicines are currently authorized in the following EU Member States: Austria, Czech Republic, France, Greece, Italy, Portugal, Slovakia and Spain.

Diacerein should only be used to treat osteoarthritis affecting the hip or knee in patients aged under 65 years who do not have current or past liver disease. Treatment should be initiated by an experienced health care professional.

Stolen trastuzumab, pemetrexed and infliximab in Europe

European Union – The European Medicines Agency (EMA) has informed the public about the theft of trastuzumab, pemetrexed and infliximab vials in Italy, some of which were later reintroduced illegally into the supply chain in other countries. There is evidence that some of the trastuzumab vials had been tampered with. National health and law enforcement authorities are working to identify all concerned batches and take appropriate measures to protect the health of EU citizens.

EMA warned that the products with the batch numbers listed in the EMA press release must not be used because they cannot be considered safe or effective. Health professionals were advised to be alert when handling any other batches of the concerned medicines, and to report any suspicion of authenticity immediately to the local health authorities.

► EMA Press releases, 16 April 2014 and 17 April 2014.
Treatment should start at half the normal dose for the first 2-4 weeks and should be stopped if diarrhoea or signs of liver problems occur.

Domperidone: adverse effects on the heart

European Union – The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has completed its review of domperidone, triggered by concerns expressed by the Belgian medicines authority about the medicine’s effects on the heart.

The Committee recommended using domperidone only to manage nausea and vomiting – not other conditions such as bloating or heartburn – and reducing the dose in adults to 10 mg up to three times daily by mouth or 30 mg twice daily as suppositories. Where the medicine is licensed in children weighing less than 35 kg it should be given orally at a dose of 0.25 mg per kg bodyweight up to three times daily. The medicine should not normally be used for longer than one week.
► EMA News, 7 March 2014.
(See also under “Reviews started”)

Hydroxyethyl starch-containing products: increased risk for patients with sepsis

Australia – The Therapeutic Goods Administration (TGA) advises the public that a recent safety review of hydroxylethyl starch-containing products (Voluven® and Volulyte®) has confirmed an increased risk of mortality and the need for dialysis when this medicine is used to treat patients with sepsis. Hydroxyethyl starch-containing solutions are administered in clinical situations, including during surgery, to treat and prevent hypovolaemia.

In 2013 the product information was updated to include new contraindications for patients with sepsis and patients with severe liver disease, as well as changes to the precautions and dosage and administration sections. The safety review has found that the updates are sufficient to mitigate the risks.
► TGA Safety Advisory, 4 April 2014.

Epidural corticosteroid injection: rare but serious neurologic problems

United States of America – The U.S. Food and Drug Administration (FDA) is requiring a warning on drug labels that epidural injection of corticosteroids may result in rare but serious adverse events, including loss of vision, stroke, paralysis, and death.

Injectable corticosteroids include methylprednisolone, hydrocortisone, triamcinolone, betamethasone, and dexamethasone. This safety issue is unrelated to the contamination of compounded corticosteroid injection products reported in 2012.

Epidural injection of corticosteroids to relieve neck and back pain has been a widespread practice for many decades; however, the FDA has not approved corticosteroids for such use. A panel of experts is working to define the techniques for such injections which would reduce preventable harm. The FDA will continue to investigate this issue.
► FDA Safety Announcement, 23 April 2014.

Zolpidem, eszopiclone: impaired next-day alertness

European Union – The European Medicines Agency (EMA)’s Coordination Group for Mutual Recognition and Decentralised Procedures – Human
(CMDh) has endorsed new advice to minimize the risk of next-morning impaired driving ability and mental alertness associated with the sleeping medication zolpidem.

The product information of zolpidem-containing medicines will be updated to include strengthened warnings and precautions. The recommended doses must not be exceeded. Patients should take the lowest effective dose of zolpidem in a single intake, should not take any alcohol, illicit drugs or medicines affecting the central nervous system together with zolpidem, and should not drive or perform activities that require mental alertness for at least 8 hours after taking zolpidem.

United States of America – The U.S. Food and Drug Administration (FDA) warns that eszopiclone – similar in structure to zolpidem – is associated with next-day impairment of alertness, often not noticed by the patient. Eszopiclone-containing medicines marketed in the United States include Lunesta® and generics.

The recommended starting dose was reduced from 3 mg to 1 mg at bedtime. Higher doses can be taken if needed, but are more likely to impair next-day alertness. Patients should not drive or engage in other activities that require mental alertness on the day after taking a 3 mg dose. Product information was updated to include these changes.

Mirtazapine: abnormal heart rhythm

Canada – Merck Canada Inc., in consultation with Health Canada, has informed health professionals of post-marketing cases of QT prolongation and torsades de pointes reported with the use of the antidepressant mirtazapine (Remeron® / Remeron RD®). Most cases occurred in association with drug overdose or in patients with preexisting risk factors for QT prolongation. Serious outcomes including torsades de pointes and death have been reported with mirtazapine overdose.

Mirtazapine should be used with caution in patients with known cardiovascular disease, a family history of QT prolongation or concomitant use of QT prolonging medications. Vital signs and cardiac rhythm should be monitored in case of a mirtazapine overdose.

Vemurafenib: liver problems

Canada – Hoffmann-La Roche Limited (Roche Canada) and Health Canada have informed health professionals of cases of drug-induced liver injury, some of them severe, reported with vemurafenib (Zelboraf®). Vemurafenib is indicated for the treatment of certain types of unresectable or metastatic melanoma. Health professionals should monitor patients’ liver enzymes and bilirubin before and during treatment. Liver problems should be managed by reducing the dose of vemurafenib, or by interrupting or stopping the treatment.

Filgrastim and pegfilgrastim: capillary leak syndrome

Canada – Health Canada in association with the manufacturer has warned about the risk of capillary leak syndrome associated with filgrastim and pegfilgrastim, two medicines used to treat neutropenia. Capillary leak syndrome has been reported in cancer patients undergoing chemotherapy who were
treated with either of the medicines, and in bone marrow donors undergoing peripheral blood progenitor cell mobilization who were receiving filgrastim.

Capillary leak syndrome, the leaking of fluid from the circulatory system into the interstitial space, can cause circulatory shock and may be fatal. In case of suspected symptoms – such as swelling or puffiness, passing water less frequently, difficulty breathing, and tiredness – treatment must be stopped and the patient closely monitored.

► Health Canada Advisory, 10 April 2014.

Belimumab: opportunistic brain infection

Canada – Health Canada in association with the manufacturer has warned health professionals about two cases of progressive multifocal leukoencephalopathy (PML), an opportunistic brain infection, reported in patients receiving belimumab (Benlysta®) for systemic lupus erythematosus.

Health professionals should suspect PML in patients with new onset deficits or deterioration in cognition, speech or eye functions, seizures and/or motor and gait disturbances. A neurologist should be consulted urgently, and where appropriate immunosuppressants including belimumab should be withheld until PML is excluded.

► Health Canada Advisory, 22 April 2014.

Temozolomide: liver injury

Canada – Health Canada in association with the manufacturer has warned health professionals about cases of liver injury, including fatal liver failure, reported in patients taking temozolomide (Temodal®) for the treatment of glioblastoma. Liver toxicity may occur several weeks after initiation of treatment or after temozolomide discontinuation. Liver function should be tested before and during treatment. In case of significant abnormalities, the benefits and risks of continuing treatment should be carefully considered.

► Health Canada Advisory, 7 May 2014.

RAS-acting agents: not to be used in combination

European Union – The European Medicines Agency (EMA)’s Pharmacovigilance Risk Assessment Committee (PRAC) has advised against the combined use of two medicines of different classes acting on the renin-angiotensin (RAS) system. RAS-acting agents are used in the treatment of hypertension and congestive heart failure and include three main classes: angiotensin-receptor blockers (ARBs or “sartans”), angiotensin-converting enzyme inhibitors (ACE-inhibitors) and direct renin inhibitors such as aliskiren.

In particular, patients with diabetes-related kidney problems should not be given an ARB with an ACE-inhibitor; where this is absolutely necessary treatment must be supervised by a specialist with close monitoring of kidney function, fluid and salt balance and blood pressure. The combination of aliskiren with an ARB or ACE-inhibitor is strictly contraindicated in those with kidney impairment or diabetes. This confirms and strengthens the conclusions of a 2012 EMA review of aliskiren.

► EMA News, 11 April 2014.

TNF-alpha inhibitors: reactivation of tuberculosis

United Kingdom – The U.K. Medicines and Healthcare products Regulatory Agency (MHRA) has warned about an increased risk of tuberculosis, or
reactivation of latent tuberculosis, during treatment with tumour necrosis factor alpha (TNF-alpha) inhibitors.

Tuberculosis in patients receiving TNF-alpha inhibitors can be life-threatening, and deaths from tuberculosis have occurred in these patients. TNF-alpha inhibitors are therefore contraindicated in patients with active tuberculosis or other severe infections.

Patients should be screened for active and latent tuberculosis before starting treatment with a TNF-alpha inhibitor, and should be monitored closely for tuberculosis and other infectious diseases before, during, and after treatment.
► MHRA Drug Safety Update 7(9); April 2014.

Arsenic-containing dental pastes: genotoxicity

European Union – The European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) has recommended that the marketing authorizations for the dental pastes containing arsenic trioxide (Caustinerf arsenical®, Yranicid arsenical® and associated names) be revoked in the EU due to concerns over genotoxic effects that could increase the risk of cancer, and the risk of cell death if the product leaks into tissues around the teeth.

The dental pastes have been used to remove damaged nerves in the dental pulp. The CHMP considered that restrictions and additional guidance to dentists would not reduce the risks to an acceptable level.

Serotonin-blocking medicines: serotonin syndrome

Canada – Health Canada has completed a safety review of the serotonin-blocking drugs dolasetron (Anzemet®), granisetron (Kytril® and generics), ondansetron (Zofran® and generics) and palonosetron (Aloxi®), which are used for treating nausea and vomiting. This review identified a potential risk of serotonin syndrome, caused by serotonin accumulation in the body.

Early diagnosis is vital as serotonin syndrome can be fatal if not treated. Symptoms may include agitation, confusion, fast heartbeat, muscle twitching or stiffness, fever, loss of consciousness or coma.

The product monographs for the affected serotonin-blocking products on the Canadian market are being updated to include this new safety information.
► Health Canada Advisory, 14 May 2014.

Panitumumab: rare but severe skin reactions

Canada – Health Canada and the manufacturer has informed health professionals of rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis reported in patients treated with panitumumab (Vectibix®), approved for the treatment of certain types of metastatic colorectal cancer. The product monograph is being updated accordingly.
► Health Canada Advisory, 27 May 2014.
## Reviews started

### Overview of safety reviews started

<table>
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<th>Medicine</th>
<th>Uses</th>
<th>Concerns</th>
<th>Reviewing authority reference</th>
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<tr>
<td>Natalizumab</td>
<td>Treatment of relapsing-remitting multiple sclerosis</td>
<td>Melanoma</td>
<td>TGA Monitoring communication, 18 March 2014</td>
</tr>
<tr>
<td>Domperidone</td>
<td>Relief of symptoms of nausea and vomiting, and delayed stomach emptying</td>
<td>Adverse effects on the heart</td>
<td>TGA Monitoring communication, 2 April 2014</td>
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<td></td>
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<td>Medsafe Monitoring communication, 31 March 2014</td>
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<tr>
<td>Oral methadone medicines</td>
<td>Relief of withdrawal symptoms in patients dependent on opioids</td>
<td>Kidney failure possibly linked to misuse</td>
<td>EMA Press release, 11 April 2014</td>
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<td>containing povidone</td>
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<td>EMA Press release, 11 April 2014</td>
</tr>
<tr>
<td>Codeine-containing medicines</td>
<td>Cough and cold in children</td>
<td>Morphone toxicity</td>
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<tr>
<td>Testosterone-containing medicines</td>
<td>Treatment of hypogonadism</td>
<td>Heart problems</td>
<td>EMA Press release, 11 April 2014 (See also FDA Safety announcement, 31 January 2014)</td>
</tr>
<tr>
<td>Ambroxol and bromhexine</td>
<td>Expectorants; treatment of breathing disorders in newborns</td>
<td>Allergic reactions and severe skin reactions</td>
<td>EMA Press release, 11 April 2014</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Treatment of symptoms in adults with long-term stable angina or long-term heart failure</td>
<td>Increased combined risk of cardiovascular death or non-fatal heart attack in patients with symptomatic angina</td>
<td>EMA Press release, 8 May 2014</td>
</tr>
<tr>
<td>Hydroxyzine-containing medicines</td>
<td>Various, including treatment of anxiety disorders, sleep disorders premedication before surgery, relief of itching</td>
<td>Adverse effects on the heart</td>
<td>EMA Press release, 8 May 2014</td>
</tr>
</tbody>
</table>
Regulatory news

Pre-marketing assessment

EMA launches adaptive licensing pilot project

European Union – The European Medicines Agency (EMA) is piloting its adaptive licensing approach, also called staggered approval or progressive licensing. This approach aims to improve timely access for patients to new medicines. It builds on existing regulatory processes, including scientific advice, centralized approval for compassionate use, conditional marketing authorization (for medicines addressing life-threatening conditions), patients' registries and pharmacovigilance tools that allow collection of real-life data and development of risk management plans.

The pilot phase will enable the Agency to further refine how the adaptive licensing pathway should be designed for different types of products and indications. EMA is inviting companies to submit ongoing medicines development programmes at an early stage of clinical development for consideration as prospective pilot cases.


EMA and TGA strengthen collaboration on orphan medicines

European Union / Australia – The European Medicines Agency (EMA) and the Australian Therapeutic Goods Administration (TGA) have announced that they have agreed to share full assessment reports related to marketing authorizations of orphan medicines received in parallel by EMA and TGA. Both regulators will still reach their own conclusions. This collaboration will enable wider use of the limited number of studies conducted on medicines used to treat rare diseases.

► EMA News, 7 April 2014.

MHRA introduces early access to medicines scheme

United Kingdom – The U.K. Medicines and Healthcare products Regulatory Agency (MHRA) has launched its Early Access to Medicines Scheme (EAMS) and invites applications from the pharmaceutical industry and research organizations. The scheme aims to give patients with life-threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorization and for which there are no suitable alternative licensed treatments.

The scheme has two parts: Firstly, medicines with early indications of potential will be given a promising innovation medicine (PIM) designation based on assessment of clinical data. Secondly, medicines with a favourable benefit-risk profile will receive a positive scientific opinion which is published on the MHRA’s website. These opinions will support prescribers in deciding whether to use an unlicensed medicine for conditions where there are no or inadequate treatment options available.

► MHRA Press release, 7 April 2014.
EMA publishes draft guidelines for parallel scientific advice with health-technology-assessment bodies

European Union – The European Medicines Agency (EMA) has invited comments on a draft best practice guidance document that aims to facilitate an early dialogue on new medicines between regulators, health technology assessment (HTA) bodies and medicines developers.

HTA bodies – such as the UK’s National Institute for Health and Care Excellence (NICE) – advise healthcare systems on the usefulness of new medicines in their respective territories. The draft guidance proposes phases and timelines of the EMA-HTA parallel scientific advice process. The aim of this process is to facilitate agreement upon a development plan that generates data for both the EMA’s benefit-risk assessment and HTA bodies’ determination of added value. Strong interaction between all stakeholders is critical for innovation to reach patients in a faster and more transparent way.

Comments on the draft guidance will be considered at the EU together with results of two other projects: the EMA’s ongoing parallel scientific advice pilot running since 2010, and the European Commission’s Shaping European Early Dialogues for health technologies (SEED) consortium.

European Parliament has voted in new rules for clinical trials

European Union – The European Parliament has voted strongly in favour of new rules on clinical trials across Europe, with strengthened rules for transparency.

Since May 2011 clinical trials authorized in the EU are published in an official EU register. The Regulation requires that the results of all clinical trials, including those with unfavourable outcomes, are made public. It is expected to come into effect in mid-2016 at the earliest.

The European Medicines Agency (EMA) has welcomed the EU Regulation. In parallel EMA has conducted a final round of stakeholder consultations on its policy on proactive release of clinical trial data, with discussions on possible data redactions on the grounds of confidentiality, and the best ways of making the data accessible.

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Clinical trials

First-in-world pilot programme on multi-regional clinical trials

Singapore – Singapore’s Health Sciences Authority (HSA) and the Duke-NUS Graduate Medical School Singapore have concluded the first-in-world pilot programme on multi-regional clinical trials. Endorsed by the Asia-Pacific Economic Cooperation (APEC), this programme provides for simultaneous conduct of a clinical trial in multiple geographical regions.

Multi-regional clinical trials play a major role in giving patients early access to innovative new medicines. APEC accounts for over 40% of the world’s population and is an increasingly important destination for such trials.

APEC is now exploring with Duke-NUS and HSA further programmes to enhance the capacity of regulatory agencies across the region, possibly also accommodating clinical trials professionals from industry and healthcare institutions.

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supportive EMA procedures to ensure full clinical trial data transparency in the EU.

HAI Europe statements, 3 April and 22 May 2014.
EMA News, 8 April 2014.
EMA Press release, 28 May 2014.

EMA and FDA propose joint clinical investigation mechanism for rare children’s disease

European Union/United States of America – The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) have released a draft joint proposal to facilitate the clinical investigation of new medicines for the treatment of Gaucher disease in children.

Gaucher disease is a rare condition in children that can be extremely severe. There is a high unmet need for medicines to treat children with neurological symptoms, in particular for new routes of administration to reduce the treatment burden. Recruitment of children for clinical trials on this rare condition is difficult and poses a burden on patients and their families.

The joint proposal aims to evaluate multiple medicines more quickly in fewer patients using two complementary approaches: extrapolating efficacy from adults to children through modelling and simulation, and conducting multi-arm, multi-company clinical trials on several new medicines at the same time, with the same control arm serving more than one medicine under evaluation.

The document is released for public consultation until 31 August 2014.
► EMA News, 14 May 2014.

Post-marketing control

EU adopts specifications for post-marketing efficacy studies

European Union – The European Commission has adopted legislation that specifies the situations where medicines regulatory authorities can require an efficacy study for a medicine after it has been granted a marketing authorization. The act will enter into force on 30 April 2014.

Post-authorization studies aim to address concerns about the efficacy of a medicine in certain situations, such as everyday medical practice, in specific populations, or over time. Such studies already existed previously, however, new pharmacovigilance legislation came into force in the EU in July 2012 to extend the legal framework in which they can be required.
► EMA News, 11 April 2014.

EMA reports on implementation of new pharmacovigilance legislation

European Union – The European Medicines Agency (EMA) has presented the European Commission with its report on the first year of implementing the EU’s new pharmacovigilance legislation on monitoring the safety of medicines and reducing their risks.

The report reveals positive first-year results in collection and analysis of data, timeliness and transparency. Patient reports of suspected adverse drug reactions increased by over 60% compared with the previous year. Product information was updated as a consequence of signals of new or changing safety issues with certain medicines, and a number of major public health reviews were initiated. Thousands of individuals
were trained in pharmacovigilance, and a catalogue with training material for the implementation of the new legislation has been published.
► EMA News, 2 May 2014.

Guidance

EMA recommendations on seasonal influenza vaccine composition

European Union – The European Medicines Agency (EMA) has issued its annual recommendations for the influenza virus strains that should be included in vaccines for the 2014/2015 season. For trivalent vaccines these include an A/California/7/2009 (H1N1)pdm09-like virus; an A/Texas/50/2012 (H3N2)-like virus and a B/Massachusetts/2/2012-like virus. Quadrivalent vaccines containing two influenza-B viruses should also include a B/Brisbane/60/2008-like virus. The annual recommendations are made on the basis of observations by the World Health Organization.

MHRA confirms position on statins

United Kingdom – The UK Medicines and Healthcare products Regulatory Agency (MHRA) has confirmed its position on the use of statins, advising that their benefits strongly outweigh the risks.

The MHRA statement follows recent controversial media coverage about side effects associated with statins. The MHRA advises that large clinical trials have shown that statins reduce the risk of heart attacks, strokes and the need for heart surgery, and that most side effects are mild.
► MHRA News, 16 May 2014.

Approvals

Miltefosine for leishmaniasis

United States of America – The U.S. Food and Drug Administration (FDA) has approved miltefosine (Impavido®) to treat leishmaniasis, a disease transmitted to humans through sand fly bites primarily in tropical and subtropical regions.

Miltefosine was approved for oral treatment of visceral, cutaneous and mucosal leishmaniasis in patients 12 years of age and older. The medicine was granted fast track designation, priority review, and orphan product designation. The medicine should not be taken during pregnancy. Women should use effective contraception during and for five months after treatment with miltefosine.
► FDA News release, 19 March 2014.

Apremilast for psoriatic arthritis

United States of America – The U.S. Food and Drug Administration (FDA) has approved apremilast (Otezla®) to treat adults with active psoriatic arthritis (PsA), a form of arthritis that affects some people with psoriasis. Currently approved treatments for PsA include corticosteroids, tumor necrosis factor blockers, and an interleukin-12/interleukin-23 inhibitor. Compared to placebo, apremilast was shown to have benefits in treating tender and swollen joints and improving physical function.

Patients treated with apremilast should be monitored for unexplained or clinically significant weight loss and for signs of depression. The FDA is requiring a pregnancy exposure registry as a post-marketing requirement to assess the risks of apremilast to pregnant women.
► FDA News release, 21 March 2014.
Vintafolide for ovarian cancer, with diagnostic medicines etarfolatide and folic acid
European Union – The European Medicines Agency (EMA) has recommended approval of vintafolide (Vynfinit®) to treat a sub-type of platinum-resistant ovarian cancer for which there are limited approved treatment options.

The medicine was recommended for approval together with two companion diagnostic medicines, etarfolatide (Folcepri®) and folic acid (Neocepri®), that will help identify patients who may benefit from treatment with vintafolide. All three medicines have an orphan designation and were recommended for conditional marketing authorizations.


Siltuximab for Castleman’s disease
European Union/United States of America – The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have both approved siltuximab (Sylvant®) for the treatment of adult patients with multicentric Castleman’s disease.

Siltuximab is the first medicine approved to treat this rare disorder, which is characterized by non-cancerous growth of the lymph nodes and related tissues. Affected patients have an increased risk of infection, kidney failure and certain cancers. Castleman’s disease is chronically debilitating and life-threatening, especially for patients with more than one affected lymph node.

Both authorities had granted an orphan designation to the medicine and evaluated it by their respective accelerated priority review mechanism.


Vedolizumab for ulcerative colitis and Crohn’s disease
European Union/United States of America – The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have both approved vedolizumab (Entyvio®) to treat moderately to severely active ulcerative colitis or Crohn’s disease in adult patients who have had an inadequate response or were intolerant to other therapies.

Ulcerative colitis and Crohn’s disease are chronic auto-immune diseases that cause considerable ill health and mortality and increase the risk of colon cancer. Vedolizumab is a monoclonal antibody that binds specifically to a key mediator of gastrointestinal inflammation, allowing for a selective, targeted activity.


Empagliflozin for type 2 diabetes
European Union – The European Medicines Agency (EMA) has recommended approving empagliflozin (Jardiance®) for type 2 diabetes both for monotherapy and as an add-on agent in combination therapy. Empagliflozin blocks a protein in the kidney, reducing glucose re-absorption and leading to glucose excretion in the urine, thereby lowering blood glucose levels and improving glycaemic control.


Simeprevir for chronic hepatitis C
European Union – The European Medicines Agency (EMA) has recommended approving simeprevir (Olysio®) for the treatment of chronic hepatitis C in adult patients in combination with other medicinal products. Simeprevir is a specific inhibitor of the hepatitis C virus NS3/4A serine protease. The medicine should be prescribed by health
professionals experienced in the treatment of chronic hepatitis C.

**Fluticasone furoate and vilanterol trifenate for asthma and COPD**

European Union – The European Medicines Agency (EMA) has recommended authorizing a fixed-dose combination of fluticasone furoate and vilanterol trifenate (Revinty Ellipta®) for the treatment of asthma and of chronic obstructive pulmonary disease (COPD) in patients not adequately controlled with other therapies. The Risk Management Plan identifies pneumonia as a risk which the applicant will investigate through further post-authorization safety studies.

**Generic oseltamivir for influenza**

European Union – The European Medicines Agency (EMA) has recommended authorizing a generic oseltamivir product (Ebilfumin®) for the prevention and treatment of influenza. This is a generic of Tamiflu® which has been authorized in the EU since 20 June 2002.

**Topiramate for migraine prevention in adolescents**

United States of America – The U.S. Food and Drug Administration (FDA) has approved topiramate (Topamax®) for prevention of migraine headaches in adolescents ages 12 to 17. This is the first FDA approval of a medicine for migraine prevention in this age group. Topiramate was approved by the FDA in 1996 to prevent seizures, and in 2004 for migraine prevention in adults.
► FDA News release, 28 March 2014.

**Long-acting recombinant coagulation factor IX concentrate for haemophilia B**

United States of America – The U.S. Food and Drug Administration has approved a recombinant coagulation factor IX linked to Fc fusion protein (Alprolix®) to help control and prevent bleeding in adults and children with haemophilia B. The Fc protein fragment is found in antibodies, making the product last longer in circulation and requiring less frequent injections. The product received orphan-drug designation for this use by the FDA.
► FDA News release, 28 March 2014.

**Albiglutide for type 2 diabetes**

United States of America – The U.S. Food and Drug Administration (FDA) has approved albiglutide subcutaneous injection (Tanzeeum®) to improve glycemic control in adults with type 2 diabetes. Albiglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist, which mimics the action of a hormone that helps normalize blood sugar levels.

Albiglutide should not be used as first-line therapy, nor should it be used in patients with type 1 diabetes, those with diabetic ketoacidosis, or those that have an increased risk of medullary thyroid carcinoma. The FDA is requiring a number of post-marketing studies and the implementation of a Risk Evaluation and Mitigation Strategy (REMS) to manage the risks associated with albiglutine.
► FDA News release, 15 April 2014.

**Two sublingual pollen extracts for allergies**

United States of America – The U.S. Food and Drug Administration (FDA) has approved two sublingual allergen extract tablets for the treatment of pollen allergies in adults (Oralair® and Ragwitek®). These
are the first sublingual allergen extracts to be approved in the United States. Treatment is initiated under the observation of a health professional four months before the start of the pollen season and continued once daily throughout the season.

► FDA News releases, 2 April 2014 and 17 April 2014.

**Ramucirumab for stomach cancer**

United States of America – The U.S. Food and Drug Administration (FDA) has approved ramucirumab (Cyramza®) to treat advanced stomach cancer. Ramucirumab is an angiogenesis inhibitor that blocks the blood supply to tumors. The medicine was reviewed under the FDA’s priority review programme and had been granted orphan product designation.

► FDA News release, 21 April 2014.

**Ceritinib for late-stage lung cancer**

United States of America – The U.S. Food and Drug Administration (FDA) has granted accelerated approval to ceritinib (Zykadia®) for patients with a certain type of late-stage non-small cell lung cancer. Ceritinib is intended to treat patients previously treated with crizotinib, the only other approved product of the class of ALK tyrosine inhibitors targeting this particular type of lung cancer. The FDA granted ceritinib breakthrough therapy designation, priority review and orphan product designation.

► FDA News release, 29 April 2014.

**Trametinib for advanced melanoma**

European Union – The European Medicines Agency (EMA)’s Committee for Medicinal Products for Human Use (CHMP) has recommended marketing authorization for trametinib (Mekinist®) for the treatment of adult patients with unresectable or metastatic melanoma.

Trametinib is the first cancer treatment that selectively targets an enzyme called MEK protein kinase, which is activated by a protein produced in patients with a BRAF V600 mutation. Together with dabrafenib, vemurafenib and imurafenib, trametinib belongs to the group of new selective treatments that have changed the therapeutic landscape for advanced melanoma.


**Vorapaxar to reduce cardiovascular risks**

United States of America – The U.S. Food and Drug Administration (FDA) has approved vorapaxar (Zontivity®) to reduce the risk of heart attack, stroke, cardiovascular death, and the need for procedures to restore the blood flow to the heart in patients with a previous heart attack or blockages in the arteries to the legs. Vorapaxar, an anti-platelet agent, is the first approved protease-activated receptor-1 (PAR-1) antagonist.

Vorapaxar increases the risk of bleeding. It must not be used in people who have had a stroke, transient ischaemic attack, or bleeding in the head. Patients should report to their health care professional any unanticipated, prolonged or excessive bleeding, or blood in their stool or urine.

► FDA News, 8 May 2014.

**Dalbavancin for skin infections**

United States of America – The U.S. Food and Drug Administration (FDA) has approved dalbavancin, (Dalvance®), for the intravenous treatment of acute skin and skin structure infections caused by susceptible bacteria like *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains) and *Streptococcus pyogenes*.
Dalbavancin is the first drug designated as a Qualified Infectious Disease Product (QIDP) to receive FDA approval. This designation is granted to antibacterial or antifungal human medicines intended to treat serious or life-threatening infections. ►FDA News release, 23 May 2014.

Ataluren for Duchenne muscular dystrophy
European Union – The European Medicines Agency (EMA) has recommended conditional approval of a first-in-class medicine for treatment of Duchenne muscular dystrophy in patients aged five years and older who are able to walk. Ataluren (Translarna®), an orphan-designated medicine for the treatment of Duchenne muscular dystrophy. Duchenne muscular dystrophy is a genetic disease characterized by the lack of the protein dystrophin, causing loss of muscle function. There are currently no approved therapies available for this life-threatening condition. The company will be required to provide comprehensive data from an ongoing confirmatory study. ►EMA Press release, 23 May 2014.

Obinutuzumab for chronic lymphocytic leukaemia
European Union – The European Medicines Agency (EMA) has recommended approving obinutuzumab (Gazyvaro®) in combination with the cancer medicine chlorambucil for the treatment of adults with previously untreated chronic lymphocytic leukaemia. Chronic lymphocytic leukaemia is a long-term debilitating disease as patients can develop severe infections. It remains incurable, although currently available treatments generally induce remission. Obinutuzumab has an orphan designation. It is a monoclonal antibody that targets B-lymphocytes, thereby helping the body’s immune system to kill the cancer cells. ►EMA Press release, 23 May 2014.

Peginterferon beta-1a for multiple sclerosis

Simoctogog alfa for patients with haemophilia A
European Union – The European Medicines Agency (EMA) has recommended approval of simoctogog alfa (Nuwiq®) for the treatment and prophylaxis of bleeding in paediatric and adult patients with haemophilia A (congenital factor VIII deficiency). The active substance is a recombinant blood coagulation factor VIII. ►EMA Opinion, 22 May 2014.

Brinzolamide / brimonidine tartrate to reduce intra-ocular eye pressure
European Union – The European Medicines Agency (EMA) has recommended approval of the combination of brinzolamide and brimonidine (Simbrinza®) eye drops for the treatment of elevated intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction. ►EMA Opinion, 22 May 2014.
Publications and events

WHO hepatitis C guidelines published
London – WHO has published its first guidelines on hepatitis C screening, care and treatment. Complementing existing guidance on the prevention of transmission of blood-borne viruses, the guidelines give recommendations on how to manage infections with the hepatitis C virus in resource-limited settings.

Two new oral medicines, sofosbuvir and simeprevir, have recently been approved for chronic hepatitis C, and others are in the pipeline. The guidelines strongly recommend the use of sofosbuvir for most hepatitis C genotypes. Quality-assured products at affordable prices will be needed for countries to scale up treatment.


WHO report reveals worldwide antibiotic resistance
Geneva – A new WHO report reveals that antimicrobial resistance is now a major global threat to public health that can affect anyone, of any age, in any country.

This is the first report to provide a global picture of antimicrobial resistance, with data from 114 countries. The findings suggest that the world may beheaded for a post-antibiotic era, in which common infections and minor injuries can once again kill.

Antibiotic resistance occurs when bacteria change so that antibiotics no longer work to treat infections. The results show that bacteria causing common, serious diseases such as bloodstream infections, diarrhoea, pneumonia, urinary tract infections and gonorrhoea have become resistant to antibiotics in all regions of the world.

While some important steps are being taken to address the problem, every country and individual needs to do more. Urgent, coordinated action by health care workers, patients, policy makers and industry is needed to prevent infections and to improve the ways in which antibiotics are produced, prescribed and used.

►WHO News release, 30 April 2014.

EU and US continue joint battle against antimicrobial resistance
Atlanta – The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) has presented its first progress report, highlighting some significant achievements.

TATFAR has identified 17 recommendations for collaborations between the US and the EU to combat antimicrobial resistance. Implementation of these recommendations has led to an increase in exchanging information, understanding of best approaches and practices, and developing peer relationships. It is hoped that the positive outcomes of this
WHO core functions need reliable funding

Financing of WHO’s work in support of essential medicines remains a cause for concern, according to a recent letter in The Lancet. In particular, reliable funding is still lacking to maintain the norms, standards, policy and pricing guidance and mechanisms that will support Member States in securing affordable supplies of appropriate, quality-assured medicines.

The authors emphasize that WHO’s work on medicines cuts across almost every component of health services in countries, and that many international organizations depend on this work. They call on WHO Member States to ensure that WHO has the necessary resources to effectively support universal health coverage at a time of complex and expanded global health needs.


WHO and Global Fund strengthen partnership

Geneva – The World Health Organization and the Global Fund have strengthened their long established partnership with a new technical agreement to support countries in developing more strategic investments in the fight against HIV, tuberculosis and malaria.

Under the agreement, WHO will provide technical assistance to Global Fund applicants under the new funding model ahead of the submission of their grant applications, or concept notes. The new funding model promotes opportunities for health interventions with a bigger impact.

WHO will provide assistance through its country or regional offices and with the Roll Back Malaria and STOP TB partnerships.

► WHO News release, 24 May 2014.
Market and supply

ViiV and MPP sign licence agreement for dolutegravir

Geneva – The Medicines Patent Pool (MPP) and ViiV Healthcare have signed a licence agreement for dolutegravir, an antiretroviral medicine approved by EMA and FDA in recent months. Access to dolutegravir could improve millions of lives in developing countries.

The agreement will enable generic manufacturers based anywhere in the world to supply low-priced products containing dolutegravir for adults and children also as fixed-dose combination with other medicines including abacavir. The countries covered by the agreement are home to over 93% of adults and 99% of children living with HIV in the developing world.


Global Fund meets with Chinese pharmaceutical manufacturers

Shanghai – The Global Fund to Fight AIDS, Tuberculosis and Malaria and the China Chamber of Commerce for Import and Export of Medicines and Health Products have held a conference with Chinese pharmaceutical manufacturers in Shanghai, with a view to source more quality-assured medicines from China.

China is the world’s leading source of active pharmaceutical ingredients. The country is currently taking steps to strengthen oversight and independence of the medicines approval process. WHO representatives attended the event to explain requirements for prequalification of medicines for procurement by international organizations.


First WHO GMP-compliant Nigerian manufacturer

Lagos – A WHO inspection and verification of follow-up action has confirmed that Swiss Pharma Nigeria Limited (Swipha) operates at an acceptable level of WHO good manufacturing practice (GMP) for the manufacture of oral solid dosage forms. A public inspection report is available on the WHO website.

Swipha is the first manufacturer in Sub-Saharan West Africa to pass a GMP inspection by the WHO Prequalification Team (PQT). The company is developing a product dossier for submission to WHO-PQT. WHO has provided technical assistance to Nigerian manufacturers since 2011, with active support from the Nigerian medicines regulatory authority.

► WHO Prequalification update, 4 April 2014.

Snapshot of patents and licences on antiretrovirals

Geneva – UNITAID and the Medicines Patent Pool (MPP) have jointly released a new report providing an overview of the patent and licensing status of selected antiretroviral (ARV) medicines in developing countries.

The document focuses on WHO-recommended ARVs, but also analyzes data on new ARVs that have either recently obtained regulatory approval or are in Phase III clinical trials. The main source of data for compiling this report is the MPP patent database.

► Medicines Patent Pool announcement, 8 May 2014.
Antiretroviral prices in middle-income countries

Geneva – The World Health Organization (WHO) has published an analysis of the prices paid by 20 middle-income countries for adult and paediatric formulations of WHO-recommended antiretroviral treatments, together with information on the patent status and license agreements of the products, their regulatory status as well as tariffs, markups and taxes.

The data show that procurement prices vary widely between the countries included in the analysis. While prices are low in India and middle-income countries in Africa for first-line and many second-line treatment regimens, they are higher in other middle-income countries, especially for newer second-line and third-line treatments sourced from originator producers.


WHO prequalifies first products manufactured in Egypt

Geneva – WHO has prequalified two products manufactured by the Egyptian Pharmaceutical Industry Co. (EIPICO): ceftriaxone, 1 gm/vial and ceftriaxone, 500 mg/vial powder for injection. These two products — antibiotics for use in treating HIV/AIDS-related conditions in adults, adolescents and children — are now eligible for procurement by international donors. They represent Egypt’s potential as a producer of quality-assured medicines for priority diseases.

WHO has been providing technical support to manufacturers and national regulatory authorities in the WHO Eastern Mediterranean region since 2008. Several other manufacturers in Egypt, Iran, Jordan, Pakistan and Oman are also actively pursuing prequalification of their products.

►Prequalification Update - 16 May 2014.

BRICS Ministers join forces for access to medicines

Geneva – At a side event to the opening of the 2014 World Health Assembly, strong statements were made by BRICS (Brazil, Russia, India, China and South Africa) country ministers and representatives to cooperate to tackle the issue of inaccessibility to affordable medicines in their countries and the developing world.

The Ministers shared national experiences and showed mutual support for the continued use of local production, compulsory licensing and parallel importations and other mechanisms to push down prices and increase access to medicines for all in need, including in middle-income countries that often do not classify for donations from health initiatives despite large parts of their populations still living in poverty.

Speaking at the event, WHO Director General Margaret Chan thanked the BRICS countries for their leadership. She referenced ongoing activities by international organizations to support quality-assured local production of medicines, the need to strengthen national regulatory capacity, and the importance of knowing the data to make the right investments in health.

►Intellectual Property Watch reporting from the World Health Assembly, 20 May 2014.
Upcoming events

16th International Conference of Drug Regulatory Authorities (ICDRA)

The 16th ICDRA will be held in Rio de Janeiro, Brazil on 24-29 August 2014. This biennial conference provides a forum for medicines regulatory authorities of WHO Member States to meet and discuss ways to strengthen collaboration. This conference provides a strategic opportunity to drug regulatory authorities to share solutions found in different parts of the globe, and to determine priorities for action in national, regional and international regulation of medicinal products.

While the ICDRA conference itself is restricted to governmental officials and regulators, the Pre-ICDRA conference, to be held on 24-25 August 2014, is open to pharmaceutical industry, academia, non-governmental and international organizations.

► Further information is found on the 16th ICDRA official website at http://www.icdra.com.br/

WHO-UNICEF-UNFPA meeting with manufacturers

This year’s joint WHO-UNICEF-UNFPA meeting with manufacturers and suppliers of diagnostic products, finished pharmaceutical products, active pharmaceutical ingredients and vaccines will take place on 22-25 September 2014 at UN City in Copenhagen, Denmark.

This meeting provides a forum at which diagnostic, pharmaceutical and vaccine manufacturers, together with quality, safety and efficacy experts, procurement agencies, and international donors working in public health, can come together to discuss issues around production and supply of quality products needed for treatment for vulnerable populations.

► Further information will be posted closer to the event on the WHO Prequalification website at http://apps.who.int/prequal/info_press/press_and_media.htm.

International Conference of Drug Regulatory Authorities (ICDRA)

The 16th ICDRA will be hosted by the Brazilian National Health surveillance Agency (ANVISA)

Rio de Janeiro, Brazil
24 - 29 August 2014

http://www.icdra.com.br/
WHO working for you

Online database of training activities

All WHO trainings on medical products in a single web database – focus on regulation

For the first time ever, training activities of an entire WHO department are publicly available in a consolidated database. The Essential Medicines and other Health Technologies (EMP) Department has created an online platform with updated information on all its past and coming training events.

WHO-EMP offers training on a wide range of topics related to the manufacture and use of medical products, including pharmaceuticals, vaccines, diagnostics and medical devices. The focus is on regulatory issues.

The training activities are grouped by organizing WHO units and by topics, including access; product efficacy / performance, good practice compliance; patents; policy; quality; regulatory practice; and safety and vigilance.

This powerful new tool enables WHO partners and stakeholders to stay informed, plan their own training schedules, access training materials of past events, or contact the organizer for further information.

► Training activities offered by Department of Essential Medicines and other Health Technologies (EMP) [webpage - see below].

► Contact WHO at emp_training@who.int with any questions or comments.

www.who.int/entity/medicines/training/emp_training_activities/en/index.html

Training activities offered by Department of Essential Medicines and other Health Technologies (EMP)

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<td>Quality</td>
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Consultation documents

The International Pharmacopoeia

Radiopharmaceuticals: General monograph

This is a revised draft proposal for The International Pharmacopoeia (Working document QAS/13.542/Rev.1, March 2014).

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, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

1.1 Introduction

Radiopharmaceuticals, as the name suggests, are pharmaceutical formulations consisting of radioactive substances (radioisotopes and molecules labelled with radioisotopes), which are intended for use either in diagnosis or therapy.

Radiopharmaceuticals are essential components of nuclear medicine practice; a modality where radiopharmaceuticals are administered to patients for diagnosing, managing and treating a large number of diseases.

In imaging, the unique properties of γ-rays emitted from the radioactive isotopes allow the radiopharmaceutical to be traced or imaged non-invasively, thus providing functional information of the target tissue or organ. In therapy, the β-ray energy from the radioisotope is delivered to the target tissue to partially or completely destroy the diseased tissues.

Radiopharmaceuticals are unlike conventional pharmaceuticals in many respects. The most striking feature is the property of the radionuclide, which disintegrates or decays with time, often resulting in a limited shelf-life of the product. The physical half-life of the radionuclides used in radiopharmaceuticals is generally short, and hence the final preparation needs to be carried out before administration to the patient. Hence, the concept of the "hospital radiopharmacy" unit to prepare radiopharmaceuticals has become a practice in nuclear medicine departments in hospitals. At the hospital radiopharmacy a trained radiopharmacist prepares the various radiopharmaceutical formulations and tests each formulation for its quality (quality control). The formulations are then provided to a nuclear medicine physician for administration into the patient for investigation or for therapy.

Radiopharmaceuticals are either ready to use (available from suppliers) or prepared in-house from "cold kits" and radioisotopes from generators, or synthesized from radioisotopes and suitable precursors as with cyclotron-produced radioisotopes. Some centres synthesize the necessary ligands at their hospital radiopharmacy and formulate the radiopharmaceuticals. All are subjected to the required quality control tests, to ensure that the formulations fulfill radiological and pharmaceutical safety and efficacy in accordance with the specifications laid down.

The use of radioactive material necessitates careful and safe handling of these products by trained and authorized personnel, in an approved/authorized laboratory facility as per the guidelines of Atomic Energy Regulatory Board (AERB) in India.
1.2 Definitions and terminology

chemical purity
Chemical purity of a chemical substance is the percentage of the chemical of interest in the specified chemical form. In the monographs on radiopharmaceutical preparations, chemical purity of the active ingredient is indicated and controlled by specifying limits on chemical impurities.

half-life period
The time in which a given quantity of a radionuclide decays to half its initial value is termed as half-life ($T_{1/2}$).

isotopes
Isotopes of an element are nuclides with the same atomic number "Z" but different mass numbers “A”. They occupy the same place in the periodic table and have similar chemical properties.

isotopic carrier
An isotopic carrier is a stable isotope of the element either present or added to the radioactive isotope of the same element. Often the radionuclides contain isotopic carriers and their content depends on the route/method followed for the production of the radionuclide.

kit for radiopharmaceutical preparation
It is a set of non-radioactive reagents to be reconstituted and/or combined with radionuclides following the protocol suggested by the manufacturer for preparing the final radiopharmaceutical formulations, prior to its administration. Such kits are also often referred to as “cold kits”, as they are devoid of radioactivity.

nuclide
An elemental species characterized by (a) its mass number “A”, (the sum of the number of protons and neutrons in its nucleus), (b) its atomic number “Z” (number of protons which is also same as number of electrons in a neutral atom) and also by (c) its nuclear energy state.

period of validity or shelf-life of the radiopharmaceutical
The time during which specifications described in the monograph are complied with by the radiopharmaceutical denoting the shelf-life of the radiopharmaceutical preparation. Any radiopharmaceutical preparations including the cold kits have limited shelf-life, which needs to be clearly stated on the label as the expiry date, and if necessary, the time.

radioactive concentration
This refers to the radioactivity of a radionuclide per unit volume of the radioactive preparation.

radioactivity
The phenomenon of emission of radiation owing to the spontaneous transformation or disintegration of a radionuclide is known as “radioactivity”. However, the term “radioactivity” is also used to express the physical quantity (activity or strength) of this phenomenon. The radioactivity of a preparation is the number of nuclear disintegrations or transformations per unit time.

radiochemical purity
The ratio, expressed as a percentage, of the radioactivity of the radionuclide of interest in a stated chemical form, to the total radioactivity of that radionuclide present in the preparation, is referred to as “radiochemical purity”. In the context of radiopharmaceuticals, radiochemical purity is an important quality parameter which needs to be within the stipulated limits. The relevant radiochemical impurities are listed with their limits in the individual monographs for each radiopharmaceutical.
**radionuclide**

Nuclides containing an unstable arrangement of protons and neutrons that transform spontaneously to either a stable or another unstable combination of protons and neutrons with a constant statistical probability by emission of radiation. These are said to be radioactive and are called radionuclides. The initial unstable nuclide is referred to as the "parent radionuclide" and the nuclide after transformation as the "daughter nuclide". Such a transformation is also known as "radioactive transmutation" or "radioactive disintegration" or "radioactive decay".

**radionuclide generator**

Any system or device incorporating a fixed parent radionuclide from which is produced a daughter radionuclide by elution or by any other method and used in radiopharmaceutical preparation, e.g. the most widely used radionuclide generator in radiopharmacy is the $^{99}$Mo-$^{99m}$Tc generator.

**radionuclidic purity**

The ratio, expressed as a percentage, of the radioactivity of the radionuclide of interest to the total radioactivity of the radioactive preparation is referred to as "radionuclidic purity". In the context of radiopharmaceuticals, radionuclidic purity is an important quality parameter and it is mandatory that the radionuclidic impurities are within the stipulated limits. Such radionuclidic impurities arise during the radionuclide production and are, hence, dependent on the production route. In the context of radiopharmaceuticals the acceptable limits for the possible radionuclides are listed in the individual monographs.

**radiopharmaceutical**

Any medicinal or pharmaceutical product which, when ready for use, contains one or more radionuclides (radioactive isotopes) intended for human use, either for diagnosis or therapy.

**radiopharmaceutical precursor**

It is a chemical compound or ligand used in the synthesis of the radiopharmaceutical preparation. It could either be an inactive chemical compound or a radiolabelled intermediate produced for the preparation of radiopharmaceutical formulation, prior to administration.

**specific radioactivity**

The radioactivity of a radionuclide per unit mass of the element or of the chemical form of the radioactive preparation is referred to as the "specific radioactivity", sometimes also referred as "specific activity".

**total radioactivity**

The radioactivity of the radionuclide per unit of the dispensed formulation (vial, capsule, ampoule, generator, etc.) is the total radioactivity, which is an important parameter in dispensing and administration of the radioactive material to the patient as well as from the regulatory requirement for safe handling of the radioactive materials in a facility.

**units of radioactivity**

In the International System (SI), the unit of radioactivity is one nuclear transmutation per second and is expressed in Becquerel (Bq), named after the scientist Henri Becquerel. The old unit of radioactivity was Curie (Ci), named after the scientists Madame Marie Curie and Pierre Curie, the pioneers who studied the phenomenon of radioactivity. One Ci is the number of disintegrations emanating from 1 g of Radium-226, and is equal to $3.7 \times 10^{10}$ Bq. Absolute radioactivity measurements require a specialized laboratory, but identification and measurement of radiation can be carried out relatively by comparing with standardized preparations provided by reference laboratories recognized by international or national authorities. (With all statements involving radioactivity, it is necessary to include a reference date of measurement in case of radionuclides with a half-life less than 30 days. The time of
standardization should be expressed to the nearest hour. For radionuclides with a half-life period of less than one day, a more precise statement of reference time should be given.)

1.3 Phenomenon of radioactive decay and the radiations

The radioactive decay or transformation, as described earlier, involves transformation of the unstable radioactive nucleus to attain a more stable configuration. As the nucleus contains protons and neutrons, such transformations involve reactions of these sub-atomic particles. In a simplified manner, it could be stated that the stability of the nucleus predominantly depends on the total number of nucleons (protons and neutrons) as well as the ratio of the protons (p) to the neutrons (n). While nearly all the isotopes beyond element Bismuth (atomic number 83) are radioactive as the total number of nucleons become too large for stability, the lower atomic number elements have stable as well as radioactive isotopes, depending on the p/n ratio and certain other properties of the nuclide. Generally, a proton rich (or neutron deficient) nuclide would transform to reduce the proton content; while a neutron rich nuclide would transform vice versa. A very heavy radionuclide may attain stability by shedding some nucleons. Such transformations may involve the emission of charged particles, capture of electron from the extra-nuclear orbits by the nucleus, also known as electron capture (EC) or isomeric transition (IT). The charged particles emitted from the nucleus may be alpha (α) particles (helium nucleus of mass number 4) or beta (β) particles. Beta particles may be either, negatively charged β–, also known as negatrons, generally equivalent to electrons or positively charged β+, and also known as positrons. The emission of charged particles from the nucleus may be accompanied by the emission of gamma (γ) rays, which are energetic photons of electromagnetic radiation and do not have any charge or mass. Gamma rays are also emitted in a process called isomeric transition (IT), where an excited state of a radionuclide decays to the de-excited state by gamma-ray emission, with no changes in atomic, mass or neutron number. The emissions of gamma rays may be partly replaced by the ejection of electrons known as internal conversion (IC) electrons, due to the interaction of the gamma ray with the extranuclear orbital electrons. This phenomenon, like the process of electron capture, causes a secondary emission of X-rays (due to the vacancies created in the electronic orbits which are then filled by reorganization of the electrons from the outer orbits in the atom). This secondary emission of X-rays may itself be partly replaced by the ejection of outer electrons known as Auger electrons, due to the interaction of the X-rays with the outer electrons.

The decay of a radionuclide is governed by the laws of probability with a characteristic decay constant (λ) and follows an exponential law. The time in which a given quantity of a radionuclide decays to half its initial value is termed the half-life (T1/2).

Each radionuclide is characterized by an invariable T1/2, expressed in units of time and by the nature and energy of its radiation or radiations. The energy is expressed in electron volts (eV), kilo-electron volts (keV) or mega-electron volts (MeV).

The penetrating power of each radiation varies considerably according to its nature and its energy. Alpha particles, which are the heaviest among the radiations, have the minimum penetration, followed by the beta particles and gamma rays have the most penetrating power. Alpha particles can be stopped within a thickness of a few micrometers to few tens of micrometers of matter, while beta particles require several millimeters to several centimeters of matter for complete attenuation. Gamma rays, on the other hand, are the most penetrating and are attenuated in an exponential manner in matter. High density materials such as lead are used to stop the gamma rays and a ten-fold reduction of energetic gamma rays may require several centimeters of lead. The denser the material used, the higher the attenuation of radiations.
Modes of radioactive decay

**Alpha decay (α).** Radioactive nuclei having too many nucleons (n and p) often undergo alpha decay, in order to achieve nuclear stability. Alpha particle has a mass of 4 units and a charge of +2 units, and is therefore, equivalent to helium+2 ion. Alpha particles from radionuclides have energy ranging from 1.8 to 11.7 MeV. But, artificially, rays (He ions) can be accelerated to energies reaching several GeV.

**Negatron decay (β⁻).** Radioactive nuclei having neutrons in excess than what is needed for a stable configuration, mostly undergo negatron or β⁻ decay, in order to achieve nuclear stability. Negatrons have the same mass and electrical charge of orbital electrons, but they originate from nucleus at the very instant of decay, when a neutron transforms to a proton. Such a transformation results in increase in atomic number by 1, while the mass does not change significantly. The β⁻ decay phenomenon could be expressed as the following nuclear reaction:

\[ n \rightarrow p + \beta^- + \nu^* \]

ν* represents “anti-neutrino” a sub-atomic entity which does not have any mass or charge, but which can possess energy. The β⁻ decay equation has to be balanced with respect to mass, charge, energy, momentum as well as spin. The ν* is important for accounting for the conservation of momentum, spin and energy. Thus, unlike particles which are emitted with a single energy from a nuclide, β⁻ particles from a certain radionuclide could have varied energies, accompanied by the ν* carrying complementary amount of energy, with the total energy being same. β⁻ particles have energies in the range from a few KeV to 14 MeV. For a given transition, negatrons have a continuum spectrum of energies.

An example of beta decay is:

\[ ^{32}\text{P} \rightarrow ^{32}\text{S} + \beta^- + \nu^* \]

**Positron decay (β⁺).** Radioactive nuclei having neutrons lesser than what is needed for a stable configuration undergo positron β⁺ decay in order to achieve stability, if adequate energy is available from the nucleus for transformation of a proton to a neutron. Such a transformation results in decrease in atomic number by 1, while the mass does not change significantly. The β⁺ decay phenomenon could be expressed as the following nuclear reaction:

\[ p \rightarrow n + \beta^+ + \nu \]

As in the case of β⁻ decay, in order to conserve momentum, spin and energy, a sub-atomic entity which does not have any mass or charge known as “neutrino” represented by ν is also emitted, which carries some energy with it. Thus, like β⁻ particles, β⁺ particles also have varying energies. However, unlike β⁻ particles, in the case of β⁺ particle emission, the proton which is lighter is transformed to the heavier particle neutron, along with a positron, resulting in the generation of mass equivalent to 2 electrons (1 positron and another the difference between a neutron and a proton). This cannot be possible, unless energy is available for conversion into the mass equivalent to 2 electrons, which is 1.02 MeV. Hence, unlike β⁻ decay, β⁺ decay can occur only when at least 1.02 MeV of energy is available. During transmutation, due to the changes in nuclear energy levels, certain nuclides have energy > 1.03 MeV, in which case, β⁺ decay can occur. The energy in excess of 1.02 MeV is shared by the β⁺ and ν.

An example of β⁺ decay is:

\[ ^{18}\text{F} \rightarrow ^{18}\text{O} + \beta^+ + \nu \]

While the β⁻ particles or negatrons, which are equivalent to electrons are found all around in matter as these are constituents of atoms, β⁺ particles or positrons are not naturally present in matter. These are “anti-matter” particles, which when meet with the corresponding “matter”
will annihilate each other, resulting in conversion of matter into energy as per Einstein’s mass-energy equation \( E=mc^2 \). In the case of \( \beta^+ \) particles, once they come in contact with the electrons, they will be annihilated. When a positron is emitted, initially it spends all its energy as it travels through matter, comes across an electron, and both undergo annihilation, resulting in two photons of 511 KeV each travelling in opposite directions. It is noteworthy that for \( \beta^+ \) emission energy of 1.02 MeV (2 times 511 keV) is necessary, which later appears as 2 photons of 511 keV each. In order to have conservation of mass, energy and momentum, the 2 photons are emitted in exactly opposite directions.

It may be noted that “positron emission tomography”, a nuclear medicine imaging technique employing radiopharmaceuticals labelled with positron-emitting radionuclide(s), is a highly sensitive imaging technique based on the coincidence counting of the 2 photons emitted at 180°.

**Electron capture (EC).** Radioactive nuclei having neutrons lesser than what is needed for a stable configuration and which do not have adequate energy available to undergo positron \( \beta^+ \) decay, decay by another route named “electron capture”, in order to achieve stability. In this mode of decay an orbital electron is captured and taken into the nucleus, thus facilitating conversion of a proton to a neutron, resulting in a nuclide with decrease in atomic number by 1. An electron capture reaction can be written as:

\[
p + e^- \rightarrow n + \nu
\]

Since there are several orbital electrons (except in the case of elements with very low Z), EC process is a statistical phenomenon, where varied probabilities for EC arise for the K-shell (inner most shell) electrons, L-shell electrons and so on. EC phenomenon results in the depletion of electron in one of the inner shells of the atom, which in turn is a vacancy that is filled by one of the outer shell electrons accompanied by emission of characteristic X-rays. Often, EC mode of decay is accompanied by \( \gamma \) rays and characteristic X-rays as well as Auger electrons that arise due to the interaction of the \( \gamma \) rays and X-rays with the outer orbit electrons.

An example of EC is:

\[
{^{125}I} \rightarrow {^{125}Te} + 35 \text{ keV } \gamma \text{ ray (7%)} + 27-32 \text{ KeV Te X-rays (136 %)} + \sim 19 \text{ Auger electrons}
\]

While positron emission can occur only if at least 1.02 MeV of energy is available from the decay reaction, EC does not need such energy and both modes of decay result in nuclides with an atomic number lower by one. However, when energy is available for \( \beta^+ \) emission, EC may also occur in some cases, while vice versa is not possible. One example is of \( ^{64}\text{Cu} \), which decays by \( \beta^- \) emission, \( \beta^+ \) emission as well as EC. It is noteworthy that several factors that influence nuclear stability are responsible in determining the modes of decay and their probabilities.

**Gamma decay (\( \gamma \)).** Gamma rays are electromagnetic rays coming out of a nucleus as a result of the difference in nuclear energy levels of the excited and the ground states of the daughter nuclide when a nuclear transmutation takes place. Most radioactive decays are accompanied by \( \gamma \) rays, although this is not essential. Since \( \gamma \) rays carry the energy arising out of the difference in nuclear energy levels, these are often highly energetic, with energy greater than those of X-rays.

**Isomeric transition (IT).** When an excited nucleus de-excites by emission of a delayed gamma ray, the daughter nucleus is a nuclear isomer of the parent and the process is called isomeric transition.

As mentioned earlier, gamma rays are emitted owing to the energy difference in the nuclear states of the excited and the ground states of the daughter nuclide after a transmutation or
decay. Such \( \gamma \) ray emissions are very quick and happen within nanoseconds. However, if the de-excitation of the daughter nuclide from the higher state to ground state does not occur easily (due to rules that govern such transitions – nuclear physics), then such transitions become slow and the excited state of the nuclide is referred to as “metastable” state, indicated by the symbol “m” after the atomic number (e.g. \(^{99m}\text{Tc}\)). Nuclear isomers have the same number of protons and the same number of neutrons, only they are arranged in a more stable configuration in the daughter nucleus.

1.4 Radiation exposure and the units of radiation dose

**Exposure**

The sum of all electrical charges of one sign produced by photons in a given mass of air. The unit is the Roentgen (R) which is equal to \( 2.58 \times 10^{-4} \) coulomb of electric charge produced in 1 kg of dry air at standard temperature and pressure (STP). This definition applies to X-rays and \( \gamma \) rays under 3 MeV of energy. The intensity of gamma radiation field is measured in terms of exposure rate at some distance from the source and is expressed as Roentgen/hour (R/h).

a) Acute exposure: a high dose of radiation is delivered within a short time. This type of exposure results in nonstochastic effects, which means that the severity of the effect increases with the dose given.

b) Chronic exposure: a low dose of radiation is delivered over a long time. Chronic exposure results in stochastic effects, which means that the probability of observing the effect increases with the dose given. Background radiation and occupational exposure of radiation workers are examples of chronic exposure. To prevent unnecessary low-level exposures of radiation workers, the principle of ALARA must be practiced at all times.

Roentgen (R), a unit of exposure of X- or \( \gamma \)-radiation equal to \( 2.58 \times 10^{-4} \) coulomb/kg in air, is superseded by the SI unit of exposure, the coulomb/kg (C kg\(^{-1}\)). 1 C kg\(^{-1}\) = 3.876 \( \times 10^3 \) R.

**Absorbed dose**

Energy transferred to and absorbed by a unit mass of a material. The special unit is the radiation absorbed dose (rad), which is equal to 0.01 joule (J) of energy absorbed per kg (10\(^{-2}\) J/kg) of any material. In the MKS system, 1 J = force of one newton (N) acting over a distance of 1 m, and 1 N = force which gives a mass of 1 kg an acceleration of 1 m/s each second. The SI unit of absorbed dose is gray (Gy) defined as 1 J/kg and supersedes the rad as a unit of absorbed dose. 1 Gy = 100 rad.

The Roentgen and the rad in soft tissue are approximately equivalent in magnitude for the moderate energies.

**Critical organ.** The organ that is functionally essential for the body and receives the highest radiation dose after administration of radiopharmaceutical.

**Quality factor (QF).** The relative effectiveness of the radiation in producing biological response.

**Dose equivalent (DE)**

Absorbed dose multiplied by quality factor (QF). QF are values, based on linear energy transfer that permit estimates of radiation energy caused by various types of radiation. They are based on degree of ionization produced in water. Radiation that produces 100 ion pairs in 1 micron of water, spends 3.5 KeV of energy per micron receives a QF = 1. Those that produce 100–200 ion pairs gets QF = 2 and so on.
The unit of DE is Roentgen-equivalent-man (rem). A rem is numerically equal to the absorbed dose in rad multiplied by the appropriate QF defining the biological effect and by any other modifying factors. The SI unit of DE is sievert (Sv) and supersedes rem as the unit of dose equivalent. The units for sievert are joule/kg (J Kg\(^{-1}\)) equal to 100 rem.

Sievert (Sv) is numerically equal to the absorbed dose in Gray multiplied by the appropriate QF defining the biological effect and by any other modifying factors expressed in J/kg.

**Annual limit of intake (ALI)**

In order to simplify the comparison of the committed effective doses from intakes with equivalent dose limits, it is convenient to define the secondary dose limit called the ALI. It normally corresponds to a committed effective dose from an intake of a given radionuclide equal to the appropriate equivalent dose limits for workers. Restrictions of intake in each year to less than ALI therefore ensures that the maximum annual equivalent dose from that radionuclide will always be less than the equivalent dose even if intake occurred every year for 50 years.

### 1.5 Production of radionuclides

A radiopharmaceutical preparation monograph describes as precisely as possible the method of production of the radionuclide. A radiopharmaceutical preparation contains its radionuclide as an element in atomic or molecular form, e.g. \([^{133}Xe]\), \([^{18}O]\)\(_2\); as an ion, e.g. \([^{131}I]\)iodide, \([^{99m}Tc]\)pertechnetate; included in or attached to organic molecules by chelation, e.g. \([^{111}In]\)oxine or by covalent bonding, e.g. 2-\([^{18}F]\)fluoro-2-deoxy-D-glucose.

The practical ways of producing radionuclides for use in, or as radiopharmaceutical preparations are by (a) neutron bombardment of target materials (generally in nuclear reactors); (b) charged particles bombardment of target materials (in accelerators such as cyclotrons); (c) nuclear fission of heavy nuclides of target materials (generally after neutron or particle bombardment); and (d) from a radionuclide generator.

**Neutron or charged particle bombardment**

The nuclear reaction and the probability of its occurrence in unit time are dependent on the nature and physical properties of the target material and the nature, energy and quantity of the incident particles.

The nuclear transformation occurring through particle bombardment may be written in the form:

target nucleus (bombarding particle, emitted particle or radiation) produced nucleus.

Examples: \(^{58}\)Fe \((n,\gamma)^{59}\)Fe; \(^{18}\)O(p,n)\(^{18}\)F

In addition to the desired nuclear reaction, adventitious transformations may occur. These will be influenced by the energy of the incident particle and the purity of the target material. Such adventitious transformations may give rise to radionuclidic impurities.

**Nuclear fission**

A small number of nuclides with a high atomic number are fissionable and the most frequently used reaction is the fission of uranium-235 by neutrons in a nuclear reactor. Iodine-131, molybdenum-99 and xenon-133 may be produced by nuclear fission of uranium-235. Their extraction of the desired radioisotope from a mixture of more than 200 other radionuclides must be carefully controlled in order to minimize the radionuclide impurities, which have to be within permissible levels.
Radionuclide generators
Radionuclide generator systems use a relatively long-lived parent radionuclide which decays to a daughter radionuclide, usually with a shorter half-life. The parent radionuclide and the daughter radionuclide exist in transient or secular equilibria depending on the ratio of the $T_{1/2}$ of parent and daughter radionuclides. The daughter radionuclide is separated from the parent radionuclide using a chemical or physical process. It is possible to use the daughter at a considerable distance from the production site of the generators despite its short half-life. The duration for which the generator can be used will depend on the $T_{1/2}$ of the parent radionuclide.

Target materials
The isotopic composition and purity of the target material determines the relative percentages of the principal radionuclide and radionuclidic impurities. The use of isotopically enriched target material, in which the abundance of the required target nuclide has been artificially increased, can improve the production yield and the purity of the desired radionuclide.

The chemical form, the purity, the physical state and the chemical additives, as well as the bombardment conditions and the direct physical and chemical environment, will determine the chemical state and chemical purity of the radionuclides which are produced.

In the production of radionuclides and particularly of short-lived radionuclides, it may not be possible to determine any of these quality criteria before further processing and manufacture of radiopharmaceutical preparations. Therefore each batch of target material must be tested in test production runs before its use in routine radionuclide production and manufacture of the radiopharmaceutical preparations, to ensure that under specified conditions, the target yields the radionuclide in the desired quantity and quality specified.

The target material is contained in a holder in gaseous, liquid or solid state, in order to be irradiated by a beam of particles. For neutron bombardment, the target material is commonly contained in quartz ampoules or high purity aluminum or titanium containers. It is necessary to ascertain that no interaction can occur between the container and its contents under the irradiation conditions (temperature, pressure, time).

For charged particle bombardment, the holder for target material is usually built of aluminum or another appropriate metal, with a low cross section for the irradiating particles and also having a good thermal conductivity to remove the heat generated. The target will have inlet and outlet ports, a surrounding cooling system and usually a thin metal foil target window. The nature and thickness of the target window have a particular influence on the yield of the nuclear reaction and may also affect the radionuclidic purity.

The production procedure shall clearly describe the target material; construction of the holder for target material; loading of target material into the irradiation system; method of irradiation (bombardment); separation of the desired radionuclide, and evaluates all effects on the efficiency of the production in terms of quality and quantity of the produced radionuclide.

The chemical state of the isolated radionuclide may play a major role in all further processing.

Precursors for synthesis
Generally these precursors are not produced on a large scale. Some precursors are synthesized by the radiopharmaceutical production laboratory; others are supplied by specialized producers or laboratories.

Tests for identity, for chemical purity and assay must be performed by validated procedures. When batches of precursors are accepted based on the data from the certificates of analysis, suitable evidence has to be established to demonstrate the consistent reliability of the
analyses by suppliers and at least one identity test must be conducted. It is recommended
to test precursor materials in production runs before their use for the manufacture of
radiopharmaceutical preparations, to ensure that under specified production conditions,
the precursor yields the radiopharmaceutical preparation in the desired quantity and quality
specified.

**Performance of the production system**

All operations, from the preparation of the target to the dispensing of the final
radiopharmaceutical preparation, must be clearly documented including their impact on the
purity of the final product and the efficiency of the procedure. Where possible, in-process
controls are performed and the results recorded at each production step to identify at which
level a possible discrepancy from the normal production procedure may have occurred.

a) The production of radiopharmaceutical preparations may make use of mechanical and
automated processes that are used in the pharmaceutical industry, subject to adapting
these for use with radioactive material and to the requirements of radioprotection.

b) For radiopharmaceutical preparations containing short-lived radionuclides, such as
certain positron emitters, remotely controlled production and automated radiosynthesis are
generally used. For radionuclides with a very short half-life (less than 20 min), the control of
the performance of the production system is an important measure to assure the quality of
the radiopharmaceutical preparation before its release.

c) Any production procedure must be validated in test/trial production runs before its use in
routine manufacture of radiopharmaceutical preparations, to ensure that under specified
production conditions, the production system yields the radiopharmaceutical preparation in
the desired quantity and specified quality.

d) The preparation of the dosage form of the final radiopharmaceutical preparation in the
practice of nuclear medicine generally involves limited radioactivity starting from ready-
to-use radiopharmaceutical preparations, generators, kits and radioactive precursors.
All conditions which may affect the quality of the product (e.g. radiochemical purity,
sterility, etc.) must be clearly defined and must include appropriate measures for radiation
protection.

1.6 Identification

**Radioactive decay**

Radioactivity decays at an exponential rate with a particular decay constant and is a
characteristic of each radionuclide.

The exponential decay (decay curve) is described by the equation:

\[ A_t = A_0 e^{-\lambda t} \]

- \( A_t \) = the radioactivity at time \( t \),
- \( A_0 \) = the radioactivity at time \( t = 0 \),
- \( \lambda \) = the decay constant characteristic of each radionuclide, and
- \( e \) = the base of Napierian logarithms.

The half-life \( (T_{1/2}) \) is related to the decay constant \( (\lambda) \) by the equation:

\[ T_{1/2} = \frac{0.693}{\lambda} \]

The radionuclide is generally identified by its half-life or by the nature and energy of its
radiation or radiations emitted or by both, as prescribed in the monograph.
Measurement of $T_{1/2}$

The $T_{1/2}$ is measured with a suitable radiation detector such as an ionization chamber, a Geiger-Müller counter, a scintillation counter (solid crystal or liquid) or a semiconductor detector. The radiopharmaceutical preparation to be tested is used as such or diluted or dried in a capsule after appropriate dilution. The radioactivity chosen, having regard to experimental conditions, must be of a sufficiently high level to allow detection during several estimated $T_{1/2}$, but not too high to minimize count rate losses, for example due to dead time.

The radioactive source is prepared in a manner that will avoid loss of material during handling. If it is a liquid (solution), it is contained in bottles or sealed tubes. If it is a solid (residue from drying in a capsule), it is protected by a cover consisting of a sheet of adhesive cellulose acetate or of some other material.

The same source is measured in the same geometry and at intervals usually corresponding to half of the estimated half-life throughout a time equal to about three half-lives. The performance of the apparatus is checked using a source of long $T_{1/2}$ and, if necessary, corrections for any changes in the count rate have to be applied (see Measurement of radioactivity).

A graph can be drawn with time as the abscissa and the logarithm of the relative instrument reading (e.g. count rate) as the ordinate. The calculated $T_{1/2}$ should not differ by more than 5% from the expected $T_{1/2}$, unless otherwise stated in the pharmacopoeia.

Determination of the nature and energy of the radiation

The nature and energy of the radiation emitted may be determined by several procedures including the construction of an attenuation curve and the use of spectrometry. The attenuation curve can be used for analysis of $\beta$ radiation. Spectrometry is mostly used for identification of $\gamma$ rays and detectable X-rays.

The attenuation curve is drawn for pure electron emitters when no spectrometer for beta rays is available or for beta/gamma emitters when no spectrometer for gamma rays is available. This method of estimating the maximum energy of beta radiation gives only an approximate value. The source, suitably mounted to at fixed geometry, is placed in front of the thin window of a Geiger-Müller counter or a proportional counter. The source is protected as described above. The count rate of the source is then measured. Between the source and the counter are placed, in succession, at least six aluminum screens of increasing mass per unit area. Within such limits that with a pure beta emitter this count rate is not affected by the addition of further screens. The screens are inserted in such a manner that constant geometrical conditions are maintained. A graph is drawn showing the mass per unit area of the screen expressed in milligrams per square centimeter as the abscissa and, the logarithm of the count rate as the ordinate for each screen examined. A graph is drawn in the same manner for a standardized preparation. The mass attenuation coefficients are calculated from the median parts of the curves, which are practically rectilinear.

The mass attenuation coefficient $\mu_m$, expressed in square centimeters per milligram, depends on the energy spectrum of the beta radiation and on the nature and the physical properties of the screen. It therefore allows beta emitters to be identified. It is calculated using the equation:

$$\mu_m = \frac{2.303(\log A_1 - \log A_2)}{(m_1 + m_2)}$$

$m_1$ = mass per unit area of the lightest screen,
$m_2$ = mass per unit area of the heaviest screen, $m_1$ and $m_2$ being within the rectilinear part of the curve,
$A_1$ = count rate for mass per unit area $m_1$,
$A2$ = count rate for mass per unit area $m2$. 
The mass attenuation coefficient $\mu_m$, thus calculated, does not differ by more than 10% from the coefficient obtained under identical conditions using a standardized preparation of the same radionuclide.

The range of $\beta^-$ particles is an additional parameter which can be used for the determination of the $\beta^-$ energy. It is obtained from the graph described above as the mass per unit area corresponding to the intersection of the extrapolations of the descending rectilinear part of the attenuation curve and the horizontal line of background radioactivity.

Liquid scintillation counting may be used to obtain spectra of $\alpha$ and $\beta^-$ emitters (see measurement of radioactivity).

Gamma spectrometry is used to identify radionuclides by the energy and intensity of their $\gamma$ rays and X-rays.

The preferred detector for $\gamma$ and X-ray spectrometry is a germanium semiconductor detector. A thallium-activated sodium iodide scintillation detector is also used but this has a much lower energy resolution.

The gamma detector has to be calibrated using standard sources because the detection efficiency is a function of the energy of the $\gamma$ and X-rays as well as the form of the source and the source-to-detector distance. The detection efficiency may be measured using a calibrated source of the radionuclide to be measured or, for more general work, a graph of efficiency against $\gamma$ and X-ray energy may be constructed from a series of calibrated sources of various radionuclides.

The $\gamma$ and X-ray spectrum of a radionuclide which emits $\gamma$ and X-rays is unique to that nuclide and is characterized by the energies and the number of photons of particular energies emitted per transformation from one energy level to another energy level. This property contributes to the identification of radionuclides present in a source and to their quantification. It allows the estimation of the degree of radionuclidic impurity by detecting peaks other than those expected.

It is possible to establish the rate of the decay of radioactivity using $\gamma$-spectrometry since the peaks diminish in amplitude as a function of the $T_{1/2}$. If, in such a source, a radioactive impurity with a different $T_{1/2}$ is present, it is possible to detect the latter by identification of the characteristic peak or peaks whose amplitudes decrease at a different rate from that expected for the particular radionuclide. A determination of the $T_{1/2}$ of the additional peaks by repeated measurements of the sample will help to identify the impurity.

The table of physical characteristics of radionuclides summarizes the most commonly accepted physical characteristics of radionuclides used in radiopharmaceutical preparations. The table also states the physical characteristics of the main potential impurities of the radionuclides.

By “transition probability” is meant the probability of the transformation of a nucleus in a given energy state, via the transition concerned. Instead of “probability” the terms “intensity” and “abundance” are frequently used.

By “emission probability” is meant the probability of an atom of a radionuclide giving rise to the emission of the particles or radiation concerned.

Irrespective of whether the one or the other meaning is intended, probability is usually measured in terms of 100 disintegrations.

**Measurement of radioactivity**

The radioactivity of a radiopharmaceutical preparation is stated at a given date and, if necessary, time. The absolute measurement of the radioactivity of a given sample may
be carried out if the decay scheme of the radionuclide is known, but in practice, many corrections are required to obtain accurate results. For this reason, it is common to carry out the measurement with the aid of a primary standard source. Primary standards may not be available for short-lived radionuclides, e.g. $\beta^+$ emitters. Measuring instruments are calibrated using suitable standards for the particular radionuclides. Standards are available from the laboratories recognized by the competent authority. Ionization chambers and Geiger-Müller counters may be used to measure $\beta^-$ and $\beta^+ / \gamma$ emitters; scintillation or semiconductor counters or ionization chambers may be used for measuring gamma emitters; low-energy $\beta^-$ emitters require a liquid-scintillation counter. For the detection and measurement of $\alpha$ emitters, specialized equipment and techniques are required. For an accurate comparison of radioactive sources, it is essential for samples and standards to be measured under similar conditions.

Low-energy $\beta^-$ emitters may be measured by liquid-scintillation counting. The sample is dissolved in a solution containing one or more often two organic fluorescent substances (primary and secondary scintillators), which convert part of the energy of disintegration into photons of light, which are detected by a photomultiplier and converted into electrical impulses. When using a liquid-scintillation counter, comparative measurements are corrected for light-quenching effects. Direct measurements are made, wherever possible, under similar conditions, (e.g. volumes and type of solutions) for the source to be examined and for the standard source.

All measurements of radioactivity must be corrected by subtracting the background due to radioactivity in the environment and due to spurious signals generated in the equipment itself. With some equipment, when measurements are made at high levels of radioactivity, it may be necessary to correct for the loss by coincidence due to the finite resolving time of the detector and its associated electronic equipment. For a counting system with a fixed dead time $\tau$ following each count, the correction is:

$$N = N_{\text{obs}}/(1 - N_{\text{obs}} \times \tau)$$

$N =$ the true count rate per second, 
$N_{\text{obs}} =$ the observed count rate per second, and 
$\tau =$ the dead time, in seconds.

With some equipment this correction is made automatically. Corrections for loss by coincidence must be made before the correction for background radiation.

If the time of an individual measurement, $t_m$, is not negligible short compared with the half-life, $t_{1/2}$, the decay during this measurement time must be taken into account. After having corrected the instrument reading (count rate, ionization current, etc.) for background and, if necessary, for losses due to electronic effects, the decay correction during measurement time is:

$$R_{\text{corr}} = \frac{R \ln 2}{T_{1/2}} \frac{T_{1/2}}{1 - \exp \left(-\frac{T_{1/2} \ln 2}{T_{1/2}}\right)}$$

$R_{\text{corr}} =$ instrument reading corrected to the beginning of the individual measurement, 
$R =$ instrument reading before decay correction, but already corrected for background, etc.

The results of radioactivity determination show variation, which mainly are derived from the random nature of nuclear transformation. A sufficient number of counts must be registered in order to compensate for variations in the number of transformations per unit of time. The standard deviation is the square root of the counts, so at least 10 000 counts are necessary to obtain a relative standard deviation of not more than 1% (confidence interval: 1 sigma).

All statements of radioactive content should be accompanied by a statement of the date and, if necessary, the time at which the measurement was made. This statement of the radioactive
content must be made with reference to a time zone (GMT, CET). The radioactivity at other times can be calculated from the exponential equation or from tables.

The radioactivity of a solution is expressed per unit volume to indicate the radioactive concentration.

**Radionuclidic purity**

In most of the cases, to state the radionuclidic purity of a radiopharmaceutical preparation, the identity of every radionuclide present and their radioactivity must be known. The most generally useful method for the examination of radionuclidic purity is by gamma spectrometry. It is not a completely reliable method because alpha- and beta-emitting impurities are not usually easily detectable and, when sodium iodide detectors are employed, the peaks due to gamma emitting impurities are often obscured by the gamma spectrum of the principal radionuclide.

The individual monographs prescribe the radionuclidic purity required (for example, the $\gamma$-ray spectrum does not significantly differ from that of a standardized preparation) and may set limits for specific radionuclidic impurities (for example, cobalt-60 in cobalt-57). While these requirements are necessary, they are not in themselves sufficient to ensure that the radionuclidic purity of a preparation is sufficient for human use. The manufacturer must examine the product in detail and especially, must examine preparations of radionuclides of short half-life for impurities of long half-life after a suitable period of decay. In this way, information on the suitability of the manufacturing processes and the adequacy of the testing procedures may be obtained. In cases where two or more $\beta^+$ emitting radionuclides need to be identified and/or differentiated, as e.g. $^{18}$F-impurities in $^{13}$N-preparations, half-life determinations need to be carried out in addition to gamma spectrometry.

Due to differences in the half-lives of the different radionuclides present in a radiopharmaceutical preparation, the radionuclidic purity changes with time. The requirement of the radionuclidic purity must be fulfilled throughout the period of validity. It is sometimes difficult to carry out these tests before authorizing the release for use of the batch when the half-life of the radionuclide in the preparation is short. The test then constitutes a control of the quality of production.

**Radiochemical purity**

The determination of radiochemical purity requires separation of the different chemical substances containing the radionuclide and estimating the percentage of radioactivity associated with the declared chemical substance. Radiochemical impurities may originate from radionuclide production; subsequent chemical processing; incomplete preparative separation and chemical changes during storage.

The requirement of the radiochemical purity must be fulfilled throughout the period of validity. In principle, any method of analytical separation may be used in the determination of radiochemical purity. For example, the monographs for radiopharmaceutical products may include paper chromatography (2.4.15), thin-layer chromatography (2.4.17), instant thin-layer chromatography (ITLC), electrophoresis (2.4.12), size-exclusion chromatography (2.4.16), gas chromatography (2.4.13) and liquid chromatography (2.4.14). The technical description of these analytical methods is set out in the monographs. Moreover, certain precautions special to radioactivity must also be taken for radiation protection.

ITLC is a rapid, miniaturized thin layer assay method developed to determine the labeling efficiency of radiopharmaceuticals. The assay uses specific cellulose backed silica gel chromatography strips as solid phase. An ILTC method offers advantages such as easy to use, rapid and can be incorporated easily in a routine quality control programme.
In a hospital environment, thin-layer and paper chromatography are mostly used. In paper and thin-layer chromatography, a volume equal to that described in the monograph is deposited on the starting-line as prescribed in the general methods for chromatography. It is preferable not to dilute the preparation to be examined, but it is important to avoid depositing such a quantity of radioactivity that counting losses by coincidence occur during measurement of the radioactivity. On account of the very small quantities of the radioactive material applied, a carrier may be added when specified in a particular monograph. After development of the chromatogram, the support is dried and the positions of the radioactive areas are detected by autoradiography or by measurement of radioactivity over the length of the chromatogram using suitable collimated counters or by cutting the strips and counting each portion. The positions of the spots or areas permit chemical identification by comparison with solutions of the same chemical substances (non-radioactive) using a suitable detection method.

Radioactivity may be measured by integration using an automatic-plotting instrument or a digital counter. The ratios of the areas under the peaks give the ratios of the radioactive concentration of the chemical substances. When the strips are cut into portions, the ratios of the quantities of radioactivity measured give the ratio of concentrations of the radioactive chemical species.

**Specific radioactivity**

Specific radioactivity is usually calculated taking into account the radioactive concentration (radioactivity per unit volume) and the concentration of the chemical substance being studied, after verification that the radioactivity is attributable only to the radionuclide (radionuclidic purity) and the chemical species (radiochemical purity) concerned.

Specific radioactivity changes with time. The statement of the specific radioactivity therefore includes reference to a date and if necessary, time. The requirement of the specific radioactivity must be fulfilled throughout the period of validity.

**Chemical purity**

The determination of chemical purity requires quantification of the individual chemical impurities specified in the monograph.

**Enantiomeric purity**

Where appropriate, the stereoisomeric purity has to be verified.

**Physiological distribution**

A physiological distribution test is prescribed, if necessary, for certain radiopharmaceutical preparations. The distribution pattern of radioactivity observed in specified organs, tissues or other body compartments of an appropriate animal species (usually rats or mice) can be a reliable indication of the expected distribution in humans and thus of the suitability for the intended purpose.

The individual monograph prescribes the details concerning the performance of the test and the physiological distribution requirements which must be met for the radiopharmaceutical preparation. A physiological distribution conforming to the requirements will assure appropriate distribution of the radioactive compounds to the intended biological target in humans and limits its distribution to non-target areas.

In general, the test is performed as follows.

A minimum of three animals are used per test and each animal is injected intravenously with the preparation to be tested. If relevant, the species, sex, strain and weight and/or age of the animals are specified in the monograph. The test injection is the radiopharmaceutical preparation as it is intended for human use. Where applicable, products are reconstituted.
according to the manufacturer’s instructions. In some cases, dilution immediately before injection may be necessary.

The administration will normally be made via the intravenous route for which purpose the caudal vein is used. Other veins such as saphenous, femoral, jugular or penile veins may be used in special cases. Animals showing evidence of extravasation of the injection (observed at the time of injection or revealed by subsequent assay of tissue radioactivity) are rejected from the test.

Immediately after injection each animal is placed in a separate cage which will allow collection of excreta and prevent contamination of the body surface of the animal.

At the specified time after injection, the animals are euthanized by an appropriate method and dissected. Selected organs and tissues are assayed for their radioactivity using a suitable instrument as described elsewhere in this monograph. The physiological distribution is then calculated and expressed in terms of percentage of the radioactivity which is found in each of the selected organs or tissues. For this purpose the radioactivity in an organ may be related to the injected radioactivity calculated from the radioactive content of the syringe measured before and after injection. For some radiopharmaceutical preparations, it may be appropriate to determine the ratio of the radioactivity in weighed samples of selected tissues (radioactivity/mass).

For a preparation to meet the requirements of the test the distribution of radioactivity in at least two of the three animals must comply with all the specified criteria.

**Sterility**

Radiopharmaceutical preparations for parenteral administration must be prepared using precautions designed to exclude microbial contamination and to ensure sterility. The test for sterility is carried out as described in the general method for sterility (2.2.11). Special difficulties arise with radiopharmaceutical preparations because of the short half-life of some radionuclides, small size batches and the radiation hazards. It is not always possible to wait for the results of the test for sterility before authorization of the release of the radiopharmaceutical product for patients’ use. Parametric release of the product manufactured by a fully validated process is the method of choice in such cases. When aseptic manufacturing is used, the test for sterility has to be executed as a control of the quality of production.

When the size of a batch of the radiopharmaceutical preparation is limited to one or a few samples (e.g. therapeutic or very short-lived radiopharmaceutical preparation), sampling the batch for sterility testing may not be applicable. If the radiopharmaceutical preparation is sterilized by filtration and/or aseptically processed, process validation is critical.

When the half-life of the radionuclide is very short (e.g. less than 20 min), the administration of the radiopharmaceutical preparation to the patient is generally on-line with a validated production system.

For safety reasons (high level of radioactivity), it is not possible to use the quantity of the radiopharmaceutical preparations as required in the test for sterility (2.2.11). The method by membrane filtration is to be preferred to limit radiation exposure to personnel.

Notwithstanding the requirements concerning the use of antimicrobial preservatives in parenteral preparations, their addition to radiopharmaceutical preparations in multidose containers is not obligatory, unless prescribed in the monograph.

**Bacterial endotoxins - pyrogens**

For certain radiopharmaceutical preparations a test for bacterial endotoxins is prescribed. The test is carried out as described in the general method (2.2.3), taking the necessary precautions to limit radiation exposure to the personnel carrying out the test. For radiopharmaceuticals made with short-lived radioisotopes, endotoxin testing after product release is permitted.
However, with the introduction of the kinetic (photometric) LAL test, which can be completed in 20 minutes, it is possible to complete the test for bacterial endotoxins before releasing the radiopharmaceuticals with $T_{1/2}$ of $>$ 30 min.

The limit for bacterial endotoxins is indicated in the individual monograph.

When the nature of the radiopharmaceutical preparation results in an interference by inhibition or activation and it is not possible to eliminate the interfering factor(s), the test for pyrogens (2.2.8) may be specifically prescribed. This happens with many of the $^{99m}$Tc-radiopharmaceuticals since their formulation uses reducing agents and metal chelating agents, which will give false negative or false positive results with the LAL test.

It is sometimes difficult to carry out these tests before releasing the batch for use when the half-life of the radionuclide in the preparation is short. The test then constitutes a control of the quality of production.

**pH**

The pH of PET-radiopharmaceuticals like all pharmaceutical preparations is important and is determined as a part of quality control (QC) testing. However, due to the small volumes involved and the radioactivity present, the conventional use of a glass pH electrode is not practical or necessary. The sample available for all the QC testing (excluding sterility) is very small and the pH range permitted is sufficiently large. Hence, the use of narrow range pH strips is adequate and is preferred as the pH can be tested with a few microlitres of the sample. Further, as they are radioactive after use, they can be easily and safely disposed. pH electrodes, even miniature electrodes, require much cleaning after use and generate radioactive washings that have to be stored and disposed.

**1.7 Storage**

Store in an airtight container in a place that is sufficiently shielded to protect personnel from exposure to primary or secondary emissions and that complies with national and international regulations concerning the storage of radioactive substances. During storage containers may darken due to irradiation. Such darkening does not necessarily involve deterioration of the preparations.

Radiopharmaceutical preparations are intended for use within a short time and the end of the period of validity must be clearly stated.

Radiopharmaceuticals intended for parenteral use should be stored in such a manner so that pharmaceutical purity of the product is maintained.

**1.8 Labelling**

The labelling of radiopharmaceutical preparations complies with the relevant national legislation and complies with the labelling requirements as per good manufacturing practices (GMP).

Apart from the general labelling requirements, the label on the direct container should state (1) notification that the product is radioactive in nature, (2) the name of the preparation and/or its reference, (3) the name of the manufacturer, (4) an identification number, (5) for liquid and gaseous preparations: the total radioactivity in the container, or the radioactive concentration per milliliter at a stated date and stated time, and the volume of liquid in the container, (6) for solid preparations (such as freeze-dried preparations): the total radioactivity at a stated date and stated time. After reconstitution with the appropriate solution, the preparation is considered
as a liquid preparation, (7) for capsules: the radioactivity per capsule at a stated date and time and the number of capsules in the container, and (8) route of administration.

The labelling can be adapted in certain cases (e.g. radiopharmaceutical preparations containing short-lived radionuclides).

The label on the outer package states, in addition to those on the direct container: (1) the route of administration, (2) the period of validity or the expiry date, (3) the name and concentration of any added antimicrobial preservative, and (4) where applicable, any special storage conditions.

Techno-legal regime in the use of radiopharmaceuticals in the Indian scenario

Widespread utilization of ionizing radiation and radioactive substances and radioactive substances for multifarious applications in medicine, industry, agriculture, research, etc., has brought in its wake the need for exercising regulatory controls to ensure safety of users, members of the public and the environment. The Atomic Energy Regulatory Board (AERB), constituted under the Atomic Energy Act, 1962 by the Government of India, is entrusted with the responsibility of developing and implementing appropriate regulatory measures aimed at ensuring radiation safety in all applications involving ionizing radiation and radioactive substances. One of the ways to meet these responsibilities is to develop and enforce specific safety codes and standards dealing with radiation safety aspects of various applications of ionizing radiation and radioactive substances to cover the entire spectrum of operations, starting from design of radiation equipment, their installation and use, to ultimate decommissioning and safe disposal.

Specific mandatory requirements are published as AERB Codes & Guides for a nuclear medicine facility, covering the entire spectrum of operations ranging from the site approval, laboratory design and setting up of a facility to its ultimate decommissioning, including procedures to be followed during an emergency situation. The Code also stipulates requirements of qualified personnel's and their responsibilities.


There is also an AERB code that elaborates on regulatory requirements and control of use, possession, transport of radioactive substances and radiation sources.

Annex 1. The dose limits for exposures from ionizing radiations for workers and the members of the public, from AERB SAFETY CODE NO. AERB/RF-MED/SC-2 (Rev. 2)

AERB Directive No. 01/2011


Ref. No. CH/AERB/ITSD/125/2011/1507 dated 27 April 2011

Subject: The dose limits for exposures from ionising radiations for workers and the members of the public

In exercise of Rule 15 of the Atomic Energy (Radiation Protection) Rules, 2004, the Chairman, Atomic Energy Regulatory Board, being the Competent Authority under the said rules, hereby issues an order prescribing the dose limits for exposures from ionizing radiations for workers and the members of the public, which shall be adhered to.

Dose limits

General
i. The limits on effective dose apply to the sum of effective doses from external as well as internal sources. The limits exclude the exposures due to natural background radiation and medical exposures.

ii. Calendar year shall be used for all prescribed dose limits.

1.0 Occupational dose limits

1.1 Occupational workers

The occupational exposures of any worker shall be so controlled that the following limits are not exceeded:

a. an effective dose of 20 mSv/yr averaged over five consecutive years (calculated on a sliding scale of five years);

b. an effective dose of 30 mSv in any year;

c. an equivalent dose to the lens of the eye of 150 mSv in a year;

d. an equivalent dose to the extremities (hands and feet) of 500 mSv in a year;

e. an equivalent dose to the skin of 500 mSv in a year;

f. limits given above apply to female workers also. However, once pregnancy is declared the equivalent dose limit to embryo/fetus shall be 1 mSv for the remainder of the pregnancy.

1.2 Apprentices and trainees

The occupational exposure of apprentices and trainees between 16 and 18 years of age shall be so controlled that the following limits are not exceeded:

a. an effective dose of 6 mSv in a year;

b. an equivalent dose to the lens of the eye of 50 mSv in a year;

c. an equivalent dose to the extremities (hands and feet) of 150 mSv in a year;

d. an equivalent dose to the skin of 150 mSv in a year.

2.0 Dose limits for members of the public

The estimated average doses to the relevant members of the public shall not exceed the following limits:

a. an effective dose of 1 mSv in a year;

b. an equivalent dose to the lens of the eye of 15 mSv in a year;

c. an equivalent dose to the skin of 50 mSv in a year.

Table: Annual limit for intake (ALI) of important radionuclides

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>ALI (ingestion) (Ci)</th>
<th>ALI (inhalation) (Ci)</th>
<th>Derived air conc. (DAC) (inhalation) (Ci/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tc-99m</td>
<td>$8 \times 10^4$</td>
<td>$2 \times 10^5$</td>
<td>$1 \times 10^{-4}$</td>
</tr>
<tr>
<td>F-18</td>
<td>$5 \times 10^4$</td>
<td>$7 \times 10^4$</td>
<td>$3 \times 10^{-5}$</td>
</tr>
<tr>
<td>I-125</td>
<td>$4 \times 10^1$</td>
<td>$6 \times 10^1$</td>
<td>$3 \times 10^{-6}$</td>
</tr>
<tr>
<td>P-32</td>
<td>$6 \times 10^3$</td>
<td>$3 \times 10^1$</td>
<td>$1 \times 10^{-6}$</td>
</tr>
<tr>
<td>I-131</td>
<td>$9 \times 10^1$</td>
<td>$5 \times 10^1$</td>
<td>$2 \times 10^{-8}$</td>
</tr>
</tbody>
</table>
Annex 2. Safety considerations

Radiopharmaceuticals, owing to their detrimental effects on cellular structures, need to be monitored for their harmful effects on the personnel involved in handling them. Critical operations include manufacture, storage, transport, compounding, testing, dispensing and administration to the patients.

Complying as per the ALARA principle, in order to minimize the harmful effects of radiopharmaceuticals, there should be specialized techniques for controlling risk. A major consideration of the ALARA principle includes exposure time, distance and radiation shielding. These factors should be carefully considered while designing the safety protocols for radiopharmaceuticals.

Radiation sign

- Restricted area: < 2 mR/h and < 100 mR/year
- Caution, Radiation Area: may exceed 5 mR/h at 30 cm from source
- Caution, High Radioactive Area: may exceed 100 mR/h at 30 cm from source
- Danger, Very High Radiation Area: may reach 500 R/h at 1 m from source (not in NM)

Caution Radioactive Material:
- 100 Ci for Cs-137 and Sr-89
- 1 mCi for Mo-99, I-123 and Co-57
- 10 mCi for Tc-99m, Ga-67 and Xe-133.

Radiation safety instruments

- GM survey meters: Laboratory survey
- Portable ion chambers (cutie pies): High level exposure rate monitoring (In RPD)
- Pocket dosimeter: Personnel exposure monitoring
- Wipe test counters: GM counters to detect low level activity
- Film badges: To detect and measure personnel exposure
- Thermoluminescent dosimeters: More sensitive than film badges
- Scintillation detectors:
  - Portable scintillation survey detectors for gamma survey of lab surfaces
  - Well type single channel analyzers for measurement of wipe tests
  - Multiwell gamma ray spectrometer to identify and quantify gamma contamination
Annex 3. Physical characteristics of radionuclides

The values are obtained from the database of the National Nuclear Data Center (NNDC) at Brookhaven National Laboratory, Upton, N.Y., USA, directly accessible via Internet at http://www.nndc.bnl.gov/nndc/nudat/radform.html.

In case another source of information is preferred (more recent values) this source is explicitly mentioned.

Other data sources:
* DAMRI (Département des Applications et de la Métrologie des Rayonnements Ionisants, CEA Gif-sur-Yvette, France),
** PTB (Physikalisch-Technische Bundesanstalt, Braunschweig, Germany),
*** NPL (National Physical Laboratory, Teddington, Middlesex, UK).

The uncertainty of the half-lives is given in parentheses. In principle the digits in parentheses are the standard uncertainty of the corresponding last digits of the indicated numerical value (Guide to the Expression of Uncertainty in Measurement, International Organization for Standardization (ISO), 1993, ISBN 92-67-10188-9).

The following abbreviations are used:
- e_A = Auger electrons,
- ce = conversion electrons,
- β− = electrons,
- β+ = positrons,
- γ = gamma rays,
- X = X-rays.

a Mean energy of the β spectrum.

b Maximum emission probability corresponding to a total annihilation in the source per 100 disintegrations.

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>Electronic emission</th>
<th></th>
<th></th>
<th>Photon emission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Type</td>
<td>*Energy (MeV)</td>
<td>*Emission probability (per 100 disintegrations)</td>
<td>Type</td>
</tr>
<tr>
<td>Tritium (3H)</td>
<td>12.33 (6) years</td>
<td>β</td>
<td>0.006 (max: 0.019)</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Carbon-11 (11C)</td>
<td>20.385 (20) min</td>
<td>β</td>
<td>0.386 (max: 0.960)</td>
<td>99.8</td>
<td>γ 0.511</td>
</tr>
<tr>
<td>Nitrogen-13 (13N)</td>
<td>9.965 (4) min</td>
<td>β</td>
<td>0.492 (max: 1.98)</td>
<td>99.8</td>
<td>γ 0.511</td>
</tr>
<tr>
<td>Oxygen-15 (15O)</td>
<td>122.24 (16) s</td>
<td>β</td>
<td>0.735 (max: 1.732)</td>
<td>99.9</td>
<td>γ 0.511</td>
</tr>
<tr>
<td>Fluorine-18 (18F)</td>
<td>109.77 (5) min</td>
<td>β</td>
<td>0.250 (max: 0.633)</td>
<td>96.7</td>
<td>γ 0.511</td>
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<tr>
<td>Phosphorus-32 (32P)</td>
<td>14.26 (4) days</td>
<td>β</td>
<td>0.695 (max: 1.71)</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Phosphorus-33 (33P)</td>
<td>25.34 (12) days</td>
<td>β</td>
<td>0.076 (max: 0.249)</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Sulphur-35 (35S)</td>
<td>87.51 (12) days</td>
<td>β</td>
<td>0.049 (max: 0.167)</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Chromium-51 (51Cr)</td>
<td>27.7025 (24) days</td>
<td>e_A</td>
<td>0.004</td>
<td>67</td>
<td>X 0.005</td>
</tr>
<tr>
<td>Radionuclide</td>
<td>Half-life</td>
<td>Electronic emission</td>
<td>Photon emission</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Type</td>
<td>*Energy (MeV)</td>
<td>*Emission probability (per 100 disintegrations)</td>
<td>Type</td>
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<tr>
<td>Cobalt-56 (56Co)</td>
<td>77.27 (3) days</td>
<td>e⁻</td>
<td>0.006</td>
<td>47</td>
<td>X</td>
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<tr>
<td></td>
<td></td>
<td>β⁺</td>
<td>0.179</td>
<td>0.9</td>
<td>γ</td>
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<td></td>
<td></td>
<td></td>
<td>0.631</td>
<td>18.1</td>
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<tr>
<td>Cobalt-57 (57Co)</td>
<td>271.79 (9) days</td>
<td>e⁻</td>
<td>0.006-0.007</td>
<td>177.4</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ce</td>
<td>0.014</td>
<td>7.4</td>
<td>γ</td>
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<td></td>
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<td></td>
<td>0.115</td>
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<td></td>
<td></td>
<td></td>
<td>0.129</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Cobalt-58 (58Co)</td>
<td>70.86 (7) days</td>
<td>e⁻</td>
<td>0.006</td>
<td>49.4</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β⁺</td>
<td>0.201</td>
<td>14.9</td>
<td>γ</td>
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<tr>
<td></td>
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<td></td>
<td>0.014</td>
<td>0.7</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.090-0.092</td>
<td>0.3</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.175</td>
<td>50</td>
<td></td>
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<td>Cobalt-60 (60Co)</td>
<td>5.2714 (5) years</td>
<td>β⁻</td>
<td>0.096(II)(max: 0.318)</td>
<td>99.9</td>
<td>γ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.333</td>
<td>100.0</td>
<td></td>
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<tr>
<td>Gallium-66 (66Ga)</td>
<td>9.49 (7) hours</td>
<td>e⁻</td>
<td>0.008</td>
<td>21</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β⁺</td>
<td>0.157(II)</td>
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<td>γ</td>
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<td>0.331</td>
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<td>0.397</td>
<td>3.8</td>
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<td></td>
<td></td>
<td></td>
<td>0.782</td>
<td>0.3</td>
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<td>1.90(II)</td>
<td>50</td>
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<tr>
<td>Gallium-67 (67Ga)</td>
<td>3.2612 (6) days</td>
<td>e⁻</td>
<td>0.008</td>
<td>62</td>
<td>X</td>
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<td></td>
<td></td>
<td>ce</td>
<td>0.082-0.084</td>
<td>30.4</td>
<td>γ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.090-0.092</td>
<td>3.6</td>
<td></td>
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<td></td>
<td></td>
<td>0.175</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Germanium-68 (68Ga)</td>
<td>270.82 (27) days (68Ga: 67.629 (24) min)</td>
<td>e⁻</td>
<td>0.008</td>
<td>42.4</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β⁺</td>
<td>0.353(II)</td>
<td>1.2</td>
<td>γ</td>
</tr>
<tr>
<td></td>
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<td>0.836(II)</td>
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<td>Gallium-68 (68Ga)</td>
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Continued (Abbreviations: see page 182)
### Radionuclide Half-life | Electronic emission | Photon emission
--- | --- | ---
**Rubidium-81 (\(^{81}\)Rb)** in equilibrium with Krypton-81m (\(^{81}\)mKr) 4.576 (5) hours | e\(_{A}\) 0.011 31.3 | X 0.013-0.014 57.2
\(^{81}\)mKr: 13.10 (3) s | \(\beta^-\) 0.253\(^{0}\) 1.8 | \(\gamma\) 0.511 54.2
|

**Strontium-89 (\(^{89}\)Sr)** in equilibrium with Yttrium-89 (\(^{89}\)mY) 50.53 (7) days | \(\beta^-\) 0.583\(^{0}\) (max: 1.492) 99.99 | \(\gamma\) 0.909 0.01
\(^{89}\)mY: 16.06 (4) s |

**Strontium-90 (\(^{90}\)Sr)** in equilibrium with Yttrium-90 (\(^{90}\)mY) 28.74 (4) days | \(\beta^-\) 0.196\(^{0}\) (max: 0.546) 100 | |
\(^{90}\)mY: 64.10 (8) hours |

**Yttrium-90 (\(^{90}\)Y)** 64.10 (8) hours | \(\beta^-\) 0.934\(^{0}\) (max: 2.280) 100 | |

**Molybdenum-99 (\(^{99}\)Mo)** in equilibrium with Technetium-99m (\(^{99}\)mTc) 65.94 (1) hours | \(\beta^-\) 0.133\(^{0}\) 16.4 | X 0.018-0.021 3.6
\(^{99}\)mTc: 6.01 (1) hours |
|

**Technetium-99m (\(^{99}\)mTc)** 6.01 (1) hours | \(\alpha\) 0.002 74 | X 0.018-0.021 7.3
\(e_{A}\) 0.015 2.1 | \(\gamma\) 0.141 89.1
\(\alpha\) 0.120 9.4 |
|

**Technetium-99 (\(^{99}\)Tc)** 2.11 x 10\(^5\) years | \(\beta^-\) 0.085\(^{0}\) (max: 0.294) 100 | |

**Ruthenium-103 (\(^{103}\)Ru)** in equilibrium with Rhodium-103m (\(^{103}\)mRh) 39.26 (2) days | \(e_{A}\) 0.017 12 | X 0.020-0.023 9.0
\(^{103}\)mRh: 56.114 (20) min |
|

Continued (Abbreviations: see page 182)
### Radionuclides and Their Properties

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<th>Electronic emission</th>
<th>Photon emission</th>
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(Continued on page 182)
### Radionuclide Half-life Electronic emission Photon emission

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<th>Photon emission</th>
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*Continued (Abbreviations: see page 182)*
Continued (Abbreviations: see page 182)

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<th>Half-life</th>
<th>Electronic emission</th>
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### Radionuclides and Their Properties

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**Abbreviations:** see page 182
**Natrii iodidi (\(^{131}\)I) capsulae**  
Sodium iodide (\(^{131}\)I) capsules

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/14.577, March 2014).

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, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

**Latin.** Natrii iodidi (\(^{131}\)I) capsulae  
**English.** Sodium \([^{131}\)I\]Iodide capsules

**Structural formula**

\[
\text{Na}^{+}\cdot\text{I}^{-}\cdot^{131}\text{I}^-
\]

\[
\text{Na}^{131}\text{I}
\]

**Relative molecular mass.** 153.895

**Chemical name.** Sodium \([^{131}\)I\]iodide

**Description.** White or coloured gelatin capsules. Iodine-131 has a half-life of 8.02 days.

**Category.** Diagnostic or therapeutic.

**Storage.** Sodium iodide (\(^{131}\)I) capsules should be preserved in well-closed containers in a fume hood or well ventilated room.

**Labelling.** The label complies with the General monograph, monograph of Radiopharmaceuticals.

**Manufacture**

Iodine-131 may be obtained by neutron irradiation of tellurium as carrier free sodium iodide or by extraction from uranium fission products.

**Requirements**

Complies with the monograph for Capsules and with that for Radiopharmaceuticals.

**Definition**

Sodium iodide (\(^{131}\)I) capsules contain radioactive iodine-131 as sodium iodide adsorbed onto a solid matrix, such as anhydrous sodium thiosulfate or anhydrous disodium hydrogen phosphate, which is contained in hard gelatine capsules. Sodium iodide (\(^{131}\)I) capsules are suitable for oral administration. The capsules contain not less than 90% and not more than 110% of the content of iodine-131 stated on the label at the reference date and time. Not less than 99.9% of the total radioactivity is due to iodine-131. Not less than 95% of the total iodine-131 radioactivity is present as iodide. The specific activity for therapeutic or diagnostic use should not less than 185 MBq per microgram of iodine at the reference date and time stated on the label. Iodide should not more than 20 µg per capsule.

**Identity tests**

A. Record the gamma-ray and X-ray spectrum using a suitable instrument with a sample of iodine-131, suitably diluted if needed. The spectrum is concordant with the *reference spectrum* of a specimen of iodine-131 in that it exhibits a major peak of 365 keV. Iodine-133
Iodine has a half-life of 20.8 hours and main peaks of 530 keV and 875 keV. Iodine-135 has a half-life of 6.55 hours and main peaks of 527 keV, 1132 keV and 1260 keV.

Standardized iodine-131, iodine-133 and iodine-135 solutions are available from laboratories recognized by the relevant national or regional authority.

B. The half-life determined using a suitable detector system is between 7.61 and 8.42 days.

Radionuclidic purity. A solution or suspension of one or more capsules in water should comply with the tests of radionuclidic purity as described under the monograph of Natrii iodidi (\(^{131}\)I) solutio – Sodium iodide (\(^{131}\)I) solution. Not less than 99.9% of the total radioactivity is due to iodine-131.

Chemical purity

Iodide. Dissolve the capsule to be examined in 10 mL of water R. Filter through a 0.2 µm filter. Carry out the test of iodide as described under the specific monograph of Natrii iodidi (\(^{131}\)I) solutio – Sodium iodide (\(^{131}\)I) solution. The area of the peak due to iodide should not be larger than the area of the corresponding peak in the chromatogram obtained with reference solution (c).

Radiochemical purity

• Either test A or test B may be applied

A. Homogenize the contents of a capsule in 5 mL of water R, add 5 mL of methanol R and centrifuge. The supernatant should meet the requirements of the test (\(1.14.2\) Paper chromatography) as described under the specific monograph of Natrii iodidi (\(^{131}\)I) solutio – Sodium iodide (\(^{131}\)I) solution. Not less than 95% of the total radioactivity is due to \(^{131}\)I iodide.

B. Prepare the capsule for testing as described under the test of iodide. Carry out the test (\(1.14.4\) High-performance liquid chromatography) as described under the specific monograph of Natrii iodidi (\(^{131}\)I) solutio – Sodium iodide (\(^{131}\)I) solution. Not less than 95% of the total radioactivity is due to \(^{131}\)I iodide.

Disintegration. In a water-bath at 37°C, warm 10 ml of a potassium iodide (2 g/l) TS solution. Add a capsule to be examined and stir with a magnetic stirrer at a rotation speed of 20 revolutions per minute. The shell and its contents dissolve completely within 15 minutes.

Uniformity of content. Determine the radioactivity of 10 capsules individually and determine the average radioactivity per capsule. The radioactivity of none of the capsules differs by more than 10% from the average radioactivity per capsule. The relative standard deviation is not greater than 3.5%.

Radioactivity

Measure the radioactivity using a suitable instrument as described under \(R.1.1\) Detection and measurement of radioactivity.

Impurities

A. \(^{131}\)I iodate ion,
B. iodine-130,
C. iodine-133,
D. iodine-135.

***
**Iobenguani (131I) injectio**
Iobenguane (131I) injection

This is a draft proposal for The International Pharmacopoeia (Working document QAS/14.578, March 2014).

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, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidt_h@who.int.

**Latin.** Iobenguani (131I) injection

**English.** Iobenguane (131I) injection

**Structural formula**

\[
\text{C}_8\text{H}_{10}\text{I}_{131}\text{N}_3
\]

**Relative molecular mass.** 279.19

**Chemical name.** 1-([3-[131I]iodophenyl]methyl)guanidine

**Other names.** m-Iodobenzylguanidine (131I) injection; (131I)-MIBG injection.

**Description.** Iobenguane (131I) injection is a clear, colourless or slightly yellow aqueous solution.

Iodine-131 has a half-life of 8.02 days.

**Category.** Diagnostic and therapy.

**Storage.** Iobenguane (131I) injection should be kept protected from light and during transportation, at a temperature below -10°C.

**Labelling.** The label complies with the General monograph, monograph of Radiopharmaceuticals. The label should include the specific activity of iodine-131 in Becquerel per gram. The label states the date of withdrawal of the first dose for multidose containers.

**Manufacture**
Iodine-131 may be obtained by neutron irradiation of tellurium or by extraction from uranium fission products. Iobenguane (131I) is generally prepared by isotope exchange reaction (the formulations contain large amounts of unlabelled MIBG molecules). The injection may contain fillers, antimicrobial preservatives, buffers and stabilizing agents.

**Additional information**
Wherever V is used within the tests of this monograph, V is the maximum recommended dose, in millilitres.
Requirements

Complies with the monograph for Parenteral Preparations and with that for Radiopharmaceuticals.

Definition. Iobenguane (\(^{131}\)I) injection is a sterile, bacterial endotoxin-free aqueous solution of iodine-131 in the form of 1-((3-[\(^{131}\)I]iodophenyl)methyl)guanidine or its salts, suitable for intravenous administration. The injection contains sufficient sodium chloride to make the solution isotonic with blood. The injection contains not less than 90% and not more than 110% of the content of iodine-131 stated on the label at the reference date and time. Not less than 99.9% of the total radioactivity is due to iodine-131. Not less than 94% of the total iodine-131 radioactivity should present as iobenguane when it is used for diagnosis. Not less than 92% of the total iodine-131 radioactivity should present as iobenguane when it is used for therapy. The radiolabelled \(^{131}\)I-MIBG for diagnosis or therapy should be with high specific activity as the cold MIBG molecules are competitively inhibitor of the uptake of radiolabelled \(^{131}\)I-MIBG by adrenergic and neuroendocrine cells expressing norepinephrine transporter. The specific activity for diagnosis should not be less than 20 GBq of iodine-131 per gram of iobenguane base at the reference date and time stated on the label. For therapy, specific activity should not be less than 400 GBq of iodine-131 per gram of iobenguane base at the reference date and time stated on the label.

Identity tests

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

A. Record the gamma-ray and X-ray spectrum using a suitable instrument with a sample of iodine-131 suitably diluted if needed. The spectrum is concordant with the reference spectrum of a specimen of iodine-131 in that it exhibits a major peak of 365 keV.

Iodine-133 has a half-life of 20.83 hours and main peaks of 530 keV and 875 keV. Iodine-135 has a half-life of 6.58 hours and main peaks of 527 keV, 1132 keV and 1260 keV. Standardized iodine-131, iodine-133 and iodine-135 solutions are available from laboratories recognized by the relevant national or regional authority.

B. The half-life determined using a suitable detector system is between 7.61 and 8.42 days.

C. Examine the radiochromatogram obtained in the test for radiochemical purity (see the high-performance liquid chromatography under the test of Radiochemical purity):

For \([^{131}\)I]Iobenguane injection for diagnostic use: Not less than 94% of the total radioactivity should be in the peak corresponding to iobenguane.

For \([^{131}\)I]Iobenguane injection for therapeutic use: Not less than 92% of the total radioactivity should be in the peak corresponding to iobenguane.

pH value

Carry out the test as described under 1.13 Determination of pH or R1.5 under the monograph for Radiopharmaceuticals, pH of the injection should be between 3.5 and 8.0.

Sterility

The injection complies with 3.2 Test for sterility, modified as described in the monograph for Radiopharmaceuticals. Test for sterility will be initiated on the day of manufacture. The injection may be released for use before completion of the test.
Bacterial endotoxins
Carry out the test as described under 3.4 Test for bacterial endotoxins, modified as described in the monograph for Radiopharmaceuticals. The injection contains not more than 175/V I.U of endotoxins per millilitre.

Radionuclidic purity
Record the gamma-ray and X-ray spectrum using a suitable instrument and measure the half-life using a suitable method. Determine the relative amounts of iodine-131, iodine-133, iodine-135 and other radionuclidic impurities that may be present. Not less than 99.9% of the total radioactivity is due to iodine-131.

Radiochemical purity
Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.0 mm) packed with silica gel for chromatography R (5µm). As the mobile phase, use a mixture of 80 g/l solution of ammonium nitrate R, ammonia (~ 35 g/l) TS and methanol R (1:2:27 V/V/V). Operate with a flow rate of 1.0 ml/min. As a detector, use detectors suitable for radioactivity and a spectrophotometer set at a wavelength of 254 nm. Prepare the following solutions: Solution (1), use the injection to be examined. Solution (2), prepare 0.1% (w/v) solution of sodium iodide R in the mobile phase. Solution (3), prepare 0.02% (w/v) solution of iobenguane sulfate R, in 50 ml of the mobile phase and dilute to 100 ml with the mobile phase. Inject separately 10 µl of solutions (1), (2) and (3). Examine the obtained radiochromatogram as follows:

\[
\text{[\text{^{131}I}]iobenguane injection (diagnostic use): In the chromatogram obtained with solution (1), not less than 94\% of the total radioactivity should be in the peak corresponding to iobenguane. Not more than 5\% of the total radioactivity corresponding to [^{131}I]iodide and not more than 1\% of the total radioactivity is found in other peaks.}
\]

\[
\text{[^{131}I]iobenguane injection for therapeutic use: In the chromatogram obtained with solution (1), not less than 92\% of the total radioactivity should be in the peak corresponding to iobenguane. Not more than 7\% of the total radioactivity corresponding to [^{131}I]iodide and not more than 1\% of the total radioactivity is found in other peaks.}
\]

Radioactivity
Measure the radioactivity as described under R.1.1 Detection and measurement of radioactivity.

Impurities
A. [^{131}I]iodide,
B. Iodine-133,
C. Iodine-135.

***
Fluconazoli capsulae
Fluconazole capsules

This is a draft proposal for The International Pharmacopoeia (Working document QAS/12.470/Rev.2, May 2014).

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, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidt@who.int.

Category. Antifungal.

Storage. Fluconazole capsules should be kept in a tightly closed container.

Additional information. Strengths in the current WHO Model list of essential medicines: 50 mg. Strength in the current WHO Model list of essential medicines for children: 50 mg.

Requirements

Comply with the monograph for Capsules.

Definition. Fluconazole capsules contain fluconazole. They contain not less than 90.0% and not more than 110.0% of the amount of fluconazole (C₁₃H₁₂F₂N₆O) stated on the label.

Identity tests

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

A. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 80 volumes of dichloromethane R, 20 volumes of methanol R and 1 volume of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 10 μl of each of the following three solutions in methanol R. For solution (A) shake a quantity of the mixed contents of the capsules, equivalent to about 100 mg of Fluconazole, with 10 ml of methanol R, filter and use the clear filtrate. For solution (B) use 10 mg of fluconazole RS per ml. For solution (C) use a mixture of 2 mg of fluconazole RS and 1 mg of ketoconazole RS per ml. After removing the plate from the chromatographic chamber allow it to dry in a current of air and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid, unless the chromatogram obtained with solution (C) shows two clearly separated spots.

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

C. To a quantity of the capsule content, containing 2 mg of fluconazole, add 10 ml of ethanol R, shake and filter. The absorption spectrum (1.6) of the resulting solution, when observed between 230 nm and 300 nm, exhibits maxima at 261 nm and 267 nm and a minimum at about 264 nm. The ratio of the absorbance of a 1 cm layer at the maximum at about 261 nm to that at the minimum at about 264 is about 1.4.
Related substances
Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under “Assay”, Method B. Prepare the following solutions in the mobile phase. For solution (1) use an amount of the mixed contents of 20 capsules to produce a solution containing 10 mg of fluconazole per ml and filter the solution. For solution (2) dilute 5 volumes of solution (1) to 100 volumes, then dilute 1 volume of this solution to 10 volumes. For solution (3) use 0.1 mg of fluconazole impurity C RS per ml. For solution (4) transfer 1.0 ml of solution (3) to a 10 ml volumetric flask, add 1.0 ml of solution (1) and make up to volume.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 260 nm.

Inject separately 20 μl each of solutions (1), (2), (3) and (4). Record the chromatograms for about 3.5 times the retention time of fluconazole.

The peaks are eluted at the following relative retentions with reference to fluconazole (retention time about 11 minutes): impurity B about 0.4; impurity A about 0.5; impurity C about 0.8.

The test is not valid, unless in the chromatogram obtained with solution (4), the resolution between the peaks due to impurity C and to fluconazole is at least 3.0.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);
- the area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.5, is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);
- the area of any peak corresponding to impurity C is not greater than 0.1 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);
- the area of any other impurity peak, other than the principal peak, is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the sum of the corrected area of any peak corresponding to impurity B and the areas of all peaks, other than the peak due to fluconazole, is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Dissolution test
Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 500 ml of pH 6.8 dissolution buffer TS, rotating the paddle at 75 revolutions per minute. At 45 minutes withdraw a sample of about 10 ml of the medium through a suitable 0.45 μm filter. Measure the absorbance (1.6) of a 1 cm layer of the filtered solution, suitably diluted if necessary, at the maximum at about 261 nm. At the same time measure the absorbance (1.6) at the maximum at 261 nm of a solution containing 0.1 mg of fluconazole RS per ml in the dissolution medium, using the same solution as the blank.

For each of the capsules tested calculate the total amount of fluconazole ($C_{13}H_{12}F_2N_6O$) in the medium from the absorbances obtained, using the declared content of $C_{13}H_{12}F_2N_6O$ in fluconazole RS. Use the requirements as described under 5.5 Dissolution test for solid oral dosage forms. Acceptance criteria to evaluate the results. The amount in solution is not less than 85% (Q) of the amount declared on the label.
Assay

• Either test A or B may be applied.

A. Mix the contents of 20 capsules and transfer a quantity containing about 50 mg of fluconazole, accurately weighed, to a 100 ml volumetric flask and dilute to volume with hydrochloric acid (~4 g/l) TS. Shake to dissolve, filter a portion of this solution and dilute 10 ml of the filtered solution to 25 ml with the same solution. Measure the absorbance (1.6) of a 1 cm layer at the maximum at about 261 nm.

At the same time measure the absorbance of a solution of 0.2 mg of fluconazole RS per ml of hydrochloric acid (~4 g/l) TS, prepared and examined in the same manner, and calculate the percentage content of fluconazole (C$_{13}$H$_{12}$F$_2$N$_6$O) in the capsules, using the declared content of C$_{13}$H$_{12}$F$_2$N$_6$O in fluconazole RS.

B. 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 particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 μm). As the mobile phase use a mixture of 86 volumes of a (0.63 g/l) solution of ammonium formate R and 14 volumes of acetonitrile R.

Prepare the following solutions in the mobile phase. For solution (1) use an amount of the mixed contents of 20 capsules to produce a solution containing 0.5 mg of fluconazole per ml and filter the solution. For solution (2) use 0.5 mg of fluconazole RS per ml. For solution (3) use a solution containing 0.01 mg of fluconazole impurity C RS per ml and 1 mg of fluconazole RS per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 260 nm.

Inject separately 20 μl of each of solutions (1), (2) and (3). The test is not valid unless in the chromatogram obtained with solution (3) the resolution between the peaks due to impurity C and to fluconazole is at least 3.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of fluconazole (C$_{13}$H$_{12}$F$_2$N$_6$O) in the capsules, using the declared content of C$_{13}$H$_{12}$F$_2$N$_6$O in fluconazole RS.

Reagent to be defined:

Ammonium formate R

CH$_5$NO$_2$. Deliquescent crystals or granules, very soluble in water R, soluble in dehydrated ethanol R. Melting range: 119°C to 121°C. Storage in an airtight container.

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1 Capcell Pak® C18 MGII (4.6×250 mm, 5 μm) has been found suitable.
Consultation documents

Fluconazoli injectio
Fluconazole injection

This is a draft proposal for The International Pharmacopoeia (Working document QAS/12.471/Rev.2, May 2014).

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, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

Description. A clear, colourless solution.

Category. Antifungal.

Storage. Fluconazole injection should be kept in a tightly closed container, protected from light.

Additional information. Strength in the current WHO Model list of essential medicines: 2 mg/ml in vial.

Requirements

Complies with the monograph for Parenteral preparations.

Definition. Fluconazole injection is a sterile solution of fluconazole in water for injections.

The solution is sterilized by a suitable method (see 5.8 Methods of sterilization). Fluconazole injection contains not less than 90.0% and not more than 110.0% of the amount of fluconazole (C₁₃H₁₂F₂N₆O) stated on the label.

Identity tests

• Either test A and C or test B and C may be applied.

A. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 80 volumes of dichloromethane R, 20 volumes of methanol R and 1 volume of ammonia (~260 g/l) TS solution as the mobile phase. Apply separately to the plate 20 μl of each of the following three solutions. For solution (A) use the injection to be examined. For solution (B) use 2 mg of fluconazole RS per ml in methanol R. For solution (C) use a mixture of 2 mg of fluconazole RS per ml and 1 mg of ketoconazole RS per ml in methanol R. After application allow the spots to dry in a current of air. Develop the plate. After removing the plate from the chromatographic chamber allow it to dry in a current of air and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots.

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

C. Dilute a volume of the injection containing 2 mg of fluconazole to 10 ml with water R. The absorption spectrum (1.6) of the resulting solution, when observed between 230
nm and 300 nm, exhibits maxima at 261 nm and 267 nm and a minimum at about 264 nm. The ratio of the absorbance of a 1 cm layer at the maximum at about 261 nm to that at the minimum at about 264 is about 1.4.

**pH value** (1.3). pH of the injection, 4.0–6.0.

**Related substances**

Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given below under “Assay”. Prepare the following solutions in the mobile phase. For solution (1) use the injection to be examined. For solution (2) dilute 5 volumes of solution (1) to 100 volumes, then dilute 1 volume of this solution to 10 volumes. For solution (3) use 0.02 mg of fluconazole impurity C RS per ml. For solution (4) mix 1 volume of solution (3) with 1 volume of solution (1).

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 260 nm.

Inject separately 20 μl each of solutions (1), (2), (3) and (4). Record the chromatograms for about 3.5 times the retention time of fluconazole.

The peaks are eluted at the following relative retentions with reference to fluconazole (retention time about 11 minutes): impurity B about 0.4; impurity A about 0.5; impurity C about 0.8.

The test is not valid unless in the chromatogram obtained with solution (4) the resolution between the peaks due to impurity C and to fluconazole is at least 3.0

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);
- the area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.5, is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);
- the area of any peak corresponding to impurity C is not greater than 0.1 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);
- the area of any other impurity peak, other than the principal peak, is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the sum of the corrected area of any peak corresponding to impurity B and the areas of all peaks, other than the peak due to fluconazole, is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0 %). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

**Assay**

- Either test A or B may be applied.
  
  **A.** Dilute an accurately measured volume of the injection equivalent to about 2 mg with hydrochloric acid (~4 g/l) TS to 10 ml and mix. Measure the absorbance of a 1 cm layer at the maximum at about 261 nm. At the same time measure the absorbance of a solution of 0.2 mg of fluconazole RS per ml of hydrochloric acid (~4 g/l) TS, prepared and examined in the same manner, and calculate the percentage content of fluconazole (C_{13}H_{12}F_{2}N_{6}O) in the injection, using the declared content of C_{13}H_{12}F_{2}N_{6}O in fluconazole RS.
B. 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 particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 μm).\(^1\)

As the mobile phase, use a mixture of 86 volumes of a (0.63 g/l) solution of ammonium formate R and 14 volumes of acetonitrile R.

Prepare the following solutions in the mobile phase. For solution (1) dilute 5.0 ml of the injection to be examined to 20.0 ml. For solution (2) use 0.5 mg of fluconazole RS per ml. For solution (3) use a solution containing 0.01 mg of fluconazole impurity C RS per ml and 1 mg of fluconazole RS per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 260 nm.

Inject separately 20 μl of each of solutions (1), (2) and (3). The test is not valid unless in the chromatogram obtained with solution (3) the resolution between the peaks due to impurity C and due to fluconazole is at least 3.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of fluconazole (C\(_{13}\)H\(_{12}\)F\(_2\)N\(_6\)O) in the injection using the declared content of C\(_{13}\)H\(_{12}\)F\(_2\)N\(_6\)O in fluconazole RS.

**Bacterial endotoxins.** Carry out the test as described under **3.4 Test for bacterial endotoxins**; contains not more than 0.416 IU of endotoxin RS per mg of fluconazole.

**Reagent to be defined:**

**Ammonium formate R**

CH\(_5\)NO\(_2\)_2. Deliquescent crystals or granules, very soluble in water R, soluble in dehydrated ethanol R. Melting range: 119°C to 121°C. Storage in an airtight container.

---

1 Capcell Pak\textsuperscript{®} C18 MGII (4.6×250 mm, 5 μm) has been found suitable.
Levamisoli hydrochloridum
Levamisole hydrochloride

This is a draft proposal for The International Pharmacopoeia (Working document QAS/14.584, May 2014).

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, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

C₁₁H₁₂N₂S·HCl

Relative molecular mass. 240.8

Chemical name. (-)-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-b]thiazole monohydrochloride; (S)-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-b]thiazole monohydrochloride; CAS Reg. No. 16595-80-5.

Description. A white or almost white, crystalline powder.

Solubility. Freely soluble in water; soluble in ethanol (~750 g/l) TS; slightly soluble in dichloromethane R.

Category. Anthelminthic drug.

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

Requirements

Levamisole hydrochloride contains not less than 98.5% and not more than 101.0% of C₁₁H₁₂N₂S·HCl, calculated with reference to the dried substance.

Identity tests

• Either tests A and D or tests B, C and D 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 levamisole hydrochloride RS or with the reference spectrum of levamisole hydrochloride.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 60 volumes of toluene R, 40 volumes of acetone R and 1 volume of ammonia (~260g/l) TS as the mobile phase. Apply separately to the plate 10 μl of each of the following two solutions in methanol R. For solution (A) use 2 mg of the test substance per ml. For solution (B) use 2 mg of levamisole hydrochloride RS per ml. Examine the chromatogram in ultraviolet light (254 nm). The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).
C. Dissolve about 0.06 g of the test substance in 20 ml of water, add 2 ml of sodium hydroxide (~80 g/l) TS, boil for 10 minutes and cool. Add a few drops of sodium nitroprusside (45 g/l) TS; a red colour is produced which fades on standing.

D. A 0.05 g/ml solution yields reaction B described under 2.1 General identification tests as characteristic of chlorides.

**Specific optical rotation.** Use a 0.050 g/ml solution in carbon-dioxide-free water R and calculate with reference to the dried substance; \([\alpha]_{D}^{20\circ} = -121.5^\circ \text{ to } -128^\circ\).

**Clarity and colour of solution.** A solution of 0.50 g in 10 ml of carbondioxide-free water R is clear and not more intensely coloured than standard colour Yw1 when compared as described under 1.11 Colour of liquids.

**Sulfated ash.** Not more than 1.0 mg/g.

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

**pH value.** pH of a 0.05 g/ml solution, 3.5–5.0.

**Related substances.** Prepare fresh solutions and perform the tests without delay.

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (10 cm x 4.6 mm) packed with particles of base-deactivated silica gel, the surface of which has been modified by chemically-bonded octadecylsilyl groups (3 µm).

Use the following conditions for gradient elution:

Mobile phase A: dissolve 0.5 g of ammonium dihydrogen phosphate R in 90 mL of water R, adjust to pH 6.5 with a 40 g/l solution of sodium hydroxide R and dilute to 100 ml with water R.

Mobile phase B: acetonitrile R.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comments</th>
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<tbody>
<tr>
<td>0–8</td>
<td>90–30</td>
<td>10–70</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>8–10</td>
<td>30</td>
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<tr>
<td>10–11</td>
<td>30–90</td>
<td>70–10</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>11–15</td>
<td>90</td>
<td>10</td>
<td>Re-equilibration</td>
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</table>

Operate with a flow rate of 1.5 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 215 nm.

As a dissolution solvent prepare a mixture of 90 volumes of methanol R and 10 volumes of ammonia (~260 g/l) TS. Prepare the following solutions: For solution (1) transfer 100 mg of the test substance to a 10 ml volumetric flask and dilute to volume with the dissolution solvent. For solution (2) dilute 10.0 ml of solution (1) to 100.0 ml with methanol R. For solution (3) dissolve 20 mg of the test substance in 5 ml of a 0.1 mol/l solution of sodium hydroxide R in a test tube. Close and heat the test tube in a water-bath at 100 °C for 5 hours. Allow to cool and dilute 1 ml of the resulting solution to 25 ml with methanol R. For solution (4) transfer 5.0 ml of solution (2) to a 50 ml volumetric flask and dilute to volume with methanol.

Inject 10 µl of solution (3). The test is not valid unless the resolution between the peak due to levamisole (retention time about 3.5 minutes) and the peak due to impurity C (relative retention of about 1.5) is at least 15.

Inject separately 10 µl each of solutions (1) and (4).
The following peaks are eluted at the following relative retention with reference to levamisole (retention time about 3.5 minutes): impurity A about 0.9; impurity B about 1.4; impurity C about 1.5; impurity D about 1.6; impurity E about 2.0.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 2.0, is not greater than 0.2 times the area of the peak due to levamisole in the chromatogram obtained with solution (4) (0.2 %);
- the area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.7, is not greater than 0.2 times the area of the peak due to levamisole in the chromatogram obtained with solution (4) (0.2 %);
- the area of any peak corresponding to impurity C, when multiplied by a correction factor of 2.9, is not greater than 0.2 times the area of the peak due to levamisole in the chromatogram obtained with solution (4) (0.2 %);
- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 1.3, is not greater than 0.2 times the area of the peak due to levamisole in the chromatogram obtained with solution (4) (0.2 %);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 2.7, is not greater than 0.2 times the area of the peak due to levamisole in the chromatogram obtained with solution (4) (0.2 %);
- the area of any other peak, other than the principal peak, is not greater than 0.1 times the area of the peak due to levamisole in the chromatogram obtained with solution (4) (0.1 %);
- the sum of the corrected areas of any peak corresponding to impurity A, B, C, D and E and the areas of all other peaks, other than the principal peak, is not greater than 0.3 times the area of the peak due to levamisole in the chromatogram obtained with solution (4) (0.3 %). Disregard any peak with an area less than 0.05 times the area of the peak due to levamisole the chromatogram obtained with solution (4) (0.05 %).

Heavy metals. Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, use procedure 1 or procedure 3 for the preparation of the test solution; determine the heavy metals content according to Method A; not more than 20 μg/g.

**Assay**

Dissolve about 0.2 g, accurately weighed, in 30 ml of ethanol (~750 g/l) TS and add 5 ml of hydrochloric acid (0.01 mol/l) VS. Titrate with sodium hydroxide (0.1 mol/l) VS, determining the two inflection points potentiometrically. Record the volume, in ml, of sodium hydroxide (0.1 mol/l) VS consumed between the two inflection points.

Each ml of sodium hydroxide (0.1mol/l) VS is equivalent to 24.08 mg of \( C_{11}H_{12}N_{2}S,\text{HCl} \).

**Impurities**

A. 3-[(2RS)-2-amino-2-phenylethyl]thiazolidin-2-one,
B. 3-[(E)-2-phenylethenyl]thiazolidin-2-imine,

C. (4RS)-4-phenyl-1-(2-sulfanylethyl)imidazolidin-2-one,

D. 6-phenyl-2,3-dihydroimidazo[2,1-b]thiazole,

E. 1,1′-[(disulfane-1,2-diyl)bis(ethylene)]bis[(4RS)-4-phenylimidazolidin-2-one].

Reference substances to be established
levamisole hydrochloride RS

***
Dextromethorphan hydrobromide

This is a draft proposal for The International Pharmacopoeia (Working document QAS/14.585, May 2014).

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, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidt@who.int.

[Note from the Secretariat. Following consumption of dextromethorphan cough syrups contaminated with levomethorphan approximately 50 persons died in Pakistan in January 2013. A further suspected drug intoxication involving 11 patients was reported several months later, in September 2013, in Paraguay. Investigations revealed that the medicines administered were manufactured using adulterated dextromethorphan hydrobromide, which contained levomethorphan at levels varying between 9.5% to 22.6%. Following these incidents the World Health Organization issued Drug Alerts Nos 126 and 129 and called on all Member States to increase vigilance against adulterated Dextromethorphan/Dextromethorphan hydrobromide API.

It is proposed to revise the monograph on Dextromethorphan hydrobromide in The International Pharmacopoeia with a view to add a statement under the section "Manufacture" requiring that the production method is validated to demonstrate that the substance, if tested, would comply with a limit of not more than 0.1% for levomethorphan hydrobromide. This limit was deemed appropriate following a scientific assessment on behalf of the WHO Prequalification Team.

A chiral method, selective for levomethorphan, is currently under development and shall be included in the "Supplementary Information Section" of The International Pharmacopoeia once elaborated.

Changes from the current monograph are indicated in the text by insert or delete.]

Molecular formula. $C_{18}H_{25}NO\cdot HBr\cdot H_2O$

Relative molecular mass. 370.3

Graphic formula.

Chemical name. (+)-3-Methoxy-17-methyl-9α,13α-14α-morphinan hydrobromide monohydrate; (+)-cis-1,3,4,9,10,10a-hexahydro-6-methoxy-11-methyl-2H-10,4a-iminoethanophenanthrene hydrobromide monohydrate; CAS Reg. No. 6700-34-1 (monohydrate).

Description. A white or almost white, crystalline powder; odourless or almost odourless.

Solubility. Sparingly soluble in water; freely soluble in ethanol (~750 g/l) TS; practically insoluble in ether R.

Category. Antitussive drug.

Storage. Dextromethorphan hydrobromide should be kept in a well-closed container.

Requirements

Definition. Dextromethorphan hydrobromide contains not less than 98.0% and not more than 101.0% of $C_{18}H_{25}NO\cdot HBr$, calculated with reference to the anhydrous substance.
**Manufacture.** The production method is validated to demonstrate that the substance, if tested, would comply with a limit of not more than 0.1% for levomethorphan hydrobromide using a suitable chiral method.

**Identity tests**
- Either tests A and E or tests B, C, D and E may be applied.
  - A. Dry a small quantity of the test substance for 4 hours under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury) over phosphorus pentoxide R and 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 dextromethorphan hydrobromide RS similarly prepared or with the reference spectrum of dextromethorphan hydrobromide.
  - B. The absorption spectrum of a 0.10 mg/ml solution in sodium hydroxide (0.1 mol/l) VS, when observed between 230 nm and 350 nm, exhibits a maximum at 280 nm; the absorbance of a 1 cm layer at this wavelength is about 0.59.
  - C. Dissolve 0.05 g in 2 ml of sulfuric acid (~100 g/l) TS. Add 1 ml of mercury/nitric acid TS drop by drop while shaking; a white, crystalline precipitate in the form of platelets is produced and the solution does not immediately turn red. Heat on a water-bath for about 10 minutes; a yellow to red colour develops.
  - D. Melting temperature, about 125°C with decomposition.
  - E. To a 5 mg/ml solution add 0.25 ml of nitric acid (~130 g/l) TS; this test yields reaction B described under 2.1 General identification tests as characteristic of bromides.

**Specific optical rotation.** Use a 20 mg/ml solution in hydrochloric acid (0.1 mol/l) VS and calculated with reference to the anhydrous substance; \[ \delta^20_{D} = +28.0° \text{ to } +30.0°. \]

**Sulfated ash.** Not more than 1.0 mg/g.

**Water.** Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using about 0.2 g of the substance; the water content is not less than 35 mg/g and not more than 55 mg/g.

**pH value.** Dissolve 0.4 g in carbon-dioxide-free water R using gentle heat, dilute to 20 ml with the same solvent and measure the pH at 20°C; the value lies between 5.2 and 6.5.

**Dimethylaniline.** Dissolve 0.5 g in 15 ml of water using gentle heat, cool and add 4 ml of acetic acid (~60 g/l) TS, 1 ml of sodium nitrite (10 g/l) TS and sufficient water to produce 25 ml. Prepare similarly a reference solution containing 5 μg of N,N-dimethylaniline R in 25 ml. The colour produced in the test solution is not more intense than that produced in the reference solution when compared as described under 1.11 Colour of liquids; the dimethylaniline content is not more than 10 μg/g.

**Phenolic substances.** To 5 mg add 1 drop of hydrochloric acid (~70 g/l) TS, 1 ml of water and 0.2 ml of ferric chloride (50 g/l) TS. Mix, add 0.2 ml of potassium ferricyanide (50 g/l) TS, dilute to 5 ml with water, shake well and allow to stand for 15 minutes; the solution is yellowish brown and shows no greenish or blue colour.

**Assay**
Dissolve about 0.5 g, accurately weighed, in 40 ml of glacial acetic acid R1 and add 10 ml of mercuric acetate/acetic acid TS, warming slightly if necessary to effect solution. Titrate with perchloric acid (0.1 mol/l) VS as described under 2.6 Non-aqueous titration, Method A. Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 35.23 mg of \( C_{18}H_{25}NO,HBr. \)
ATC/DDD Classification

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 2014. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology before 1 September 2014. If no objections are received before this date, the new ATC codes and DDDs will be considered final and included in the January 2015 version of the ATC/DDD Index.

New ATC 5th level codes:

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New DDDs:

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Administration Route: O=oral; P=parenteral

1) ATC code valid from January 2015 (current code L01XC04).

***
The following ATC codes, DDDs and alterations were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in October 2013. These are considered as final and will be included in the January 2015 version of the ATC/DDD Index.

The WHO Collaborating Centre for Drug Statistics Methodology can be contacted at whocc@fhi.no. The inclusion of a substance in the lists does not imply any recommendation for use in medicine or pharmacy.

**New ATC 5th level codes:**

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*Continued*/
### New ACT 5th level codes, continued:

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### Change of ATC codes:

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### Change of ATC level names:

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### New DDDs:

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* Administration Route: O=oral; P=parenteral

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