SAHPRA
South African
Health Products
Regulatory Authority

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Communication to Stakeholders

MD010: Regulatory Requirements, Technical Specifications, Licence Conditions and Authorisation for Use of Unregistered Rapidly Developed Invasive and Non-Invasive Ventilators for Covid-19

Background

1. In response to the anticipated shortage of medical supplies and equipment in the health care system as a result of the outbreak of the Covid-19 pandemic, the South African Health Products Regulatory Authority (the Authority) has drafted minimum requirements for the manufacture, importation and distribution of rapidly developed invasive and non-invasive ventilators.
2. These products are regulated by the Medicines and Related Substances Act, 1965 (Act 101 of 1965) (the Medicines Act) and the Hazardous Substances Act, 1973 (Act 15 of 1973) (the Hazardous Substances Act).
3. Invasive ventilation refers to the administration of ventilatory and respiratory support using an invasive artificial airway (endotracheal tube or tracheostomy tube).
4. Non-invasive ventilation refers to the administration of ventilatory support without using an invasive artificial airway.
5. A non-invasive ventilator can be used as an alternative to invasive mechanical ventilation to treat at least some patients with Covid-19 related acute respiratory distress syndrome (ARDS).
6. In April 2020, the World Health Organisation (WHO), published "Technical specifications for invasive and non-invasive ventilators for Covid-19.[1] This document serves as an interim guidance and provides technical specifications for the minimum requirements that invasive and non-invasive ventilators must comply with, to ensure quality, safety and performance when used during the current Covid-19 pandemic.

[1] https://apps.who.int/iris/bitstream/handle/10665/331792/WHO-2019-nCoV-Clinical-Ventilator_Specs-2020.1-eng.pdf?sequence=1&isAllowed=y

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7. In March 2020, the Medicines and Healthcare Products Regulatory Agency (MHRA) published specifications on "Rapidly Manufactured CPAP System (RMCPAPS)[2] and "Rapidly Manufactured Ventilator System (RMVS)".[3] These specifications include in Appendix B a "Testing protocol for final validation of safety and performance of RMCPAP/ RMVS" that provides the advisory testing protocol that invasive and non-invasive ventilators should undergo.
8. An invasive or non-invasive ventilator must comply with the latest version of the above referenced WHO specification (refer clause 6) and Appendix B of the MHRA specifications (refer clause 7), with adaptations in line with relevant South African legislation and standards, for purposes of emergency use during the Covid-19 pandemic in South Africa.

Current Medical Device Licence and Regulatory Process

Medicines Act

9. The Medicines Act and the Regulations relating to medical devices and in vitro diagnostic medical devices (IVDs), published in Government Gazette No. 40480, GN. 1515 of 9 December 2016, (the Regulations) provide for regulatory oversight of medical devices in South Africa.
10. Definitions of a medical device, IVD, and medical device or IVD establishment are provided in the Medicines Act, while definitions of a manufacturer, distributor and wholesaler are provided in the Regulations.
11. In terms of Section 22C(1)(b) of the Medicines and Related Substances Act, 1965 (Act 101 of 1965), the Authority may, on application in the prescribed manner and on payment of the prescribed fee, issue to a medical device or IVD establishment, manufacturer, wholesaler or distributor of a medicine, Scheduled substance, medical device or IVD a licence to manufacture, import, export, act as a wholesaler of or distribute, as the case may be, such medicine, Scheduled substance, medical device or IVD upon such conditions as to the application of such acceptable quality assurance principles and good manufacturing and distribution practices as the Authority may determine.

[2] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/876593/RMCPAPS001.pdf
[3] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/879382/RMVS001_v4.pdf

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12. In terms of Regulation 5(1)(d) a manufacturer, distributor or wholesaler referred to in section 22C(1)(b) of Act 101 of 1965 must specify, as determined by the Authority, the medical devices or IVDs or group or family of medical devices or IVDs to be manufactured, distributed or wholesaled.
13. In terms of Regulation 5(4) *Licence to manufacture, import, export, or act as a distributor or wholesaler of medical devices or IVDs*, the Authority may approve an application for a medical device establishment licence, with or without conditions, and issue a licence.
14. In terms of Regulation 28(3) *Transitional arrangements regarding unregistered medical devices and IVDs*, the Authority may require a medical device or IVD to comply with the requirements that the Authority may determine in order to ensure that the medical device or IVD meets the Essential Principles of Safety and Performance, as determined by Authority.
15. In terms of Section 21 of the Medicines and Related Substances Act, 1965 (Act 101 of 1965), the Authority may authorise the sale of unregistered medicines, medical devices or IVDs for certain purposes—
    (1) The Authority may in writing authorise any person to sell during a specified period to any specified person or institution a specified quantity of any particular medicine, medical device or IVD which is not registered.
    (2) Any medicine, medical device or IVD sold in pursuance of any authority granted under subsection (1) may be used for such purposes and in such manner and during such period as the Authority may in writing determine.
    (3) The Authority may at any time by notice in writing withdraw any authority granted in terms of subsection (1) if effect is not given to any determination made in terms of subsection (2).
16. An invasive ventilator is classified as a **Class C Medical Device** according to Classification Rule 9(i)(b) for medical devices – *"Active Medical Devices for Therapy".* [4]
17. Accessories to invasive ventilators such as tracheostomy tubes supplied separately are classified as **Class B Medical Devices** according to Classification Rule 5 for medical devices - *Invasive Devices Intended to be used to penetrate body orifices".* [5]

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[4] https://www.sahpra.org.za/wp-content/uploads/2020/01/Classification_Medical_Devices_IVDs_Nov19_v2.pdf
[5] https://www.sahpra.org.za/wp-content/uploads/2020/01/Classification_Medical_Devices_IVDs_Nov19_v2.pdf

18. A non-invasive ventilator, such as a Continuous positive airway pressure (CPAP) ventilator or a Bi-level positive airway pressure (BiPAP) ventilator, is classified as a **Class C Medical Device** according to Classification Rule 11 for medical devices – *"Active Medical Devices Intended to Administer or Remove Medicines, Body Liquids or Other Substances from a Patient's Body".* [6]
19. Accessories to the ventilators such as tubing and masks, supplied separately are classified as **Class B Medical Devices** according to Classification Rule 2 for medical devices - *Non Invasive Devices Intended to Channel or Store Body Liquids or Tissues, Liquids or Gases".* [7]
20. A ventilator may only be manufactured, imported, exported and/or distributed by a medical device establishment that holds a valid licence issued by the Authority, in terms of Section 22C (1)(b) of the Medicines Act.
21. The relevant application forms and guidelines for licensing of a medical device establishment can be accessed via the Authority's website. [8]

Hazardous Substances Act

22. The Hazardous Substances Act, the Regulations concerning the control of electronic products published in Government Gazette Notice 3991, R.1332 of 3 August 1973[9] and the Schedule of listed electronic products published in Notice 13299, R. 1302 of 14 June 1991[10] provide for the licensing of listed electronic products and the licensing of premises where the listed electronic product is used.
23. In terms of section II.2 of the Hazardous Substances Act, no person shall use a listed electronic product unless such product has been licensed.
24. The Schedule of listed electronic products (refer to clause 22) lists **'any electronically controlled ventilator'** under sub-section 8 "**Any high risk electronic product used for medical or dental applications",** as a Group III hazardous substance.

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[6] https://www.sahpra.org.za/wp-content/uploads/2020/01/Classification_Medical_Devices_IVDs_Nov19_v2.pdf
[7] https://www.sahpra.org.za/wp-content/uploads/2020/01/Classification_Medical_Devices_IVDs_Nov19_v2.pdf

[8] https://www.sahpra.org.za/medical-devices/
[9] https://www.sahpra.org.za/wp-content/uploads/2020/01/Regulation-R1332-of-1973..pdf
[10] https://www.sahpra.org.za/wp-content/uploads/2019/09/Schedule-of-Listed-Electronic-Products-Regulation-R1302-14-June-1991.pdf

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Minimum Regulatory and Licensing Requirements for a manufacturer or distributor of a rapidly developed ventilator for emergency use during the Covid-19 pandemic

25. A rapidly developed invasive or non-invasive ventilator classified as a Class C medical device in terms of the Medicines Act must comply with the latest version of the above referenced WHO specification (refer clause 6) and Appendix B of the MHRA specifications (refer clause 7), with adaptations in line with relevant South African legislation and standards, for purposes of emergency use during the Covid-19 pandemic in South Africa.
26. Medical device establishments that hold a valid licence issued in terms of Section 22C(1)(b) of the Medicines Act may not manufacture, import, export or distribute medical devices that have not been specified in terms of Regulation 5(1)(d) of the Regulations relating to Medical Devices and IVDs on their licence application.
27. Medical device establishments that hold a valid licence issued in terms of Section 22C(1)(b) and authorised to manufacture, import, export or distribute Class A, B, C and/or Class D medical devices must apply for an amendment to such licence and update the product listing to include any ventilator (classified as Class C medical devices) to be manufactured, imported, exported or distributed.
28. The notification process as defined in the communication to stakeholder "Amendment of Device Establishment Licence" [11] for the amendment of a medical device establishment licence issued in terms of Section 22C(1)(b) of the Medicines Act may not be used for Class C ventilators.
29. Medical device establishments that hold a valid licence issued in terms of Section 22C(1)(b) to manufacture, import, export or distribute medical devices or IVDs may not manufacture, import, export or distribute ventilators, specified in the application for the amendment of a licence, until authorisation has been received in terms of section 21 of the Medicines Act to do so.
30. The Authority regards it as a minimum requirement for sale of ventilators as medical devices on the South African market that the-

    a.

[11] https://www.sahpra.org.za/wp-content/uploads/2020/01/Communication-to-industry_licence_amendment_nov2019.pdf

b. medical device establishment responsible for the manufacture, import, export or distribution of any ventilator is licensed by the SAHPRA;
c. ventilator is specified in terms of regulation 5(1)(d) of the Regulations Related to Medical Devices made in terms of the Medicines Act; and
d. sale of the unregistered medical device is authorised in terms of Section 21 of the Medicines Act.

31. An application for a new licence for a medical device establishment, and an application for an amendment to an existing licence of a medical device establishment to manufacture, import and/or distribute an unregistered rapidly developed ventilator will be reviewed using a tier-based evaluation approach.
32. Applications will be classified into the tiers and processed accordingly based on the documentation submitted.
33. The documentation submitted must comply with the requirements provided in tier 1 or tier 2 or tier 3. This allows for the submission of alternative documentation/ evidence to support the application, in the event that Tier 1 documentation requirements are not met.
34. The documentation and supporting evidence required for each tier is presented in Annexure A.

Licence Application Process and Timelines

35. Any natural or juristic person may submit an application to the Authority for a licence issued in terms of Section 22C(1)(b) of the Medicines Act to manufacture, import, or export a ventilator/s.
36. The application forms are available on the SAHPRA website (www.sahpra.org.za):
    a. 6.21 Licence to Manufacture (Manufacture/Import/Export/Distribute)
    b. 6.22 Licence to Distribute (Import/Export/Distribute)[12]
37. 16.03 Guideline for a Licence to Manufacture, Import, Export or Distribute Medical Devices and IVDs provides guidance pertaining to the requirements for the licence application process.[13]

[12] http://www.sahpra.org.za/wp-content/uploads/2020/03/6.22_Licence_Application_Medical_Device_Import_Distribute_Jul16_v1.2.xls
[13] https://www.sahpra.org.za/wp-content/uploads/2020/01/Licence_Medical_Devices_IVDs_Nov19_v3.pdf

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38. Applications must be submitted electronically to the following email address: mdcovid@sahpra.org.za
39. The fee for a medical device establishment licence application (new/amendment) is payable upon application and proof of payment should be submitted together with the completed licence application. ***Note: Fees may be updated from time to time. The onus is on the applicant to ensure that payment is made in line with the current fees structure, as published in the Government Gazette.***
40. Payments should be made as per 17.02 "Guideline for the direct transmission of fees payable to SAHPRA" guideline.[14]
41. The licence application process will be expedited and will be completed within seven (7) working days provided that the application submitted is complete and meets the applicable requirements, and that timely responses to any queries raised by the Authority are received from applicant (as applicable).
42. An electronic letter of acknowledgment of receipt of the application will be emailed to the applicant.
43. A licence application with supporting documentation and evidence will first be reviewed. If the application is found to comply with the applicable requirements, a second review will be undertaken by an expert technical committee, against evaluation criteria determined by the Authority.
44. Identified deficiencies will be emailed to the applicant in the event that a licence application does not meet the evaluation criteria. The applicant is required to respond in writing (by email) to the deficiencies noted in the correspondence letter within two (2) working days of receipt of said correspondence.
45. The response will be reviewed by the Authority. If the evaluation criteria are met, the application will be recommended. If the evaluation criteria are not met in the response, a second deficiency letter will be emailed to the applicant.

[14] https://www.sahpra.org.za/wp content/uploads/2020/01/992cfdc6SAHPRA_Fees_24.05.2019ExtractfromGovernmentGazette42474-5.pdf

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46. The second response will be reviewed. If the evaluation criteria are met, the application will be recommended. If the predetermined specifications and evaluation criteria are not met the application will not be recommended.
47. If the application is approved the medical device establishment licence for import, export or manufacture and distribution will be prepared. A notification of licence approval will be emailed to the applicant. The licence will be emailed to the applicant upon submission of proof of payment for collection of the licence.

Local manufacturers of invasive or non-invasive ventilators

48. Local manufacturers of invasive or non-invasive ventilators must ensure that validation and formative usability tests are conducted at both prototype and final production stages, as per ISO62366 in a realistic environment, prior to submission of the licence application or to amendment of a licence application to the Authority.
49. The relevant MHRA testing protocol for final validation of safety and performance of RMCPAP/ RMVS (refer to clause 7), must be followed for invasive and non-invasive ventilators

Conditions of Licence and Authorisation for use of unregistered ventilators

50. The instructions for use (IFU) for the ventilator must include:
    a. the device's specifications (including the ventilatory parameters),
    b. information regarding alarms,
    c. requirements for the service, maintenance and repair of the ventilator;
    d. conditions for decommissioning and disposal of the equipment; and
    e. reprocessing of reusable accessories and shelf-life information of the device.
51. The IFU and the labelling of the device must state that: "This ventilator is not registered by the Authority and is only authorised for emergency use during the Covid-19 pandemic"
52. The ventilator must be affixed with a permanent label with the words 'Restricted non-invasive or invasive ventilator for emergency use during the Covid-19 pandemic, only to be used for emergency ventilation"

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53. The holders of a medical device establishment licence must report any adverse event or product quality incidents to the Authority, as specified in regulation 17 of the Regulations relating to medical devices and IVDs.
54. The additional licence specific conditions, made in terms of Regulation 5(4), will be listed in Section 11 of the Medical Device Licence to Manufacture and Section 8 of Medical Device Licence to Distribute.
55. Authorisation for the sale of an unregistered medical device, in terms of Section 21 of the Medicines and Related Substances Act, 1965 (Act 101 of 1965), for rapidly developed ventilators will be issued by SAHPRA provided that they meet the above referenced WHO specification (refer clause 6) and Appendix B of the MHRA specifications (refer clause 7), with adaptations in line with relevant South African legislation and standards.
56. Where a new medical device establishment licence is required, the medical device licence is valid for up to twelve (12) months and may be withdrawn or extended by the SAHPRA at any time.
57. Where an amendment to a current medical device establishment licence is required, the medical device licence relating to the import, export, manufacture and distribution of a ventilator is valid for up to twelve (12) months and the authorisation to import, export or manufacture and distribute such ventilator may be withdrawn or extended by the SAHPRA at any time.

DR B SEMETE-MAKOKOTLELA

CHIEF EXECUTIVE OFFICER OF SAHPRA

DATE: 26 MAY 2020

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ANNEXURE A

LICENSING APPLICATION REQUIREMENTS: DOCUMENTS AND SUPPORTING EVIDENCE			
GENERAL DOCUMENTATION	**DOCUMENTATION TIER 1**	**DOCUMENTATION TIER 2**	**DOCUMENTATION TIER 3**
i. Cover letter on company letter indicating intention to apply for a new licence or amendment to licence issued in terms of Section 22C(1)(b) of the Medicines Act ii. Licence Application (6.21 Manufacturer / 6.22 Distributor / 6.26 Wholesaler) a. Completed licence application form in MS Excel format; b. Completed licence application form in PDF format, including signed declaration and initialed on each page by the Authorised Representative). iii. Proof of Payment	i. Pre-market approval or registration of the ventilator by the relevant regulatory authority for medical devices in at least one of the six jurisdictions recognised by the Authority i.e. Australia, Brazil, Canada, Europe, Japan and the United States of America. ii. A Certificate of Free Sale or USA Certificate of Foreign Government to confirm that the ventilator is legally sold or distributed in the open market, freely without restriction, or is listed for emergency use in at least one of the six jurisdictions referred to above recognised by the Authority.	i. Pre-market approval or registration of the ventilator by the relevant regulatory authority for medical devices in at least one of the following countries: China, Russia, Singapore or South Korea. ii. Certificate of Free Sale to confirm that the ventilator is legally sold or distributed in the open market, freely without restriction or listing for emergency use in at least one of the following countries: China, Russia, Singapore or South Korea. iii. A technical file (dossier) must be submitted to the Authority in the format aligned with the	i. A technical file (dossier) must be submitted to the Authority in the format aligned with the table of contents described in **Guideline 8.09 "Registration of a Medical Device – non-IVD Technical Dossier".** ii. Certification of the original manufacturer's Quality Management System (QMS) to either: ISO 13485 Medical devices — Quality management systems — Requirements for regulatory purposes; **or** ISO 9001 Quality Management Systems – Requirements **and** compliance to ISO 14971 Application of Risk Management to Medical Devices.

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LICENSING APPLICATION REQUIREMENTS: DOCUMENTS AND SUPPORTING EVIDENCE			
GENERAL DOCUMENTATION	**DOCUMENTATION TIER 1**	**DOCUMENTATION TIER 2**	**DOCUMENTATION TIER 3**
iv. Completed application for registration of a medical device ZA CH1.04 v. Curriculum Vitae of the Authorised Representative vi. Quality Manual (Applicable to Manufacturers/Distributors) or Site Master File (Applicable to Wholesalers) vii. Certification of the original manufacturer's Quality Management System (QMS) to ISO13485 Medical devices – Quality management systems – Requirements for regulatory purposes viii. Technical file (dossier) in the format aligned with the table of contents described in **Guideline 8.09 "Registration of a Medical Device – non-IVD Technical Dossier"** including: a. Evidence to support compliance to the *Essential*		table of contents described in **Guideline 8.09 "Registration of a Medical Device – non-IVD Technical Dossier".**	

LICENSING APPLICATION REQUIREMENTS: DOCUMENTS AND SUPPORTING EVIDENCE			
GENERAL DOCUMENTATION	**DOCUMENTATION TIER 1**	**DOCUMENTATION TIER 2**	**DOCUMENTATION TIER 3**
Principles of Safety and Performance specifically relating to the ventilator b. Evidence of conformity assessment c. validation and formative usability tests at both prototype and final production stages, as per ISO62366 in a realistic environment. ix. A copy of the Instructions for Use (IFU) of the medical device as provided in Regulation 23 of the Regulations relating to Medical devices and IVDs and where the following must be noted; - a. the device's specifications (including the ventilatory parameters), b. information regarding alarms, c. requirements for the service, maintenance and repair of the ventilator; and			

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d. conditions for decommissioning and disposal of the equipment must be identified. e. Reprocessing of reusable accessories and shelf-life information of the device; x. A copy of the labelling and packaging; where the packaging and labelling must clearly indicate; a. the ventilator has been listed by the SAHPRA for the purposes of emergency use during the Covid-19 pandemic; and b. contact details (name, physical address, telephone and email) of the South African licence holder.			