World Health Organization

EXECUTIVE BOARD
153rd session
Provisional agenda item 8

EB153/10
19 May 2023

Matters for information: report on meetings of expert committees and study groups[1]

Report by the Director-General

DRUG DEPENDENCE

Forty-fifth report of the Expert Committee on Drug Dependence, Geneva, 10-13 October 2022[2]

1. WHO is mandated by *The International Drug Control Conventions* to evaluate the scientific evidence related to dependence, abuse and harm to health of psychoactive substances and their therapeutic use and make recommendations on whether psychoactive substances should be placed under international control. These recommendations are made through the Expert Committee on Drug Dependence and are the result of rigorous, evidence-driven procedures.

Main recommendations

2. The Committee convened its forty-fifth meeting to consider whether nine new psychoactive substances present significant harms to public health that would warrant their placement under international control. The Committee also carried out a preliminary assessment of the medicine zopiclone.

3. The Committee recommended that four new psychoactive substances be placed under international control under the Single Convention on Narcotic Drugs of 1961: 2-Methyl-AP-237, etazene, etonitazepyne and protonitazene. These synthetic opioids do not have any recognized therapeutic uses and deaths associated with the use of these substances have been reported.

4. The Committee further recommended that three psychoactive substances be placed under international control under the Convention on Psychotropic Substances of 1971. These substances comprised the synthetic cannabinoid ADB-BUTINACA, as well as the cathinones and/or stimulants alpha-PiHP and 3-methylmethcathinone.

[1] The Regulations for Expert Advisory Panels and Committees provide that the Director-General shall submit to the Executive Board a report on meetings of expert committees containing observations on the implications of the expert committee reports and recommendations on the follow-up action to be taken.

[2] WHO Technical Report Series, No. 1046, 2023.

5. The Committee recommended that the benzodiazepines adinazolam and bromazolam, and the medicine zopiclone, be placed under WHO surveillance to facilitate continued monitoring and data reporting by countries regarding the harms pertaining to their use.

6. The Committee's recommendations were considered for a vote by the 66th session of the United Nations Commission on Narcotic Drugs in March 2023. The Commission voted to accept all recommendations made by the Committee, thereby placing nine harmful psychoactive substances under international control.

Significance for public health policies

7. The new psychoactive substances recommended for international control by the Committee have no therapeutic use and have contributed to substantial numbers of deaths by overdose, in addition to other significant harms to public health. The placement under international control will restrict their availability for use, and oblige Member States to implement national control for these substances to prevent their misuse and abuse and to protect public health.

8. WHO's mandate to assess psychoactive substances and make recommendations to the United Nations Commission on Narcotic Drugs ensures that a science-driven methodology informs the international control of psychoactive substances. WHO's public health mandate within *The International Drug Control Conventions* ensures that psychoactive substances that cause harms to public health are appropriately regulated, and that excessive drug control measures are not placed upon substances that have recognized therapeutic use.

Implications for the Organization's programmes

9. Novel synthetic opioid drugs and benzodiazepines, such as those reviewed by the Committee, are falsely sold as medicines, and may pose threats to the health of individuals. WHO's work to tackle the problem of substandard and falsified medical products, including the WHO Global Surveillance and Monitoring System for substandard and falsified medical products, should facilitate detection of these dangerous substances and falsified medicines.

10. To ensure that essential medicines under international control, such as many opioids, are available for legitimate use where they are needed, the secretariat of the Committee works closely with the Expert Committee on the Selection and Use of Essential Medicines, which is responsible for the WHO Model List of Essential Medicines. This is to ensure that for controlled medicines, information is shared on their appropriate use for various conditions, including the management of pain and palliative care.

11. The secretariat of the Committee also works closely with technical departments across the WHO Secretariat towards the promotion of universal health coverage policies for controlled medicines and to ensure that health is central in addressing the world drug problem. This includes collaboration with technical teams working on bloodborne viruses and drug dependence treatment in ensuring access to and availability of opioid agonist therapies. The recommendations of the Committee present broad implications for public health at regional and country levels. These include raising awareness of public health risks of psychoactive substances, and promoting the use of guidelines for improving access to and safe use of controlled medicines at country level, including those for pain and palliative care, neurological and mental health diseases and for the prevention and treatment of drug use disorders.

BIOLOGICAL STANDARDIZATION

Seventy-sixth report of the Expert Committee on Biological Standardization, virtual meeting,[1] 24–28 October 2022[2]

12. The Expert Committee on Biological Standardization reviews developments in the field of biological products used in human medicine. Such products include vaccines, biotherapeutics, blood products, cell, tissue and gene therapy products, and in vitro diagnostics. The Committee coordinates activities leading to the adoption of WHO recommendations, guidelines and guidance documents (written standards) that help to ensure the quality, safety and efficacy of such products, as well as to the establishment of WHO international reference standards (measurement standards).

13. The adoption and publication of WHO written standards and the establishment and use of WHO measurement standards designating the activity of biological products used for the diagnosis, prevention or treatment of disease allow for the comparison of nonclinical and clinical data worldwide. Ensuring the comparable quality, safety and efficacy of biological products is a vital step in facilitating their equitable global availability and thus contributes towards attainment of the key strategic WHO goal of universal health coverage.

14. During its seventy-sixth meeting, the Committee made recommendations on a broad range of recent WHO activities, including several biological standardization activities relating to the continuing coronavirus disease (COVID-19) pandemic.

Main recommendations

15. Following detailed discussion and review, the Committee recommended the adoption of two revised WHO written standards:

(a) Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated); and

(b) WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices.

16. Following careful consideration of the reports of international collaborative laboratory studies, the Committee also recommended the establishment of 24 new or replacement WHO measurement standards. In addition, the Committee endorsed seven proposals to develop new or replacement WHO measurement standards.

17. The Committee once again addressed a number of standardization issues arising from the continuing COVID-19 pandemic and acknowledged the particular challenges of developing appropriate biological standards in a timely manner during a public health emergency. This is particularly the case when faced with a rapidly evolving and antigenically diverse pathogen such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In the case of the acutely needed replacement of the First WHO International Standard for anti-SARS-CoV-2 immunoglobulin, the only pragmatic solution had been to

[1] Coordinated from WHO headquarters, Geneva.

[2] WHO Technical Report Series, No. 1045 (in press).

replace this with a similar early material while at the same time establishing a new WHO international standard based on plasma containing antibodies specific to the more recent Omicron variant.

18. The Committee reviewed the practice of establishing an antibody standard in international units explicitly for use in neutralization assays while allowing the same material to be used to compare antibody binding assays based on the use of the arbitrary binding antibody unit. Although widely accepted in the field, this unit has no formal status with respect to WHO international standards and its use has been criticized by sections of the metrology community. The Committee noted the potential for confusion and associated risk of loss of confidence in WHO international standards. The Committee therefore recommended that a working group be established to identify and review the fundamental issues in this area and to present proposals to the Committee at its next meeting on how these issues would best be addressed.

19. The Committee also discussed the numerous challenges in developing WHO guidance on establishing regulatory frameworks for cell, tissue and gene therapies. Such therapies involve the use of highly diverse and complex products, many of which address otherwise unmet medical needs, while presenting significant regulatory challenges. The Committee acknowledged the efforts made to date to develop a WHO guidance document as a first step in this area and suggested a number of improvements and refinements for consideration during its further development. The Committee looked forward to the scheduled submission of this document for proposed adoption at its next meeting in March 2023.

20. The Committee continued in its efforts to evaluate and advise on the potential applications of emerging and novel assay technologies and analytical methods. The utility of high-throughput sequencing technologies in the quality control of vaccines was extensively discussed, including in relation to the revised WHO Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated) mentioned above. The Committee recognized the potentially far-reaching implications of such technologies in ensuring the quality, safety and efficacy of vaccines and other biological products. The Committee specifically requested that WHO give consideration to the role it could play in providing guidance on the use of high-throughput sequencing in the quality control of vaccines and other biological products in the future.

21. As the range of potential clinical applications for monoclonal antibodies continues to proliferate, awareness is increasing of the factors that mediate their biological function, and thus their therapeutic activity and safety during treatment. The Committee endorsed a proposal to develop reference reagents to support assay development in this area, thus underscoring both the need to increasingly incorporate the standardization of emerging and diverse technologies and analytical methods into its work, and the need to ensure the required expertise within the Committee.

22. The Committee reviewed current WHO priorities for the development of new and revised WHO written standards for biological products. The Committee indicated its overall support for the approach taken, and for the specific proposals made in relation to the development or revision of product-specific and more general WHO recommendations, guidelines and guidance documents.

Significance for public health policies

23. As with all WHO written standards, the two that were adopted at the seventy-sixth meeting are scientific and advisory in nature and are intended to provide accurate, up-to-date guidance to national regulatory authorities and to manufacturers of biological products. If so desired, such guidance, suitably modified where required, may be adopted as definitive national regulatory requirements by countries.

24. Oral poliomyelitis vaccines have been the mainstay of the Global Polio Eradication Initiative since its inception. The above-mentioned revised WHO Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated) now cover issues such as the application of high-throughput sequencing technologies in quality control and their potential to replace in vivo neurovirulence testing, which currently requires animal studies. The revised Recommendations have also been aligned with other recently published WHO documents in this area to facilitate compliance by countries and manufacturers with current polio eradication approaches.

25. The effective regulation of medical products has long been recognized by WHO Member States as an essential component in strengthening health systems and improving public health. Following recent technological advances, increasing product complexity and the emergence of new developers and regulators with only limited experience in this field, the above-mentioned substantially revised and updated WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices was adopted. This Framework sets out the guiding principles and characteristics of effective regulatory systems for medical devices that can be incorporated into law, with a particular focus on the responsibilities of legislators and national regulatory authorities. New or expanded guidance is provided in key areas such as the use of risk-based classification systems, the role of regulatory reliance and recognition, emergency use authorization and the regulation of donated devices.

26. The timely availability of internationally recognized WHO measurement standards is crucial for countries and manufacturers in harnessing the benefits of scientific advances in the production and evaluation of vitally needed biological products. The establishment of the 24 WHO measurement standards recommended by the Committee will directly facilitate the broader and more equitable availability of such products and thus contribute towards attainment of the global public health goal of universal health coverage.

Implications for the Organization's programmes

27. The Committee's review and approval of proposed WHO priorities for the development of new and revised WHO written standards for biological products is an important step in ensuring that published WHO guidance on the development, manufacture and regulation of biological products remains relevant and up to date.

28. The development, establishment and promotion of globally required biological measurement standards remain core normative WHO activities as set out in its Constitution. The decision of the Committee to recommend establishment of the 24 new or replacement WHO measurement standards will directly support the continuation of these core activities. In addition, the endorsement by the Committee of the proposed development of seven new or replacement WHO measurement standards will ensure that priority standards continue to become available in a timely manner to support the work of WHO programmes in addressing both the existing and emerging global health priorities of the Organization.

29. The decisions and recommendations of the Committee have direct implications for the regulation and quality control of biological products and are thus relevant not only to regulators in all countries but also to the numerous programmes and initiatives within WHO and other international organizations that rely on the availability of vaccines, biotherapeutics, blood products, cell, tissue and gene therapy products, in vitro diagnostics and other biological products.

TOBACCO PRODUCT REGULATION

Report of the eleventh meeting of the WHO Study Group on Tobacco Product Regulation, Tbilisi, Georgia, 13–15 December 2022[1]

30. The WHO Study Group on Tobacco Product Regulation publishes a series of reports to provide a scientific basis for tobacco product regulation. They are a WHO technical product (formerly known as a global public health good) and are in line with resolutions WHA53.8 (2000), WHA53.17 (2000) and WHA54.18 (2001). In line with Articles 9 and 10 of the WHO Framework Convention on Tobacco Control as well as relevant decisions of the Conference of the Parties to the WHO Framework Convention on Tobacco Control[2] and WHO reports to the Conference of the Parties,[3] the reports of the Study Group identify evidence-based approaches to regulating nicotine and tobacco products, including new and emerging products, such as electronic nicotine delivery systems, electronic non-nicotine delivery systems and heated tobacco products.

31. The Study Group discussed six background papers: Additives that facilitate inhalation, including cooling agents, nicotine salts and flavourings; Synthetic nicotine: science, global legal landscape and regulatory considerations; Nicotine pouches: characteristics, use, harmfulness and regulation; Biomarkers of exposure, effect and susceptibility for assessing electronic nicotine delivery devices and heated tobacco products, and their possible prioritization; Internet, influencer and social media marketing of tobacco and non-therapeutic nicotine products and associated regulatory considerations; and The WHO Study Group on Tobacco Product Regulation: two decades of recommendations – translating evidence into policy action. The sixth background paper was to inform the future work of the Study Group on translating science into policy and will be considered separately by the Study Group. Therefore, the report focuses on five background papers. The information in these five background papers, as featured in the report, will update knowledge and advance nicotine and tobacco product regulation to inform policy at national and global levels.

32. The Study Group examined emerging issues in tobacco product regulation and repeated requests by Member States for the Secretariat to provide technical assistance in areas considered to inform development of national policy. A number of the background papers focused on newer ways in which non-therapeutic nicotine in nicotine and tobacco products is delivered and promoted to people in different age groups, including children and adolescents. Such requests – as well as the Secretariat's and the Study Group's knowledge of the above-mentioned areas and the relevant literature – informed the development of the content of the background papers for the report. The WHO Secretariat invited subject matter experts who, in addition to drafting background papers and contributing to the discussions, provided up-to-date empirical data on nicotine and tobacco product regulation. Selected regulators, other experts and the Secretariat of the WHO Framework Convention on Tobacco Control also contributed to discussions. The report will guide Member States in achieving the most effective and evidence-based means to bridge regulatory gaps in tobacco control and aid the development of coordinated regulatory frameworks for tobacco products. Additionally, it identifies future areas of work, focusing on the regulatory needs of countries, thus providing a strategy for continued technical support to Member States.

[1] WHO Technical Report Series, No. 1047 (in preparation).

[2] Decisions FCTC/COP6(9) (2014), FCTC/COP6(12) (2014), FCTC/COP7(9) (2016) and FCTC/COP7(14) (2016).

[3] Documents FCTC/COP/6/10 Rev.1 and FCTC/COP/7/11.

Main recommendations

33. The main recommendations to policymakers and all other interested parties include, but are not limited to, the following:

(a) noting the aggressive promotion of both tobacco and nicotine products globally, the Study Group urged Member States to ensure a continuing focus on evidence-based measures to reduce tobacco use as outlined in the WHO Framework Convention on Tobacco Control, and not to be distracted by the tobacco industry or other vested interests;

(b) to ensure that regulations of tobacco products are extended and applied to all forms of nicotine and tobacco products and not restricted to conventional cigarettes;

(c) to require manufacturers to disclose information on these products regarding:

(i) emission levels for selected harmful chemicals; and

(ii) levels of biomarkers in the panel used in premarketing evaluation;

(d) to ensure that tobacco advertising promotion and sponsorship laws are comprehensive and in line with the WHO Framework Convention on Tobacco Control as a minimum. Measures related to tobacco advertising, promotion and sponsorship should encompass online digital media platforms, including social media and any other forms of direct or indirect marketing;

(e) to strengthen monitoring and enforcement and cooperate internationally to address cross-border practices related to tobacco and related industries, including online digital tobacco advertising, promotion and sponsorship;

(f) to require tobacco and related industries to disclose to government authorities all advertising, promotion and sponsorship activities, including those on online digital media platforms;

(g) to address the content and emissions of tobacco products and support product evaluation, monitoring and disclosure, in keeping with Articles 9 and 10 of the WHO Framework Convention on Tobacco Control, when formulating, adopting or updating tobacco product regulations;

(h) to ban the addition of menthol and other ingredients that facilitate inhalation in non-therapeutic nicotine products and all tobacco products. The ban should include synthetic coolant chemicals with a chemical structure or physiological and sensory effects similar to those of menthol;

(i) to amend national tobacco control laws if a regulatory gap for synthetic nicotine products exists, to ensure that synthetic nicotine products fall within their scope. Regulations should cover the full range of synthetic nicotine products and pharmacologically similar analogues that are currently marketed as well as products that may emerge in the future;

(j) to require uniform labelling rules for manufacturers for products containing synthetic nicotine, or mixtures of nicotine from multiple sources, either natural or synthetic, so that the content of different nicotine forms or analogues are declared separately;

(k) to establish or expand surveillance of products and their users, including demographics, use of other tobacco and related products, brand, type and flavour used in nicotine pouches to acquire knowledge and assess prevalence of use and user profiles;

(l) to regulate nicotine pouches to prevent all forms of marketing of them and take all other action necessary to minimize: young people's access to them, their appeal to young people and initiation of use by young people;

(m) to regulate non-therapeutic nicotine products in the same manner as products to which they are similar in appearance, content and use;

(n) to ensure that nicotine pouches are not classified as pharmaceutical products unless they are proven to be nicotine replacement therapies by following the stringent pharmaceutical pathways for licensing as nicotine replacement therapies, as prescribed by the appropriate national regulatory authority;

(o) to include biomarker-based findings, relying on industry-independent biomarker data, and country experiences in making policy decisions on electronic nicotine delivery systems, heated tobacco products and other novel and emerging nicotine and tobacco products; and

(p) to implement the recommendations of the Study Group that address specific challenges posed in regulating non-therapeutic nicotine and all forms of tobacco products.

Significance for public health policies

34. The Study Group's report provides helpful guidance in understanding research and evidence on the scientific basis of the regulation of nicotine and tobacco products. It highlights: the effects of additives that facilitate inhalation; the public health implications of social and digital marketing; the challenges associated with the marketing of nicotine pouches and synthetic nicotine and the regulatory implications of marketing these products; synthesizes the current evidence on biomarkers of, exposure, effect and susceptibility for assessing electronic nicotine delivery systems, electronic non-nicotine delivery systems and heated tobacco products. The report also considers the potential impact of the key considerations in the background papers on tobacco control efforts, identifies research gaps and makes some recommendations. The recommendations directly address some of the unique regulatory challenges faced by Member States due to direct and indirect product market advertising and penetration of products, such as nicotine pouches and products with synthetic nicotine, to several markets globally. In addition, the report will update Member States' knowledge and aid the formulation of effective regulatory strategies for nicotine and tobacco products.

35. The Study Group, because of its unique composition of regulatory, technical and scientific experts, navigates and distills complex data and research and synthesizes them into policy recommendations, which inform policy development at country, regional and global levels. Such recommendations promote international coordination of regulatory efforts and the adoption of best practices in regulating non-therapeutic nicotine and tobacco products, strengthen product regulation capacity-building across all WHO regions, provide a ready resource to Member States based on sound science and support the implementation of the WHO Framework Convention on Tobacco Control by its Parties. Given the aggressive promotion of nicotine and tobacco products, globally, the Study Group urges Member States to ensure a continued focus on evidence-based measures to reduce tobacco use as outlined in the WHO Framework Convention, without entertaining any distractions from tobacco and related industries.

Implications for the Organization's programmes

36. The report fulfils the mandate of the WHO Study Group on Tobacco Product Regulation to provide the Director-General with scientifically sound, evidence-based recommendations for Member States about tobacco product regulation,[1] which is a highly technical area of tobacco control in which Member States face complex regulatory challenges. The outcomes of the Study Group's deliberations and main recommendations will improve Member States' understanding of conventional and newer products and the promotional strategies employed by manufacturers. The report's contribution to the body of knowledge on regulating non-therapeutic nicotine and tobacco products will play a critical role in informing the work of the Secretariat, especially in providing technical support to Member States. It will also contribute to updating regulators, through the Global Tobacco Regulators Forum, and Parties to the WHO Framework Convention on Tobacco Control, through WHO's reports to the tenth session of the Conference of the Parties in November 2023. This will contribute to meeting target 3.a of the Sustainable Development Goals (Strengthen the implementation of the World Health Organization Framework Convention on Tobacco Control in all countries, as appropriate).

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[1] In November 2003, the Director-General formalized the status of the former Scientific Advisory Committee on Tobacco Product Regulation from a scientific advisory committee to a study group.