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# Accelerated national lot release on COVID-19 vaccines in Republic of Korea

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## ABSTRACT

Independent quality testing of samples from vaccine lots is part of quality assurance, especially to ensure the consistency of production lot by lot. Effective national lot release system that ensures the quality of each lot of vaccine before it is on the market is important because vaccines are intended to healthy people. In order to respond more quickly to public health crises such as the COVID-19 pandemic, the MFDS implements accelerated national lot release for rapid vaccination in Republic of Korea.

For the accelerated system, improvement has been made in terms of timing of application for lot release and required documents. In addition, the processing period has been shortened and sampling method and test items have been streamlined. A thorough preparation for accelerated lot release has been developed by establishing test methods for a new platform in advance. As a result, a total of 43.88 million doses have been released within eight days on average. The accelerated lot release system has contributed significantly to rapid COVID-19 vaccination in Korea.

## 1. Introduction

In March 2020 with the rapid increase in the number of confirmed cases and deaths after the declaration of COVID-19 pandemic by the WHO [1], it has become necessary to have a technology to produce effective vaccines rapidly [2]. Accordingly, virus-vectored vaccine and mRNA vaccine with a completely new platform that enables rapid manufacturing and mass production within a short period of time and contains genetic materials have been developed and manufactured to replace conventional vaccine platforms such as inactivated vaccines and live attenuated vaccines. According to WHO data, 112 COVID-19 vaccine candidates are in clinical trial stage as of Aug. 2021 and more than 45% of them are virus-vectored, RNA and DNA vaccines [3]. In addition, as it is a vaccine of a new platform that has not been used in the past, it is necessary to confirm the safety and effectiveness of the vaccine through national quality control.

As the number of deaths reached 1.9 million and confirmed cases was over 84 million worldwide in Dec. 2020 [4], many countries believed that vaccinating to substantial number of people quickly was a top priority to end the pandemic situation. Korea also established a strategy to vaccinate people rapidly with a safe and effective vaccine to help people return to normal. The MFDS (Ministry of Food and Drug Safety)

made a thorough preparation to establish new test methods starting before marketing authorization and has implemented the accelerated lot release on the new platform COVID-19 vaccines starting from February 17, 2021.

This paper explains how MFDS could implement the accelerated national lot release system effectively and rapidly including reducing the time to release national lot, streamlining the document requirements and determination of test items in an aim to rapid COVID-19 vaccination in Korea. The total number of COVID-19 vaccines released was about 44 million doses up until Aug. 2021 by the MFDS, 29 million people (56.5%) completed their first dose vaccination, and 15 million (29.6%) people were vaccinated with the second and final dose of the COVID-19 vaccine.

## 2. Procedure for lot release in Korea

Vaccines are biologics mainly used for healthy people. As the distribution of vaccines that do not meet quality standards and result safety accidents have a significant ripple effect in our society, Korea has implemented the national lot release system. Under the system, the quality of biological products such as vaccine is confirmed by the nation considering the public safety before they are distributed on the market

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[5–8].

Korea's national lot release system started from a national inspection system in 1953. In 2012, a review on Summary Protocol (SP) was added to existing general tests (sterility test, pH, endotoxin test, etc.) and special tests (potency test, identification test, content test, etc.) which are designed to confirm the efficacy and safety of each product [5,6]. Since 2016, the review system has been continuously improved such as the introduction of "risk-based national lot release system". In this system, the risk attributes of each product are comprehensively reviewed, and accordingly the test items are differentiated by the determined risk level of the product. The factors evaluating the risk level such as history and results of national lot release and inspection on the manufacturing, quality control at a manufacturing site and domestic and overseas safety information related to quality comprehensively [5,6]. Under the system, products with quality risk are subject to more test items to prevent risk factors before distribution while products whose excellent quality has been maintained continuously are exempted from test and obtain lot release based on only SP review [5,6].

### 3. Accelerated national lot release procedure for COVID-19 vaccines

The MFDS organized task force and manpower and established processes for products subject to the accelerated national lot release in early 2020 to make sure that approved COVID-19 vaccines can be provided rapidly in the COVID-19 pandemic situation.

The accelerated national lot release of Korea is in accordance with the Regulation on the 「Designation, Approval Procedure and Method of Biological Products Subject to National Lot Release」 and the Article 12 of the regulation specifies that 'if the head of a central administrative body requests the accelerated lot release of vaccines against infectious diseases caused by bioterrorism or pandemic for reasons such as public health and national defense, the request can be processed as priority before other lot release by determining test items or required documents to be submitted' [9].

The MFDS designated COVID-19 vaccine as "the vaccine for the accelerated lot release" and made every effort to implement the accelerated lot release. The period of national lot release was minimized as the application for national lot release was handled in **parallel with marketing authorization and review(applicant) for vaccines released** for the first time. In addition, COVID-19 vaccines subject to the accelerated national lot release go through quality control before other vaccine release and processing period has been reduced as much as possible.

For quality control, all test items in the first three lots were tested, and after confirming the consistency of each vaccine through the test results of three lots, **major test items** were determined and tested from the fourth lot. In addition, Korea was responding to changes in international vaccine regulatory environment flexibly by deciding required documents depending on circumstances [10–13]. In addition, the MFDS has been improved to enable an applicant to **submit the sample directly** in consultation with the MFDS by applying the method such as special packaging and transport that can keep the vaccine storage temperature well and ensure no quality change by external temperature in case where a government official is difficult to collect samples directly.

### 4. Method verification of independent test for accelerated national lot release

The rapid establishment of independent test method before approval with new technology like COVID-19 vaccines is far more difficult than conventional vaccines [14]. The COVID-19 vaccines that have been approved so far are imported, so it was hard to secure sufficient quantity of important reagents and reference standard, to adjust supply schedule and to secure final products as a few manufacturers supply vaccines

around the world. It was also difficult to establish test methods for multiple vaccines simultaneously in a short time. Because different manufacturers have different testing methods and different equipment used. More than anything else, the time allowed for establishing a test method was reduced further due to reduced flight schedules due to COVID-19 pandemic.

The method verification guidelines of the FDA, ICH and the MFDS were used to establish a test method for COVID-19 vaccine [15–18]. Even though the quantity of reference standards and samples was not enough, the verification test was conducted at least 3 times. For potency test and content test, accuracy, preciseness and linearity were confirmed to establish a test method and specificity was used for verification in the identification test. In case of virus-vectored vaccine, the method for potency, identification, content and purity tests was established and for mRNA vaccine, method for potency, identification, content, purity and lipid nano particle tests was established.

The verification test results on each vaccine showed the compliance with specification of final products and results of checking accuracy, preciseness, linearity and repeatability for verification were within qualification standards of manufacturers. It is judged that each test method was well established in a national laboratory based on comprehensive review on all results.

## 5. Results

### 5.1. Statistics on accelerated national lot release

The end of August, a total of 43.88 million doses have been released under the accelerated lot release system including AstraZeneca COVID-19 Vaccine Inj (AZ) 41 lots-20 million doses, Comirnaty Inj (Pf) 30 lots-20 million doses, COVID-19 Vaccine Janssen Inj (J&J) 1 lot-0.1 million doses, Moderna COVID-19 Vaccine Inj (Mo) 7 lots-3.5 million doses for six months starting from lot release for AZ in February 2021 (Fig. 1) (Table 1) [19].

It took 15 days (calendar day) on average for national lot release for the first three lots for which test was conducted for all test items. Because the sterility test takes more than 14 days and is the longest test. But it took eight days on average from the fourth lots for which test was conducted on major test items. It is performed both control lab testing and SP review within this period and each test was carried out in parallel, enabling accelerated lot release. So it reduced the period of release by more than three times compared to conventional vaccines (Table 1).

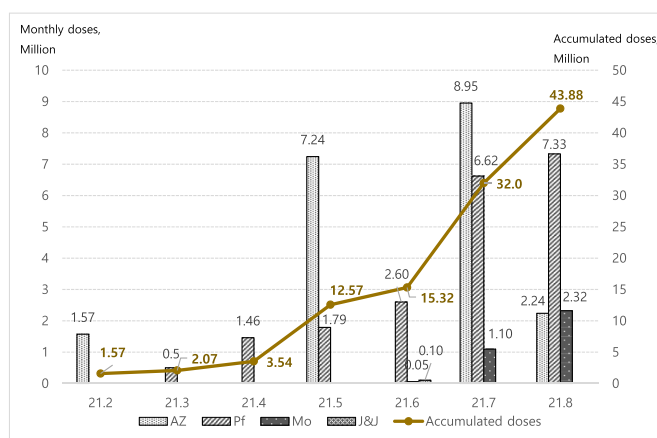


Fig. 1. Status of national lot release for COVID-19 vaccines.

Starting with 1.57 million doses of AstraZeneca Vaxzevria (AZ) in February 2021, a total of 43.88 million doses, including Pfizer (Pf), Janssen (J&J) and Moderna (Mo) vaccines, were released by August 2021. The monthly bar graph shows the released doses of each product and the line graph shows the accumulated doses of COVID-19 vaccines in Korea.

**Table 1**  
Processing period for COVID-19 vaccines.

Item name	Processing period on average (Calendar day)	Lots released	Volume released (10,000 doses)
AstraZeneca	–	41	2001
Pfizer	–	30	2030
Janssen	–	1	10
Moderna	–	7	347
COVID-19	8	79	4388

The end of August in 2021, a total of 43.88 million doses have been released under the accelerated lot release system including AZ 41 lots-20 million doses, Pf 30 lots-20 million doses, J&J 1 lot-0.1 million doses, Mo 7 lots-3.5 million doses since the first lot release of AZ in February 2021. The average processing time of accelerated national lot release for COVID-19 vaccine was shortened to eight days.

As of Aug. 2021, the number of people who got first dose of COVID-19 vaccine was 29.03 million (56.5%) and 15.22 million people (29.6%) completed COVID-19 vaccination [20].

**5.2. Designation of test items to approve accelerated lot release by platform**

The tests required for lot release of COVID-19 vaccine are classified into general tests (property, volume of injection, pH measurement test), product specific tests (potency test, content test, identification test and purity test) and safety test (sterility test, endotoxin test). For the first three lots, quality conformity is checked thoroughly with all test items required for final products and if the products comply with all efficacy and safety test standards. The test is conducted with major test items starting from fourth lots and accelerated release is possible while checking the consistency of the quality. Major test items, which are essential items to secure consistency of the quality such as potency test, were selected considering purpose of tests, opinion of independent experts and overseas guidelines comprehensively [11–13]. All test items and major items for national lot release by COVID-19 vaccine manufacturing platform are shown in Table 2.

**5.3. Results of trend analysis on potency tests for national lot release of COVID-19 vaccine**

The trend analysis was conducted for the results of potency (infectious titer) test, which is a major test item for AZ, which has the largest

**Table 2**  
Whole test items and major test items for COVID-19 vaccines.

Test item		Adenovirus-vectored vaccine		mRNA vaccine	
		Whole items tested	Major items tested	Whole items tested	Major items tested
General test	Appearance	O	O	O	O
	Volume of injection in container	O	–	O	–
	pH	O	–	O	–
Product-specific test	Content	O	–	O	–
	Identity	O	O	O	O
	Potency	O	O	O	O
	Purity	O	–	O	O
Safety test	Sterility	O	–	O	–
	Endotoxin	O	–	O	–

General tests, product-specific tests and safety tests were conducted for the first three lots of Adenovirus-vectored vaccine and mRNA vaccine. From fourth lot, as major tests, appearance, potency and identity test were conducted for quality control. For mRNA vaccine, purity test was additionally performed as the main test due to the characteristics of the preparation.

number of lots released so far. Potency test measures the infectious titer to confirm whether the non-replicating adenoviral vector carrier into which the coronavirus surface protein is inserted has entered the cell well. The measurement is conducted using vector antigen protein based on antigen-antibody reaction. The results of test for 41 lots are shown in Fig. 2. The results are displayed in a million unit and are converted into log value and analysis is conducted. The results of analyzing 41 lots showed the infectious titer unit (IFU) of 9.1 log IFU/mL on average. All results met the potency test criteria and within the range of MEAN±3SD (8.8–9.5 log IFU/mL).

**5.4. Results of trend analysis on identity tests for national lot release of COVID-19 vaccine**

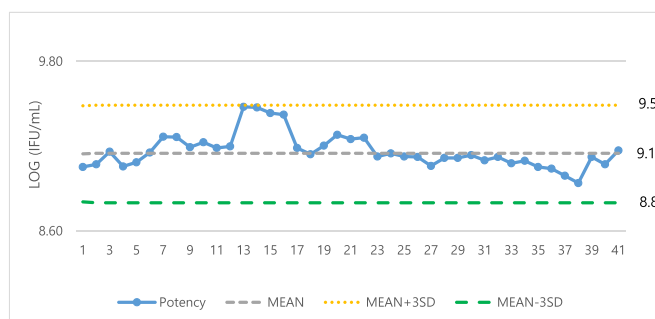
In the identity test for AZ, it is checked whether the non-replicating adenovirus vector and inserted coronavirus surface protein gene are well connected (JUNC) and inserted gene is properly conserved (SPIKE) using real-time PCR method. When the negative Ct (cycle threshold) value is over 30 or determinants, the identity test results of total 41 lots showed 22 and 21 Ct (Cycle Threshold) on average for each JUNC and SPIKE gene. All result mean value is 21 Ct and SD (standard deviation) is 1.2. All results of identity test were within the range of MEAN±3SD (17–25 Ct) (Fig. 3).

**6. Conclusion and discussion**

Many countries believed that vaccinating large numbers of people quickly was a top priority to end the pandemic situation. Therefore, Korea has tried to every effort to quickly release COVID-19 vaccine lots. Currently, in a situation where it is difficult to import COVID-19 vaccine due to the limited number of manufacturers, Korea introduced accelerated national lot release system to reduce the time required for vaccination by reducing the quality control time as much as possible.

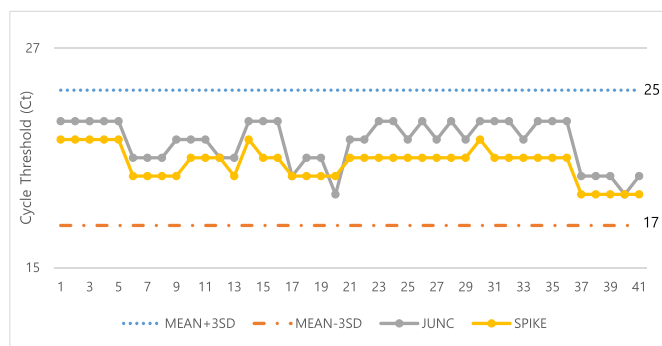
As a result, the end of August, an average processing time for COVID-19 vaccine release was in average of eight days, and 79 lots, 43.88 million doses were released. The number of people who got first dose of COVID-19 vaccine is 29.03 million (56.5%) and 15.22 million people (29.6%) completed COVID-19 vaccination. The accelerated lot release system has contributed significantly to rapid vaccination.

Since the beginning of the 20th century, new infectious diseases with high infectivity and transmission power have occurred every three to five years [21], so it is necessary to develop and produce new vaccines. With increasing number of COVID-19 variant virus infections, it is urgent to develop a new COVID-19 vaccine to respond to them [2,22]. It is judged that global vaccine development and vaccination system need to be established as new infectious diseases such as COVID-19 will be easily spread globally, not being limited to one country.



**Fig. 2.** Trend analysis on potency test for national lot release of AstraZeneca Covid-19 Vaccine Injection.

In the infectious titer test, the value was converted to log and the mean results was 9.1 log IFU/mL on average from February to August in 2021. It was confirmed that the value for 41 lots was within the MEAN±3SD range (8.8–9.5 log IFU/mL).



**Fig. 3.** Trend analysis on identity test for national lot release of AstraZeneca COVID-19 Vaccine Injection.

In the identity test for AZ, the area where vector and inserted gene is connected (JUNC) and inserted gene (SPIKE) were checked by RT-PCR. When the negative Ct value is over 30 or determinants, the identity test results of total 41 lots showed 22 and 21 Ct (Cycle Threshold) on average for each JUNC and SPIKE gene. All result mean value is 21 Ct and SD (standard deviation) is 1.2. All results of identity test were within the range of  $MEAN \pm 3SD$  (17–25 Ct).

Therefore, efforts at an international level are required to establish an international framework for sharing lot release results and real-time discussion, minimize the delay in vaccine supply due to duplicate tests and build trust on each country's lot release result. It is also necessary to share establishing a new lot release system at the national level in order to manage quality for vaccines against new infectious diseases.

Korea has taken just a small step in a marathon of the accelerated national lot release for vaccine against new infectious diseases. For the vaccination of the entire population, it is necessary to release COVID-19 vaccine 5 to 10 times more than what has been approved so far and preparation should be made to test new platforms under development and vaccines against new variants. In order for Korea to emerge as a leading country in vaccine development and manufacturing for new infectious diseases, the private and public sectors should cooperate closely and national quality control should be managed thoroughly. At the same time, it is necessary to explore ways to share methods and results with other countries in need of help together with international organizations.

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