May 26, 2020

CLEW Medical Ltd.
c/o Ms. Yarmela Pavlovic
Manatt, Phelps & Phillips, LLP
1 Embarcadero Center, 30th Floor
San Francisco, CA 94111

Dear Ms. Pavlovic:

This letter is in response to your request on behalf of CLEW Medical Ltd. that the U.S. Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of the CLEWICU System[1] to be used by healthcare providers (HCP) in the Intensive Care Unit (ICU) for adult patients for the computation of proprietary patient status indices referred to as CLEWRF[2] and CLEWHI[3] as an adjunct to patient monitoring during the Coronavirus Disease 2019 (COVID-19) outbreak. The CLEWRF and the CLEWHI indices provide HCP with predictive screening information to assist with the early identification of patients who are likely to be diagnosed with respiratory failure or hemodynamic instability which are common complications associated with COVID-19.[4]

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[1] This EUA includes the emergency use of the CLEWICU System, which includes the ClewICUServer and ClewICUnitor. The CLEWICU System is standalone software as a medical device. In general, the CLEWICU System uses commonly recorded vital signs, nursing assessments, flowsheet data, medications and lab data to compute patient status indexes that have been defined by the device developer as CLEWRF and CLEWHI. The ClewICUServer is a software platform that imports patient data from various sources including Electronic Health Record (EHR) data and medical device data. The data are then used by analytical models operating within the ClewICUServer to compute and store the CLEWRF index and the CLEWHI index. The ClewICUnitor is the web-based user interface that displays CLEWRF and CLEWHI, associated notifications, and presents the overall unit status. The CLEWICU System is comprised entirely of software which is distributed via electronic media for implementation within a healthcare facility's own dedicated on-premises or cloud application and database servers. The CLEWICU System is not FDA-cleared or approved for marketing in the United States. CLEWICU has been approved by Israeli Ministry of Health, for use at 3 medical centers in Israel for the duration of the COVID-19 crisis or through the end of 2020.

[2] CLEWRF is a measure of a patient's predicted physiologic condition within the next 8 hours based on the aggregate statistical risk of respiratory deterioration or failure. For purposes of this authorization, the condition of respiratory deterioration or failure refers to the patient needing intubation.

[3] CLEWHI is a measure of a patient's predicted physiologic condition within the next 8 hours based on the aggregate statistical risk of hemodynamic instability. For purposes of this authorization, the condition of hemodynamic instability refers to the patient needing vasopressor/inotrope therapy.

[4] Under the circumstances of this public health emergency, it would not be feasible to require healthcare providers to limit the use of the product only to adult patients with suspected or confirmed COVID-19; therefore, this authorization does not restrict use to such adult patients.

On February 4, 2020, pursuant to section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the Act), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19.[5] Pursuant to section 564 of the Act, and on the basis of such determination, the Secretary of HHS then declared on March 24, 2020, that circumstances exist justifying the authorization of emergency use of medical devices pursuant to section 564 of the FD&C Act, subject to the terms of any authorization issued under that section.[6]

There are no FDA approved or cleared devices to provide predictive screening information to assist with the early identification of adult patients who are likely to be diagnosed with respiratory failure or hemodynamic instability which are common complications associated with COVID-19.

During ICU hospitalization, continuous monitoring results in the accumulation of vast amounts of multidimensional data. Without predictive analytics, floor management and discharge decisions are determined based on patients' current state of health. During the COVID-19 outbreak, ICUs are at capacity and patients are requiring care for an extended period of time. By identifying high risk patients, prioritizing treatment based on patient acuity, and reducing the false alarm rate this likely provides better care for patients and reduces the strain on the ICU personnel. The CLEWICU system utilizes the full range of available patient data to provide continuous predictions based on data driven algorithms and machine learning models. The CLEWICU system delivers workflow improvements and dynamic worklist prioritization, enabling healthcare providers to spend less time on administration and more time on patient treatment. In this way, CLEWICU may reduce the contact between ICU personnel and patients by providing the ICU clinician the ability to view the patient risk status from a remote location. Based on retrospective clinical validation and human factors validation, FDA has concluded that the CLEWICU System may be effective for use by HCP in the ICU as a diagnostic aid to assist with the early identification of adult patients who are likely to be diagnosed with respiratory failure or hemodynamic instability which are common complications associated with COVID-19.

Having concluded that the criteria for issuance of this authorization under section 564(c) of the Act are met, I am authorizing the emergency use of the CLEWICU System, as described in the Scope of Authorization of this letter (Section II) and pursuant to the Conditions of Authorization (Section IV) of this letter.

I. Criteria for Issuance of Authorization

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[5] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*. 85 FR 7316 (February 7, 2020).

[6] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 17335 (March 27, 2020).

I have concluded that the emergency use of the CLEWICU System, as described in the Scope of Authorization (Section II) of this letter, for treating COVID-19, when used by HCP in the ICU as a diagnostic aid to assist with the early identification of adult patients who are likely to be diagnosed with respiratory failure or hemodynamic instability which are common complications associated with COVID-19, meets the criteria for issuance of an authorization under section 564(c) of the Act, because I have concluded that:

1. SARS-CoV-2, the virus that causes COVID-19, can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that the CLEWICU System may be effective in treating COVID-19, when used by HCP in the ICU as a diagnostic aid to assist with the early identification of adult patients who are likely to be diagnosed with respiratory failure or hemodynamic instability which are common complications associated with COVID-19, and that the known and potential benefits of the CLEWICU System, for such use, outweigh the known and potential risks; and,

3. There is no adequate, approved, and available alternative to the emergency use of the CLEWICU System in treating COVID-19, when used by HCP in the ICU as a diagnostic aid to assist with the early identification of adult patients who are likely to be diagnosed with respiratory failure or hemodynamic instability which are common complications associated with COVID-19.[7]

II. Scope of Authorization

I have concluded, pursuant to section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the CLEWICU System by HCPs in the ICU in treating COVID-19, when used by HCP in the ICU as a diagnostic aid to assist with the early identification of adult patients who are likely to be diagnosed with respiratory failure or hemodynamic instability which are common complications associated with COVID-19. The CLEWICU System is not intended to replace patient monitoring. The software is intended to be used as a decision support tool and is to be used together with the patient's clinical history, continuous monitoring data, diagnostic test results, and clinical judgment. The CLEWICU System is not able to predict sudden deteriorations (such as those caused by a clot blocking blood flow in the lungs), because the tool analyzes trends in data that occur over time.

The Authorized CLEWICU System

[7] No other criteria of issuance have been prescribed by regulation under section 564(c)(4) of the Act.

The CLEWICU System is a stand-alone analytical software product. It uses models derived from machine learning to calculate the likelihood of occurrence of certain clinically significant events (respiratory failure for CLEWRF and hemodynamic instability for CLEWHI) for adult patients in the intensive care unit (ICU). Notifications regarding individual patients are displayed on the user-interface based on these models. The software product includes the ClewICUServer and the ClewICUnitor, which are both software-only devices that are installed on user-provided hardware. CLEWICU System integrates with existing electronic health record (EHR) systems and medical devices and is designed to be deployed on hospital servers.

The CLEWICU System is comprised of the following components:

- ClewICUServer
- ClewICUnitor

Each of these components of the CLEWICU are described further below.

The CLEWICU System requires the following components, which are not provided with the stand-alone software but must be used in conjunction with the CLEWICU System:

- User-provided hardware for installation of the software according to the CLEWICU Instructions for Use (e.g., servers)

The CLEWICU System also requires the use of EHR data and medical device data commonly used in hospital facilities.

ClewICUServer

The ClewICUServer is a backend software platform that imports patient data from various sources including EHR data and medical devices data. The data is then used by models calculated within the CLEWICUServer to compute and store the CLEWRF index and CLEWHI index.

ClewICUnitor

The ClewICUnitor is the frontend web-based user interface for displaying CLEWRF- and CLEWHI-associated notifications and related measures, as well as a presentation of the overall unit status. The displays include a worklist view and unit view.

The CLEWRF Index and CLEWHI Index use commonly recorded vital signs, nursing assessments, flowsheet data, medications and lab data to compute patient status indices. The CLEWRF Index is a measure of a patient’s physiologic condition based on the aggregate statistical risk of respiratory deterioration/failure. The CLEWHI Index is a measure of a patient’s physiologic condition based on the aggregate statistical risk of hemodynamic instability.

ClewICUServer and ClewICUnitor are intended for the care of adult patients in the ICU where there is interest in generating CLEWRF, CLEWHI, and/or associated configurable notifications as an adjunct to patient monitoring. They are not intended to replace patient monitoring.

The CLEWICU System calculates CLEWRF Index and CLEWHI Index by employing two statistical models developed using machine learning methods that identify key variables and interrelations among them, which define the patient's clinical risk level. The algorithms were trained using supervised learning. Based on these models, clinical events (respiratory failure and/or hemodynamic instability) are predicted.

The above described CLEWICU System, is authorized to be accompanied with labeling, entitled "CLEWICU – Instructions for Use," "Inbound Data Integration Specification" guide, and "System Specification and Infrastructure Guide" (available at https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations), together with the following product-specific information pertaining to emergency use, which is required to be made available to HCP and patients, respectively:

- Fact Sheet for Healthcare Providers: Emergency Use of the CLEWICU System During the COVID-19 Pandemic
- Fact Sheet for Patients: Emergency Use of the CLEWICU System During the COVID-19 Pandemic

The above described product, when accompanied with the Instructions For Use (identified above) and the two Fact Sheets (referred to as "authorized labeling") is authorized to be distributed under this EUA, despite the fact that it does not meet certain requirements otherwise required by federal law.

I have concluded, pursuant to section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of the CLEWICU System when used as described within, and consistent with the Scope of Authorization of this letter (Section II), outweigh the known and potential risks of this product.

I have concluded, pursuant to section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that the authorized CLEWICU System may be effective when used as described within and consistent with the Scope of Authorization of this letter (Section II), pursuant to section 564(c)(2)(A) of the Act.

FDA has reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, and concludes that the authorized CLEWICU System, as described within, and used consistent with the Scope of Authorization of this letter (Section II), meets the criteria set forth in section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of the CLEWICU System must be consistent with, and may not exceed, the terms of this letter, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section IV). Subject to the terms and conditions of this EUA and under the

circumstances set forth in the Secretary of HHS's determination under section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under section 564(b)(1), the CLEWICU System described above is authorized to be used in treating COVID-19, when used by HCP in the ICU as a diagnostic aid to assist with the early identification of adult patients who are likely to be diagnosed with respiratory failure or hemodynamic instability which are common complications associated with COVID-19.

III. Waiver of Certain FDA Requirements

I am waiving the applicable good manufacturing practice requirements otherwise applicable to the manufacture, processing, packing, or holding of products subject to regulations under the Act, including the quality system requirements under 21 CFR Part 820, for CLEWICU System during the duration of this EUA.[8]

IV. Conditions of Authorization

Pursuant to section 564(e) of the Act, I am establishing the following conditions on this authorization:

CLEW Medical Ltd., as Sponsor of Authorized Product

A. CLEW Medical Ltd. must comply with the labeling requirements under 21 CFR 801 Subpart A (general labeling provisions) and 21 CFR 801.109 (labeling for prescription devices), as well as those described in Section II of this letter, Scope of Authorization. As such, compliance with unique device identification regulations (see Subpart B of 21 CFR Part 801) is not required under this EUA.

B. CLEW Medical Ltd. will make the CLEWICU System available with authorized labeling. CLEW Medical Ltd. may request changes to the authorized labeling. Such changes require review and concurrence from Office of Health Technology 2 (OHT2)/Office of Product Evaluation and Quality (OPEQ)/Center for Devices and Radiological Health (CDRH).

C. CLEW Medical Ltd. may request changes to the Scope of Authorization (Section II in this letter) of the authorized CLEWICU System. Such requests will be made by CLEW Medical Ltd., in consultation with OHT2/OPEQ/CDRH, and require concurrence of the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS)/Office of the Commissioner (OC) and OHT2/OPEQ/CDRH.

D. CLEW Medical Ltd. may request changes to the device. Such requests will be made in consultation with and require concurrence of OHT2/OPEQ/CDRH.

E. CLEW Medical Ltd. will have process in place for reporting, and will report to FDA, adverse events of which they become aware to FDA under 21 CFR Part 803. CLEW

[8] The requirements under 21 CFR Part 806 (Reports of Corrections and Removals) and 21 CFR Part 807 (Registration and Listing) are not required under this EUA.

Medical Ltd. will establish a process to collect adverse event information from healthcare facility customers.

F. CLEW Medical Ltd. will notify FDA of any authorized distributor(s)[9] of the CLEWICU System, including the name, address, and phone number of any authorized distributor(s), and provide authorized distributor(s) with a copy of this EUA and any updates.

CLEW Medical Ltd., and any Authorized Distributor(s)

G. CLEW Medical Ltd., and authorized distributors will distribute the authorized CLEWICU System with the authorized labeling only to healthcare facilities with HCP who are adequately equipped, trained, and capable of using the CLEWICU System according to the criteria set forth by CLEW Medical Ltd.

H. CLEW Medical Ltd., and authorized distributors will make authorized labeling available on their websites.

I. Authorized distributors will make CLEW Medical Ltd. aware of any adverse events of which they become aware.

J. Through a process of software license control, CLEW Medical Ltd. and authorized distributors will maintain records of the healthcare facilities to which they distribute the CLEWICU System and the number of each product they distribute.

K. CLEW Medical Ltd. and authorized distributor(s) are authorized to make available additional information relating to the emergency use of the product that is consistent with, and does not exceed, the terms of this letter of authorization.

L. CLEW Medical Ltd. and authorized distributor(s) will ensure that any records associated with this EUA are maintained until otherwise notified by FDA. Such records will be made available to FDA for inspection upon request.

Healthcare Facilities

M. Healthcare facilities using the authorized CLEWICU System must make available to patients the accompanying Patient Fact Sheet and make available to HCP the accompanying Healthcare Provider Fact Sheet. Healthcare facilities using the authorized CLEWICU System must also make available the CLEWICU – Instructions for Use to HCP.

N. Healthcare facilities using the CLEWICU System must make CLEW Medical Ltd., and

[9] "Authorized Distributor(s)" are identified by CLEW Medical Ltd. in an EUA submission as an entity allowed to distribute the device.

FDA aware of any adverse events under 21 CFR Part 803.

O. Healthcare facilities will ensure HCP using the CLEWICU System are adequately equipped, trained, capable, and will maintain records of device usage. All HCP using the device must also be trained in and be familiar with the interpretation of results of the CLEWICU System.

Conditions Related to Printed Matter, Advertising and Promotion

P. All descriptive printed matter, including advertising and promotional materials, relating to the use of the authorized CLEWICU System shall be consistent with the authorized labeling, as well as the terms set forth in this EUA and the applicable requirements set forth in the Act and FDA regulations.

Q. No descriptive printed matter, including advertising or promotional materials, relating to the use of the authorized CLEWICU System may represent or suggest that this product is safe or effective.

R. All descriptive printed matter, including advertising and promotional materials, relating to the use of the authorized CLEWICU System shall clearly and conspicuously state that:

- The CLEWICU System has neither been cleared or approved;
- The CLEWICU System has been authorized for the above emergency use by FDA under an EUA; and,
- The CLEWICU System has been authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of medical devices under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

V. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the CLEWICU System is terminated under section 564(b)(2) of the Act or the EUA is revoked under section 564(g) of the Act.

Sincerely,

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RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures