DEVELOPMENT OF AN ORGANISATIONAL MODEL FOR THE PREPARATION OF THE MRNA-BNT162B2 VACCINE: THE EXPERIENCE OF THE CLINICAL GALENICS LABORATORY OF THE HOSPITAL PHARMACY OF THE MAURIZIANO HOSPITAL, TURIN

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ABSTRACT

The centralised preparation of the mRNA-bnt162B2 vaccine *at the Clinical Galenics Laboratory* of the Hospital *Pharmacy* of the Mauriziano Hospital in *Turin is an organisational* model *designed to guarantee the quality of the drug to be administered, the safety of both the vaccinee and the vaccinating personnel, and the traceability of all operations performed. The preparation* in ready-for-use *syringes individually packaged and labelled, according to the Good Manufacturing Practice (GMP) of the Official Pharmacopoeia, was entrusted to the Biomedical Laboratory Technician (BLT) under the responsibility of the Hospital Pharmacist. In compliance with the GMP, the model was developed through dedicated premises, specific staff training and written procedures concerning the handling of vaccines. The entire production process was guaranteed by: a Hospital Pharmacist and two interchangeable BLTs, one preparer and one assistant. They were necessary to maintain the aseptic technique and the cross-checking of all operations. Labels were prepared showing qualitative-quantitative composition, batch and expiry date, validity of the preparation, pharmacist's signature. The label applied to each syringe, together with the daily work plan, ensured traceability of the process at every stage. The efficient* model *proposed has always proved adaptable to the changes that characterised the vaccination campaign. From 27/12/2020 to 31/03/2022 a total of 48.017 doses were prepared. The centralisation of the vaccine preparation* in the *Clinical Galenics Laboratory* of the Hospital *Pharmacy also reduced handling errors, as well as the waste from unused residues, which proved to be only 0.08%.*

INTRODUCTION

The devastating effects of the SarS-CoV-2 pandemic have led to a pressing demand for the identification of an effective protective vaccination for the largest number of people within a short timeframe.
The promise of the anti-SarS-CoV-2 vaccine became reality on 21st December 2020 with the authorisation of Pfize -BioNtech's Comirnaty vaccine by the European Medicines Agency (EMA) and on 22nd December 2020 by the Italian Medicines Agency (AIFA).
The vaccines, even those authorised subsequently, were made available free of charge to the entire population according to an order of priority that took into account the risk of disease, the types of vaccine and their availability. The vaccination campaign started on 27th December 2020 in Italy and Europe with Vaccine-Day. The aim was to get as much involvement as possible from the health facilities.
The Mauriziano Hospital has thus started its vaccination campaign: the Clinical Galenics Laboratory of the Hospital Pharmacy has proposed itself as an active part in tackling it, both as regards the vaccine storage phase and all the preparation phases. We started in the first instance with the vaccination of all the hospital's health workers followed by the highly fragile patients, for whom due to their immunodeficiency status, the preferential use of messenger RNA vaccines had been confirmed
Comirnaty (Tozinameran) is a messenger RNA (mRNA) vaccine encoding for the viral spike (S) protein of SarS-CoV-2.
According to the Summary of Product Characteristics

Fig. 1

(SPC), the concentrate for injectable dispersion must be prepared using aseptic techniques to ensure the sterility of the preparation. To this end, the Hospital Pharmacy has developed an organisational model to guarantee the quality of the drug to be administered. This ensures the safety of both the vaccinee and the vaccinating personnel, as well as the traceability of the entire process. The model envisages the use of the aseptic technique for the preparation of pre-filled syringes ready for use, individually packed inside sterile bags, sealed with an automatic heat-sealing machine and finally labelled

The vaccine preparation phase is part of a broader and more articulated process: it ranges from receiving the drug in frozen vials (-60/-90 °C) to preparing it in ready-made syringes and finally to administration. In order to run smoothly the whole process, a careful scheduling of daily bookings agreed upon by a multidisciplinary team consisting of the medical management, doctors, pharmacists and administrative staff is therefore necessary. This scheduling takes into account not only the physical stock but also the stock required to complete the vaccination cycle (second dose) and the time required to thaw individual *vials*.

Fig. 2

METHODOLOGY AND MATERIALS

According to the provisions of the Italian Official Pharmacopoeia XII Edition, the preparation of sterile prefilled syringes is an operation that can be assimilated to the processing of magistral galenic preparations. Therefore it must be carried out under the responsibility of the hospital pharmacist, in compliance with the Good Manufacturing Practice (GMP). The preparation, according to GMP, has the objective of:

- ensuring that the sterility of the preparation is maintained;
- allowing safe preparation for the operator;
- ensuring that the dosage required for administration is correct;
- guaranteeing the traceability of all operations.

In compliance with the GMP and in order to guarantee organisational appropriateness, dedicated rooms, appropriate equipment and qualified personnel, as well as suitable disinfection procedures are also required.

It is for this purpose that the Hospital Pharmacy has set up a special room equipped with:

- vertical flow hood with HE A filters
- freezer for storage at -80 °C, equipped with a temperature (T) monitoring system;
- refrigerator for thawing the drug at a controlled T (2-8 °C), equipped with a T-monitoring system;
- automatic thermosealing machine for syringe packaging.

Vaccine preparation was entrusted to the professional figure of the Biomedical Laboratory Technician (BLT), under the direct and indispensable responsibility of the Hospital Pharmacist.

Taking Art. 16 of its Code of Ethics as a reference, the BLT with specialist skills participates in the production process of clinical galenics guaranteeing quality and safety.

The proposed organisational model envisages the presence of two BLTs: one preparer and one assistant, interchangeable. They were necessary for the maintenance and observance of the aseptic technique as well as for the cross-checking of all operations to be performed.

The BLTs engaged in the preparation of vaccines were subjected to:

1. initial training by the multidisciplinary team of the Clinical Galenic Laboratory regarding the *modus operandi* of the aseptic technique, such as dressing, preparation of the hood, operating modes as preparatory technician and assistant technician;
2. specific training on the preparation of mRNA vaccines according to the specifications in the SPCs
3. ongoing training and refresher courses: acquisition of knowledge and transversal skills regarding vaccine storage, preservation of pre-filled syringes and inoculation.

The quality, safety and effectiveness of a process does not depend only by the individual, but by the careful organisation and constant control of all its stages, as described below.

Preparation Labelling

Each sterile bag containing the single dose of vaccine was labelled with the following specifications

- Pharmacy and Hospital references, where the preparation was carried out;
- first name, surname and date of birth of the vaccinee;

- quali-quantitative composition of the preparation;
- batch number and expiry date;
- date and time of preparation and validity of the preparation;
- mode of administration;
- instructions for proper storage;
- signature of the responsible Hospital Pharmacist.

From December 2020 to December 2021 it was possible to vaccinate with a good schedule thanks to the close cooperation between the Clinical Galenics Laboratory and the Administrative Department to whom the bookings were entrusted.
Knowing in advance the numbers of daily bookings and their personal details, the Hospital Pharmacy was able to produce customised labels with the specific -tions of each vaccination.
As of the end of December 2021, the Mauriziano Hospital of Turin, at the behest of the Piedmont Region has become a vaccination HUB thus breaking down the numerical limits of daily vaccinations with which the Hospital used to work. With this new mode, it was no longer possible to work with a daily schedule: both for the mass of users booked, both for the opening of the HUB without reservation (through free access). Consequently, the Hospital Pharmacy readjusted the label structure, removing the individual's personal details. This was however possible considering that the vaccine is not prepared and administered in customised doses. The specifications of the preparation, indispensable for its recognition, remained unchanged.

Process Tracking

On each vaccination day, a work plan was drawn up as a record of the preparations carried out by the Clinical Galenics Laboratory. The work plan is a necessary tool for tracking daily activity, especially the dilution time of each vial, the total number of vials prepared, the batch and the expiry date of the vaccine and NaCl 0.9% solution used. Also the responsible Pharmacist, the preparing Technician and the assistant Technician. During registration on the Regional Information System for Vaccination Management (SIRVa), the presence on the label of the batch of the vaccine used, with its expiry date, allows the Administrative Staff the batch-vaccine association. The aim is to guarantee traceability from a vaccine-vigilance point of view as well as safety.

Validity Of The Preparation

The stability characteristics of this preparation are such that fractionated doses must be administered in a timely manner. The administration should be carried out within a very short period of time and in accordance with the Summary of Product Characteristics, i.e. within 6 hours of dilution of Comirnaty. Fractionated doses of the drug should be stored at 2-30 °C.
With this in mind, the production of ready-for-use syringes by the Clinical Galenics Laboratory takes place in close cooperation with the staff in charge of accepting the users to be vaccinated. With this method, a quantity of vials is diluted to reflect the physical number of people present at the vaccination site.

Quality Controls

To ensure compliance with the Good Manufacturing Practice (Pharmacopoeia XII Edition), in addition to the double check performed by the two Technician,

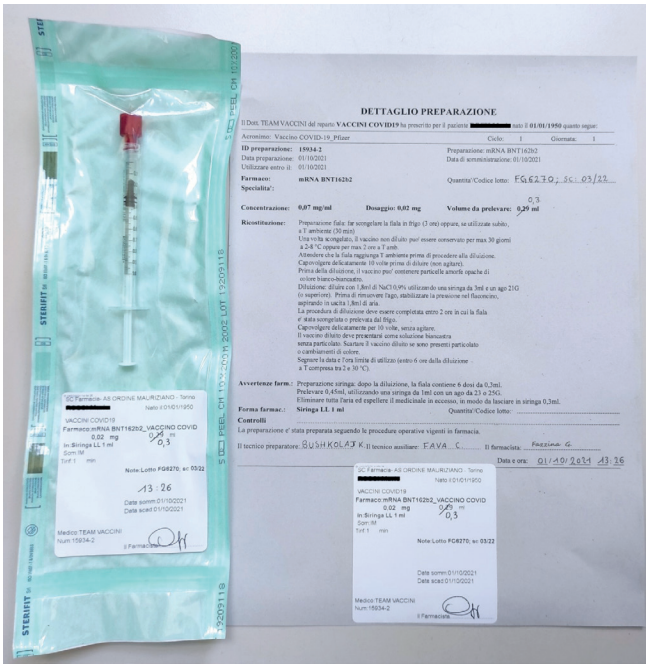

Fig. 3

the pharmacist carries out a series of final checks to ensure the validity of the finished product

- visual check of the volume taken, appearance and absence of visible particles;
- checking the integrity and tightness of the primary and secondary packaging;
- control of residues of unused drugs to check the appropriateness of the volumes taken;
- checking that the data on the label are correct.

The signature affixed by the pharmacist authorises the dispensing and administration of the final preparation guaranteeing quality, safety and efficac .

Transport Of Ready-To-Use Vaccine Syringes

The proper transport of the ready-to-use syringes from the Clinical Galenics Laboratory to the premises intended for the administration of the Covid19 vaccine is intended to ensure the safety of the operators involved and the preservation of the quality characteristics of the doses sent.
On request of the Piedmont Region, from 14th May 2021, the Mauriziano Hospital of Turin took part, together with other Turin's Hospitals, in the vaccination of the 'Lorusso e Cutugno' prison and from 1st July 2021 also of the 'Ferrante Aporti' Juvenile Penal Institute.
Consequently, the transport of fractionated doses has been structured in such a way that both internal and external transport of the Hospital is guaranteed. In the case of internal transport, the finished products are placed in a rigid container suitable for the transport of drugs. Instead, in the case of external transport the rigid container is in turn placed in a refrigerator inside the vehicle to ensure the maintenance of a controlled temperature (2-8 °C).
The transport must be accompanied by appropriate documentation showing the date, time and content.

Archiving Documentation

The work plan, relating to the activities described and the results of the checks carried out, must be appro-

priately filed to ensure control and traceability. This is also important in a period after the date of preparation and administration, such as when an adverse drug reaction (ADR) is reported in the context of vaccine-vigilance.

RESULTS AND DISCUSSION

The application of this organisational model allowed us to prepare all the doses required to meet the needs of users in real time. The daily schedules and objectives imposed by the Piedmont Region were respected. From 27th December 2020, the so-called Vaccine-Day, to 31st March 2022, the day on which the vaccination campaign closed for the Mauriziano Hospital of Turin, a total of 48.017 doses were prepared, including first, second, third and fourth doses

The organisational model proved to be successful, as it was flexible and adaptable to the changes that characterised the vaccination campaign. Moreover, having entrusted each professional figure with a very precise phase of the process, the involvement of each actor was widely appreciated and valued in a highly collaborative context.

The centralisation of mRNA vaccine preparations in the Clinical Galenics Laboratory of the Hospital Pharmacy also reduced handling errors, as well as waste from unused residues, which proved to be only 0.08%.

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