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Official batch control of influenza vaccines: Is it still useful?

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ABSTRACT

Introduction: The governmental quality control of human vaccines is a long established tradition in many European countries. In Germany, vaccines have been controlled by a governmental agency since 1935. In the beginning, vaccine production and control was a purely national activity. However, that changed fundamentally in 1994 when the so-called Official Control Authority Batch Release Network (OCABR) was implemented shortly after the establishment of the European Union. Today, Official Medicinal Control Laboratories (OMCLs) are part of the European OCABR Network. In many European countries, OMCLs experimentally test every batch of human vaccines before they enter the market. We wanted to gain insights into the benefits of batch release by the Network and address the question whether batch release is still useful. This question was investigated in the context of influenza vaccines.
Methods: Notifications on influenza vaccines circulated from 2006 to 2016 within the OCABR network were compiled and organized into 32 cases. The impact of these findings was evaluated, and the communication pathways between companies and respective European control laboratories were examined.
Results: Approximately 5850 batches were tested by the OMCL network between 2006 and 2016. Among these, notifications belonging to 32 cases were observed. The predominant proportion of the circulated notifications related to manufacturing issues. In most cases, the manufacturer itself had withdrawn the batches before they entered the market. However, in three cases, batches of insufficient quality were detected by the respective European Control Laboratory leading to withdrawal of 13 batches.
Conclusion: 13 batches which did not meet the specifications of influenza vaccine were detected by the OMCL network between 2006 and 2016 which would not have been identified by the manufacturer. This demonstrates the impact of governmental batch release. Together with the intrinsic values of the OCABR system and keeping in mind that vaccines are given to healthy often young individuals, governmental batch release of influenza vaccines is still justified.

1. Introduction

The need for regulatory surveillance of biological medicinal products became evident in Germany after Robert Koch had introduced Tuberculin as a promising new therapy in 1890. It soon turned out that batches had an unstable composition and varied in quality. A few months after being introduced, the product was withdrawn after several Tuberculin-treated patients had died [1]. Another new biological, diphtheria antitoxin, was successfully tested for therapeutic use by Emil Behring, but it also proved difficult to produce in constant therapeutic concentrations. The concentration of diphtheria antitoxin administered to patients was often too low. As a result, very high volumes or repeated doses had to be given to the patients [2] which induced intoxication due to the phenol content of the serum. This happened even though the vials of serum had left the manufacturer after having successfully passed a company-specific test for potency.

These incidents showed that biological products with their inherent variability (Table 1) were difficult to produce consistently, due to insufficient quality control by the manufacturer, and some governments introduced official quality controls to minimize public health risks. One of the pioneering countries in Europe was Germany, where an imperial law from 1894 listed the first products that were subject to state control. At that time, Paul Ehrlich was a key figure in the introduction of new methods for the standardization of drugs: he developed a method to measure the efficacy of therapeutic sera, such as diphtheria antitoxin and tetanus antitoxin [3]. In May 1896, Paul Ehrlich described his experiences with the governmental quality control of diphtheria serum as follows: “During the first two months, nine out of 37 sera had to be rejected due to inferiority” [4].

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Table 1
Special aspects of biological and immunological products (amended after [5]).

Aspect	Example
Use of biological systems for production which are subject to variability	Virus growth in embryonated egg Cell growth in fermenters
In process controls and/or final product controls often involve biological systems	In vivo potency tests Extraneous agents tests Test for inactivation
Manufacturing process (often complex) has major impact on final product	Multicomponent products Use of adjuvants
Potential safety risk	Incomplete inactivation/removal of contaminating agents Virus contamination of blood donations used for plasma-derived products Reversion to virulence Quality of the starting material
Administered to large healthy populations as prevention	Vaccines for infants
Administered to already compromised patients	Clotting factors for emergency surgical procedures or long term treatment of disease (e.g. hemophilia)
Often used in government mandated/supported vaccination/eradication programs	Rabies eradication in Europe Infant vaccination programs

The situation of purely national batch release activities changed fundamentally with the formation of the European Union: licensing was harmonized, and in addition, the quality control of marked medicinal products for human and veterinary use was harmonized. Thus, in 1994, the Commission of the EU and the Council of Europe created a network of official medicines control laboratories (OMCL) – the General European OMCL Network (GEON) – with the goal to independently test the quality of medicines. This Network is coordinated by the European Directorate for the Quality of Medicines (EDQM).

GEON is comprised of networks with different activities, where different sets of laboratories fulfil certain tasks, such as market surveillance. Another task is the official batch release for human biologicals, which involves OMCLs from the Official Control Authority Batch Release (OCABR) network. The legal basis for batch release is provided in Directive 2001/83/EC, Article 114 respectively [5]. The member states can request samples from each batch of the bulk and/or medicinal product for testing. In addition, the testing protocols of the manufacturers are controlled. This applies to immunological medicinal products or medicinal products derived from human blood or plasma. The combined process of protocol review and testing is referred to as OCABR [6].

To harmonize official batch release of products licensed in several countries, OCABR certificates for specific products or product classes were introduced at European level. Such certificates are issued for every batch that is in compliance with the approved specifications described in the relevant monographs of the European Pharmacopeia and the marketing authorization, i.e. the governmental license for bringing products on the market. All member states requiring OCABR for that product (Article 114 of [5]) are legally obligated to accept these certificates. This represents the principle of mutual recognition. Currently, the OCABR human network consists of 32 member states from the EU/EEA and other member states having signed a formal agreement, which includes recognition of OCABR (Table 2). Switzerland joined the network via a Mutual Recognition Agreement (MRA), and Israel signed an "Agreement on Conformity Assessment and Acceptance of Industrial Products (ACAA)" by which Israel can fully participate in OCABR activities regarding vaccines.

The framework, concepts and scopes for these OCABR procedures are defined in the "EU Administrative Procedure for Official Control Authority Batch Release" [7], and the tests to be performed are described in the product-specific guidelines [7]. This assures harmonized testing procedures – a prerequisite for the idea of mutual recognition. The guidelines are regularly updated with current specifications from the European Pharmacopeia monographs and marketing authorizations. The tests performed by the OMCL focus on the measurement of key quality parameters for a given product, and do not cover the full spectrum of release tests performed by the manufacturer.

For influenza vaccines and many other vaccines, the process of OMCL testing is often performed at the same time as the testing done by the manufacturer (i.e., as "parallel testing"), to ensure timely supply on the market. This means the OMCL will receive samples of the batch before the manufacturer has completed its own tests and before submission of the completed protocol.

Historically, governmental batch release was introduced to deal with problems of consistency and potency of biologicals, a new

Table 2
Official and associated members involved in OCABR.

EU Member States		EAA Member States	Mutual Recognition Agreement	ACAA[a]
Austria	Italy	Iceland	Switzerland	Israel
Belgium	Latvia	Liechtenstein		
Bulgaria	Lithuania	Norway		
Croatia	Luxemburg			
Cyprus	Malta			
Czech Republic	Netherlands			
Denmark	Poland			
Estonia	Portugal			
Finland	Romania			
France	Slovac Republic			
Germany	Slovenia			
Greece	Spain			
Hungary	Sweden			
Ireland	United Kingdom			

[a] ACAA (Agreement on Conformity Assessment and Acceptance of Industrial Products), for vaccines.