Benefits of official batch control and surveillance for immunological VMPs

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Keywords

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Abstract

Medicinal products on the European market are regulated through marketing authorisation, inspection, pharmacovigilance and European Pharmacopoeia (Ph Eur) standards and, for selected biological products, official batch release. Regulatory oversight relies on independent agencies with specialised scientific and technical expertise to ensure public and animal health and consumer protection, and to foster the "one health" aspect to ensure the food chain safety.

Independent experimental testing in general secures the maintenance of know-how at Official Medicines Control Laboratories (OMCLs), where all stakeholders (assessors, inspectors, manufacturers, consumers, animals and political decision-making bodies) derive benefit. The most prominent experimental testing is made for Official Control Authority Batch Release (OCABR), which provides an evaluation of batches before they are marketed. This is particularly important for biologicals, as they can be prone to variability in their production and testing and are administered under particular conditions. This article describes the successful system of regulatory testing with special attention to OCABR of immunological veterinary medicinal products, its benefits and proposals for further improvement.

Introduction

Regulatory surveillance by testing of biological medicinal products (BMPs) began at the end of the 19th century. The introduction of the Diphtheria antiserum was a milestone in infectious diseases therapy; however, the quality of the sera produced varied considerably, which consequently had adverse effects on efficacy. Implementation of a method developed by Paul Ehrlich to measure the potency of the Diphtheria antitoxin made it possible to test different batches of sera before they reached patients and thus reduced the risk of using the less efficacious sera. In May 1896, Paul Ehrlich described his experiences with the national batch control: "During the first two months alone, nine out of 37 sent sera had to be rejected due to inferiority," in the journal *Berliner Klinische Wochenschrift*.

The tradition of independently testing BMPs continues today under the auspices of the Official Medicines Control Laboratories (OMCLs). While manufacturers now have specifications for quality, safety and efficacy set out by the licensing authorities and an obligation through their own quality control to ensure compliance, independent testing by regulatory authorities remains important. The legal provisions[1] to test certain BMPs after release by the marketing authorisation holder (MAH) but before release onto the market are required due to the inherent variability of these products, which are linked to their special characteristics, as outlined in Table 1.

The added value of independent pre-release testing is supported by data, for example, from the area of medicinal products derived from human blood. In the first year after the introduction of national batch control for such products in Germany in 1994, the number of batches which failed release criteria was greater than 8%. This percentage decreased progressively and after five years a stable level of 1% was reached. In a related field, a comparable case was reported by a Polish OMCL – the introduction of a national initiative for official control of syringes and needles by market surveillance led to a significant decrease in the number of deficient batches. Notably, following the subsequent suspension of official control for these products, the number of deficient batches increased again (*Z Fijalek, National Medicines Institute, Warsaw, Poland – personal communication*). Demonstrably, the official control at independent OMCLs is still of vital importance for the quality control of biomedical products. Immunological veterinary medicinal products (IVMPs), like the other categories of biologicals, benefit from this independent batch-to-batch surveillance.

The control of BMPs often requires complex test methods performed according to harmonised protocols and the use of reference materials. The OMCLs, sometimes in collaboration with the manufacturers, contribute to the development methods and reference materials to ensure that product testing is performed according to the current scientific knowledge in a repeatable, reliable way.

Acronyms and abbreviations

- **3Rs –** Reduction, replacement and refinement
- **BMP –** Biological Medicinal Product
- **BSP –** Biological Standardisation Programme
- **CA –** Competent Authority
- **DBO –** Department of Biological Standardisation, OMCL Network & HealthCare
- **EDQM –** European Directorate for the Quality of Medicines & HealthCare, Council of Europe
- **EEA –** European Economic Area
- **EMA –** European Medicines Agency
- **GDP –** Good Distribution Practice
- **GEON –** General European OMCL Network
- **GMP –** Good Manufacturing Practice
- **IVMP –** Immunological Veterinary Medicinal Product
- **MA –** Marketing Authorisation
- **MAH –** Marketing Authorisation Holder
- **MJA –** Mutual Joint Audit
- **MS –** Member State
- **NCA –** National Competent Authority
- **OBPR –** Official Batch Protocol Review
- **OCABR –** Official Control Authority Batch Release
- **OMCLs –** Official Medicines Control Laboratories
- ***Ph Eur* –** European Pharmacopoeia
- **VBRN –** Veterinary Batch Release Network

The role of OMCLs

In the EU, OMCLs are officially recognised in the legislation.[1] According to the rules of the General European OMCL Network (GEON) an OMCL is by definition a public institution which performs laboratory testing either for a competent authority (CA), or as a CA, independently from the manufacturer to ensure quality, safety and efficacy of medicinal products.[2]

OMCLs carry out testing activities in different contexts depending on their specific mandates and technical competence. Important contributions made in the field of independent regulatory testing include:

- Post-marketing surveillance programme
- Pre-licensing sampling and analysis
- Pre-marketing sampling and analysis
- Sampling and testing of generic medicines
- Analysis of unlicensed (unauthorised) medicines
- Analysis of counterfeit/illegal medicines
- Support in evaluation of the quality part of marketing authorisation application dossiers Support of pharmacovigilance assessments
- Support of good manufacturing practice (GMP) inspections as experts
- Support in the framework of the European Pharmacopoeia (*Ph Eur*)
- Evaluation of quality defect reports.

In addition, OMCLs are very active in the field of research and development (R&D), contributing in particular to the development of new reference methods and reference materials, with a particular focus on reduction, replacement and refinement of animal use in testing (3Rs).

Independent testing provides regulatory authorities with first-hand scientific knowledge of BMPs for the benefit of the users. By combining research with routine testing, test methods remain state-of-the-art techniques. These scientifically advanced tests improve the basis for decision-making in marketing approvals, inspections or pharmacovigilance. Furthermore, this research and development on methods is of considerable importance for innovative products. OMCLs are also in a unique position to compare similar products from different manufacturers. This can lead to important insights and advances with respect to standardisation and control.[3]

The General European OMCL Network (GEON)

The General European OMCL Network is coordinated by EDQM, a Directorate of the Council of Europe which is also responsible for the *Ph Eur*. Established in 1994, the GEON now consists of 70 OMCLs from 40 countries[4] and continues to expand. The network is open to all countries that have signed the European Pharmacopoeia Convention as well as observers to the European Pharmacopoeia Commission, provided they fulfil the criteria of the network (independence, public funding, ISO/IEC 17025 standard in the laboratory, etc).[5] This approach has also led to the increasing importance and acceptance of *Ph Eur* and its provisions throughout the world.[6]

The GEON contains a number of activity-related specific networks that group together different sets of OMCLs depending on the task at hand, for example, post-market testing of centrally authorised medicinal products, market surveillance testing of chemical pharmaceuticals, etc. Official batch release of IVMPs involves OMCLs in the Veterinary Batch Release Network (VBRN). The activity is based on EU legislation and is restricted to member states of the EU/EEA or countries that have an established mutual recognition agreement with the EU which includes batch release (eg, Switzerland).

One of the main benefits of the GEON is the cooperation between the network members. Exchange of information and expertise, along with worksharing, means an increase in resources and a decrease in workload for the individual OMCLs, with the ultimate goal of mutual recognition of results throughout the network as far as the legal framework allows. Examples of collaboration and optimisation of resources in the OMCL networks include:

- Exchange of know-how within the EDQM/OMCL network through meetings (annual plenary sessions and specific ad hoc working groups)
- Worksharing: OMCLs perform practical testing on request from other OMCLs
- Inter-OMCL collaborations and data exchange, eg, an individual OMCL performs a maximum of 50 surveillance studies per year. Throughout the network, 850 products are tested per year. Each OMCL contributes and the results are shared, with increased benefit for all
- OMCLs with established tests will mentor those wishing to learn via one-to-one training
- Existing OMCLs will provide assistance to new OMCLs. For example, within the VBRN, the first step would be for the new OMCL to conduct "official batch protocol review" (OBPR) in-house, while practical testing may be outsourced to other OMCLs. The second step would see the OMCL build capacity for OCABR performance with support from the network
- Established OMCLs together with licensing authorities support small national MAHs to enter the European and third country markets.

A key component of this coordination is the introduction

Table 1: Special aspects of biological and immunological products.

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

of common quality assurance procedures to provide mutual confidence between the results for different OMCLs. A programme of mutual joint visits (MJVs) and mutual joint audits (MJAs) of OMCL laboratories together with the analytical proficiency testing scheme and other collaborative studies support this mutual recognition. This concept of worksharing has gradually expanded to a large array of OMCL activities.

Official batch control and release of IVMPs

As mentioned earlier, IVMPs are particular medicinal products, for which variability in product and procedures combined with the user characteristics (see Table 1) warrant special measures. In the EU, this takes the form of an official batch release whereby there is an independent batch-to-batch evaluation of the product after release by the MAH but before release onto the market. Official batch release of IVMPs always involves the review of batch protocols for compliance with the marketing authorisation. As a stand-alone process this is referred to as official batch protocol review (OBPR). All IVMPs are eligible to undergo OBPR. A defined group of IVMPs may also be tested by OMCLs to verify compliance prior to release. This combined process of protocol review and testing is referred to as official control authority batch release (OCABR). The legal basis for these controls is provided in EU Directive 2001/82/EC as amended, Articles 81 and 82 respectively. It is up to each member state to decide which of these procedures they wish to apply for the different products on their market, within the limits of the legislation. To harmonise official batch release of IVMPs which are authorised in several countries, certificates of OCABR and OBPR were introduced at the European level to facilitate mutual recognition. When a batch is in compliance, a certificate is issued which is accepted by all other control authorities of the VBRN. OCABR certificates are mutually recognised by legal obligation supported by mutual confidence, whereas OBPR certificates are recognised by common agreement based on mutual confidence only. The framework for these activities, including the scope of the tests to be performed in the case of OCABR, are defined in EU Administrative Procedures for OBPR and OCABR, in product-group-specific VBRN-Batch-Release Guidelines, as well as some general VBRN guidelines internal to the network.[7–12] Thus, it is ensured that IVMPs to be placed on the European market and beyond are in compliance with consistent standards. It also avoids repeat testing of the same batch by more than one OMCL.

Ongoing trend analyses performed by the OMCLs have detected, in a number of cases, a change in quality of IVMPs, eg, a decline in titres at release or changes in trends of test results, when technical personnel are changed. Such observations will lead to a dialogue with the manufacturer and often result in investigations that allow a correction of the situation before major problems occur. They can also lead to feedback to the other regulatory branches (licensing, inspection) for follow-up action, as needed.

The groups of IVMPs subject to OCABR testing are identified by the regulatory authorities via a risk assessment. This risk assessment helps to determine priorities for testing, with the aim of promoting animal health and consumer protection. The criteria for the evaluation of candidate product groups for OCABR of IVMPs, as codified in an internal network document, are as follows:

- Transmissible disease that has the potential for rapid spread, irrespective of national borders, that is of social and/or economic and/or public health (human and animal health and environmental protection) importance and that may have negative impact on the trade of animals and animal products
- IVMP used in official control programmes anywhere in the EU or

mutually recognised partners
- IVMP where licences are based on a restricted set of data on quality, safety and efficacy
- Widely used IVMP where disease can only be controlled by vaccination and the IVMP is not part of an official control programme
- IVMP against zoonotic diseases
- IVMP used to avoid the spread of diseases for animals with the probability of travelling and/or crossing borders or which is in fluctuating populations. The occurrence of crowding diseases should be decreased by vaccination
- IVMP with possible negative impact to consumers and/or the environment
- IVMP produced from starting materials, which may have an increased negative impact on the vaccinated animals
- IVMP where the variability of the batch tests method is known to be high from results with multicentre studies or from marketing authorisation documentation.

The more criteria a product group meets increases the priority for testing. These criteria are intended to be used as part of the evaluation process for determining which IVMPs require testing by OCABR. It is, however, not intended as a stand-alone tool to determine whether products should be tested. It should be used in the context of other defined internal procedures of the VBRN (eg, the procedure to include a product group on the restricted list, the procedure for temporary testing of products not on the restricted list) which take into consideration numerous other scientific and practical considerations.

Over the years a number of deficient batches, which were not released to the national and European markets, were reported by OMCLs. These deficient batches currently represent between 1% and 1.5% of all batches being subject to OCABR and OBPR. The introduction in 1991 of European legislation on GMP for production and control of IVMPs, including validation of production processes and test methods, has had a major positive impact on the consistency and quality of batches produced; however, a low number of out-of-specification (OOS) batches continue to be detected by OMCLs each year. Some selected examples are provided in Tables 2 and 3.[13]

OCABR and OBPR are regularly subject to discussion between national competent authorities (NCAs) and MAHs. Despite some constraints, such as the time needed for the performance of OCABR/OBPR and fees to be paid, the system is designed so that the benefits to the users outweigh the constraints. The system enhances the harmonisation of information provided to all members of the VBRN, and testing the same batch in multiple member states is avoided. This enables the NCAs/OMCLs and MAHs to save resources which can be used for development or improvement of analytical methods, including reduction, replacement and refinement of *in vivo* methods. A more detailed overview on benefits and constraints is provided in Table 4.

Some of the benefits of pre-market testing can be listed as follows:
- Prevention is preferred over cure: testing can highlight problems with OOS batches before they are used in animals as placement of these batches onto the market is blocked
- OCABR may prevent post-marketing withdrawals: IVMPs are sensitive medicinal products. Withdrawals from the market concerning IVMPs may not only affect the batch concerned but may have a negative impact on public perception of that product and vaccination in general
- The performance of OCABR/OBPR fosters a continuous and close interaction between MAHs and regulatory authorities with a better balance between MAHs and regulatory "enforcement power"
- Continuous regulatory oversight, in particular with testing, provides an external impetus to encourage good application of the requirements by the MAH.

Without the option of official batch release, any problems (product defects, trend changes etc.) are found only after the batch

Table 2: Examples of findings during OCABR.

Category	Observation	Conclusion
Visual aspect	• Lyophilisate colour does not comply with description in the dossier	• Wrong vaccine – No release
Composition	• Amount of adjuvant not homogeneous (separation during filling) • Reduced stability of emulsion • Residual moisture content too high	• No release • No release • No release
Quality	• Prolonged dissolution time of the lyophilisate pellet (problems with lyophilisation) • Foreign object in the lyophilisate pellet • Bacterial and fungal contamination detected • Non approved primary container	• No release • No release, GMP-inspectors informed • No release • Release after approval
Safety	• Endotoxin content too high • Extraneous agent testing not performed according to accepted validated test	• No release • Release after validation and approval of new test
Potency	• Result of potency test OOS • Product inconsistencies: inconsistency of protein content due to blending faults.	• No release • No release

Table 3: Examples of findings during OPBR.

Category	Observation	Conclusion
Production	• Use of unapproved changes (filling volume, time of blending, in process storage, changes in addition of antibiotics, changes in virus inactivation) • Non-approved interruption of the production process • Preparation of IVMPs in non-licensed facilities	• No release • No release • No release
Quality	• Physical-chemical tests (viscosity, residual moisture, pH) out of specification • Tests deleted without acceptance by competent authorities (CAs) • New Working Seed not tested according *Ph Eur* • Replacement potency test not validated properly	• No release • Release after performance of missing tests • No release • Not release
Safety/efficacy	• Titre too low	• No release or withdrawal of application by the MA
Efficacy	• Use of unapproved (shortened) shelf life	• Release after acceptance of variation
Labelling/ packaging	• Change of primary packaging • Faults in product literature	• Release withheld until approval of variation • Commitment to change labels or recall from the market: depending on the status of delivery of the product.

has been marketed, through post-marketing product monitoring, inspection or pharmacovigilance. This detection after the fact can have a significant impact on vaccination schemes employed for eradication programmes, etc. It is the manufacturer's responsibility to ensure good quality, safe products, but the expertise of the OMCLs is supportive in cases where unexpected events may occur in the field.

OMCL interactions with other competent authorities, institutions and networks

OMCLs are an important part of all activities concerning licensing, testing and post-marketing surveillance. Figure 1 illustrates the interaction between OMCLs and the various agencies and institutions. OMCLs can support the NCAs, the European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMAs) in the decision-making process regarding the quality of medicinal products, in particular biomedical products pre- and post-marketing.

The various inspections (GMP, good distribution practice (GDP) and pharmacovigilance) and OMCL product testing serve the same ultimate goal of ensuring the quality of IVMPs as stipulated in the relevant legislation. However, they differ in focus and method. Inspections usually cover a broad spectrum of topics, while OMCL product testing focuses on the measurement of a restricted number of key quality parameters for a given product (product group).

OMCL product testing is an independent analytical approach, whereas inspections cover staff interviews, examination of premises and equipment and the evaluation of written documents, therefore both systems complement each other. Cooperation between the two systems, including information exchange, is beneficial to both. Identified risks can be dealt with either by inspection or product testing or both. Inspection reports may trigger or defer product testing and *vice versa*. As inspections and product testing require different expertise and training, they are sometimes performed by independent institutions in the same member state. There might be room for improvement regarding mutual information-sharing in such situations. Bilateral discussions between inspectors and product experts from OMCLs and inspection teams consisting of inspectors and product experts from OMCLs and licensing authorities (assessors) are already established in some member states, with positive results.

Pharmacovigilance data are another important factor. Information from the field that directly reflects the outcome of use of the products should be readily available to assessors, inspectors and OMCLs to ensure appropriate actions are taken. Information-sharing among member states is also of utmost importance. While there is cooperation between inspectors of different member states supported in particular by EMA, and also cooperation between testing laboratories, supported by the EDQM of the Council of Europe, the flow of information from the inspection service in one member state directly to the testing laboratory in another member state or to the licensing authorities and *vice versa* is almost non-existent. However, a database has been established at the EMA (EudraGMP) for GMP certificates, for both active substances (for human medicines) and finished products, issued by NCAs after inspections performed inside and outside the EEA. GMP non-compliance reports are also placed on this database. Effective use of this tool would improve data flow.

In addition, the collaborative work of OMCLs to validate newly developed tests for final batch testing has led in a number of cases to revisions of *Ph Eur* monographs. The increasing cooperation between the OMCL-network and *Ph Eur* and its working groups is very advantageous. Indeed, the development of reference methods and materials is an important task of the OMCLs and

manufacturers. In most cases the OMCLs are the instigators in developing common methods and references, but more and more manufacturers contribute to these activities. Unfortunately there are still some areas which require the use of animals in product testing, especially in final batch testing. Therefore the current efforts concentrate on the 3Rs of these tests.[14] The Biological Standardisation Program (BSP) of the EDQM plays an important role in establishing validated methods,[15,16] with OMCLs as major contributors to the programme.

Given the huge investment necessary to establish and to run a testing laboratory, and given the impossibility of establishing and running all testing methods in a single laboratory, the benefit of a close collaboration between testing laboratories is obvious. Economics suggest that it makes sense to assign certain test procedures to one or a few laboratories which can then perform these tests on behalf of laboratories of other member states.

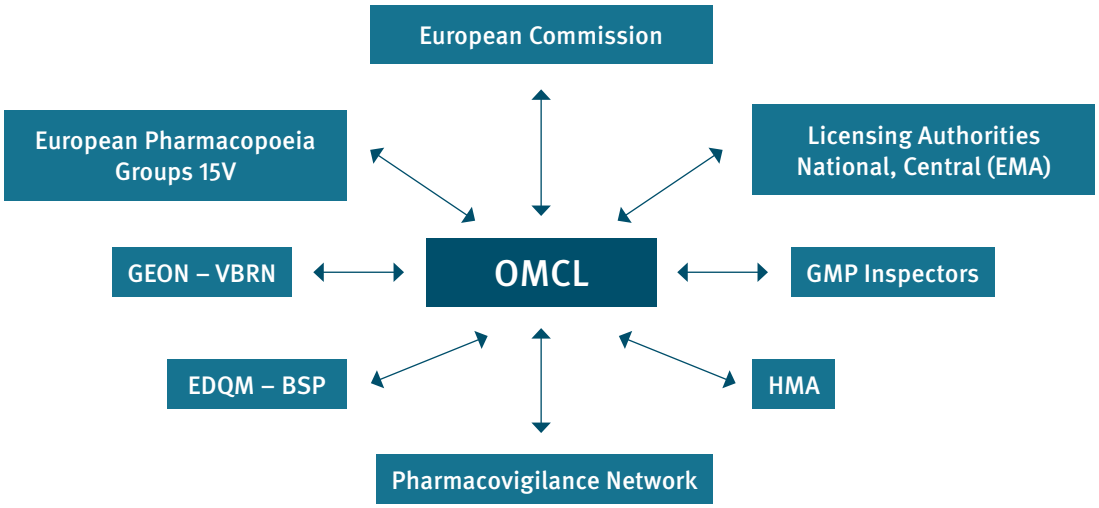
Conclusion

Product testing, and in particular OCABR, provides a concrete, evidence-based means to independently evaluate medicines. OCABR and OBPR are excellent tools to ensure the quality of batches of IVMPs prior to placing them onto the market. The use of validated tests performed by externally audited OMCLs allows mutual recognition of OMCL certificates and avoids duplicate testing. This is particularly important in the case of *in vivo* tests. The technical expertise of OMCLs and experience with the products supports the full regulatory process and provides important feedback to assessors, inspectors and many other institutions at national and EU levels. While remaining independent, OMCLs act as an important point of contact and exchange with the manufacturers to

Table 4: Benefits and constraints of OCABR and OBPR.

Benefits	Constraints
Independent testing increases confidence in medicinal products (patients, animal owners, medicinal personnel, consumers)	None
OCABR/OBPR complements GMP inspections and MA assessment systems	OCABR/OBPR requires fees from MAHs
The same information is provided to all national competent authorities (NCAs)/ OMCLs	None
EU certificates provide a quality label for the EU and beyond	OCABR may take up to 60 days, which could increase time to market (OMCLs offer parallel testing to alleviate this)
Compliance with MA and *Ph Eur* prevents placing of OOS batches on the market	None
Information about OOS batches are communicated immediately throughout the OMCL network and save resources within the OMCLs	OOS batches cannot be sold in EU member states without OCABR/OBPR
OCABR/OBPR is a predictable system for MAHs	Differences in work culture between MAHs and OMCLs hamper the integration of the different systems
Mutually recognised testing saves resources (animals) at OMCLs and MAHs and enhances free movement of goods	OCABR requires use of animals for potency testing
The network enables coordination of resources and sharing of expertise between OMCLs	None
Trend analysis gives an overview on the evolution of a particular product	None
Long-term investigations on quality, safety and efficacy foster knowledge of IVMPs	None
Independent expertise contributes to development of *Ph Eur* and 3Rs methods	Exact repeating of MAHs test methods hampers the investigative approach, which could detect unexpected weaknesses in products
Increased product confidence as contribution to “one health” approach	None
CAs (licensing, GMP inspection, pharmacovigilance), animal owners and the public benefit from the expertise developed through independent product testing at OMCLs	None
Qualified scientific advice for ministries and other political decision-making bodies is readily available, eg, to ensure food safety (public health)	None
Expertise in experimental testing contributes to preparedness for crisis situations.	None.

Figure 1: Interactions between OMCLs involved in control of IVMPs and regulatory partners.



BSP: *Biological standardisation programme;* ***EDQM:*** *European Directorate for the Quality of Medicines & HealthCare;* ***EMA:*** *European Medicines Agency;* ***GEON:*** *General European OMCL Network;* ***GMP:*** *Good manufacturing practice;* ***Group 15V:*** *Expert group responsible for immunological veterinary medicinal products;* ***HMA:*** *Heads of Medicines Agencies;* ***OMCL:*** *Official Medicines Control Laboratory;* ***VBRN:*** *Veterinary Batch Release Network.*

facilitate dialogue for problem solving. A strong network of OMCLs competent in testing IVMPs is crucial to the ongoing surveillance of the quality of these medicinal products for the benefit of the animals and consumers. ■

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