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REVIEW

Drug product registration and marketing authorization procedures in EU-A perspective

Ashish Kekare[2], Jagadish PC [3], Manthan Janodia[1], Krishnamurthy Bhat[3], Swati Karande[4], N Udupa[1]

ABSTRACT

There are 27 European Union (EU) member states, 3 European Economic Area (EEA) and European Free Trade Association (EFTA) states. For a company willing to market the medicinal product in to the EEA, marketing authorization (MA) for the respective product must be issued by competent authority of member state or authorization granted according to Regulation (EC) No. 726/2004 for entire community. Europe constitutes large population and European government is alert regarding safety of the public in EU. There are changes in the procedures for the marketing authorization by the EU. Different types of procedures for the application of marketing authorization are available in the EU and these procedures are discussed here.

KEYWORDS: European Economic Area, marketing authorization.

AFFILIATIONS
[1]Manipal College of Pharmaceutical Sciences, Department of Pharmacy Management, Manipal, Karnataka, India
[2]Manipal University, Department of Advanced Pharmaceutical Studies, Manipal, Karnataka, India
[3]Manipal College of Pharmaceutical Sciences, Department of Pharmaceutical Quality Assurance, Manipal, Karnataka, India
[4]Bioplus Pharma, Regulatory Affairs, Bangalore, India

CORRESPONDENCE
Jagadish PC

E-mail:
jagadishpc@gmail.com

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INTRODUCTION

The primary objective of European regulation is to safeguard public health, encouraging the development of the pharmaceutical industry of the EU. Prior to marketing a medicinal product in the EU, a marketing authorization (MA) (product license) must be obtained. The company (more specifically "Marketing Authorization Holder") responsible for placing the medicinal product on the market must be established within the EEA (Iceland, Liechtenstein, Norway and the Member States of the European Union). European regulation has established and harmonized many aspects of regulating the production, distribution, and use of medicines in the EU (1).

A major and important step was taken in 1995 by creating the European agency for the evaluation of medicinal products (European Medicines Evaluation Agency, EMA) and the establishment of a Centralized procedure, leading to a single EU wide evaluation and approval of new medicines (2).

HISTORY

Need for the initiation of the regulation of pharmaceuticals by the impact of the Thalidomide disaster in the early 1960s. Thalidomide is a sedative designed to prevent morning sickness in pregnant women. But result of the use of this drug lead to birth of thousands of deformed babies.

This tragedy exposed the inadequacies of safety control mechanisms. In a time where pharmaceutical scientific research progressed and international trade flows increased, the existing regulatory regimes were inadequate to face the nature of the risk involved (2).

In 1965, the first European piece of legislation in the pharmaceuticals sector, the regulation (EC) was pursuing three main lines of action:

1) It clarified what a "medicinal product" was considered to be;

2) A drug would be approved for marketing, if it shows its safety, effectiveness and therapeutic value with proper documentation;

3) Laid down a number of common rules guiding testing requirements and labeling (2-3).

After this in 1975, a new wave of legislative intervention came and regulation (EC) approved three changes:

1) It developed a set of detailed common rules to standardize the tests and trials that medicinal products were subject to in the European Community.

2) A multi-state mutual recognition procedure was established, whereby a company which had received authorization to market a certain medicine in a Member State could seek the recognition of that authorization in at least five other Member States.

3) A Committee for Proprietary Medicinal Products (CPMP), including representatives of the Commission and national authorities, was created with the objective of supervising the multi-state application process and submit an opinion on whether medicines subject to that procedure complied with the requirements laid down by Council Directive 65/65/EEC (2).

Formal procedure as per Directive 75/319/EEC marketing authorization of medicinal product was; 120 days: Examination of application, member state concerned could raise reasoned objective, 60 days: Opinion of Committee for Proprietary Medicinal Products, 30 days: Statement of member states concerned on their position.

By this procedure, 41 dossiers were filed from 1978 to 1985, which covers a total of 253 individual applications made to 5 member states or more. This is shown in Table 1.

In this as per respective country, dossiers are:

TABLE 1. Dossiers filed between 1978 to 1985.

Country	Dossier	Application
UK	16	18
France	7	15
Denmark	7	28
Germany	5	25
Belgium	5	33
Ireland	1	24
Luxembourg	-	37
Netherlands	-	35
Italy	-	28
Greece	-	12

Out of 253 applications 175 got marketing authorization and 63 are definite refusals (2,4).

In 1986 multi-state procedure was introduced by Directive 83/570/EEC, the council reformed many important aspect of the previous procedure which has been established by Directive 75/319/EEC.

Changes made were,

1. Member states must in future take into due consideration the initial authorization, save in exceptional cases when they refer reasoned objectives to the opinion of the committee.
2. To make the procedure more attractive and effective, the minimum member states concerned has been reduced from 5 to 2, and firms have at their disposal direct access to the committee.
3. To reach a decision with full knowledge of all the aspects, the concerned member states have at their disposal a detailed description of the content of the initial authorization in the form of a "Summary of Product Characteristics" as well as critical evaluation report prepared by the original country, at least in the case of new medicines.

Result of this all change in the procedure is that, in between 1986 to Feb. 1988 the numbers of dossiers submitted were 36 which cover 198 individual national applications, which is more as compared to previous applications (4). This is shown in Table 2 below.

TABLE 2. Dossiers filed between 1986 to 1988 after changes in procedure.

Country	Dossier	Application
UK	14	13
France	9	12
Denmark	2	16
Germany	5	21
Belgium	2	23
Ireland	3	12
Luxembourg	-	22
Netherlands	-	19
Italy	1	21
Greece	-	21
Spain	-	18

OBJECTIVES

This paper was prepared with the following objectives.

- To understand Marketing Authorization procedures and types of applications.
- Selection of the process and basic requirements to get medicinal product into the EU market.
- The structure of Marketing Authorization process according to EU.

RESEARCH METHODOLOGY

Type of Study

This was an exploratory study to understand the Drug Registration and Marketing Authorization Procedures in EU.

Data Collection

The study is based mainly on the basis of data collected from various sources like various regulatory agencies such as EMA, European Economic Council (EEC) etc. The data was also collected from available literature in journal articles published.

DISCUSSION

PROCEDURES FOR MARKETING AUTHORIZATION OF MEDICINAL PRODUCTS IN EU MARKET:

1. CENTRALIZED PROCEDURE
2. MUTUAL RECOGNITION PROCEDURE
3. DECENTRALIZED PROCEDURE
4. NATIONAL PROCEDURE (5).

1. CENTRALIZED PROCEDURE

As per the regulation (EC) No 726/2004, Centralized procedure is describe for marketing application of medicinal products, for which only one application, single evaluation and single authorization required for marketing medicinal product

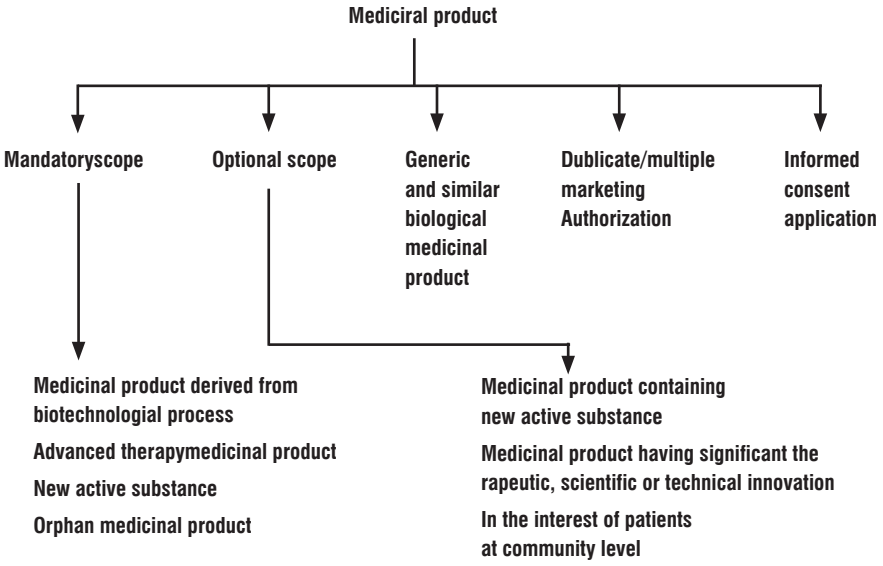


FIGURE 1. Application Process for medicinal products.

into entire community market. By this procedure medicinal product can be put into all member states.

Application for this type of authorization is directly send to EMA (6-7).

Applications of medicinal product are processed by following ways, which is shown in Figure 1 (6,8-9).

Admissibility of application

At least 7 month before the submission of application, applicant should inform EMA about the submission of application and give estimate of month of application. After discussion with the Committee for medicinal products for human use (CHMP), EMA will inform applicant for whether application is acceptable or not. If applicant is willing to apply for multiple applications then applicant must inform EMA about the submission before at least 4 months.

Before actual start of procedure rapporteur and corapporteur are appointed by the CHMP members and EMA (6).

Dossier

Dossier submitted to EMA and rapporteur, co-rapporteur both parallel.

1 full copy of dossier,

2 additional copy of module 1 & 2 including draft Summary of product characteristics (SmPC), labeling and package leaflet (PL) in English,

1 electronic copy of module 1 & 2 (6).

Payment of fees

Payment of fees should be done within 45 days of notification. The invoice will be sent to the billing address indicated by the applicant and will contain clear details of the product and procedures involved, the type of fee, the amount of the fee, the bank account to where the fee should be paid and the due date for payment (6).

Conditional marketing authorization

Request for accelerated assessment can be submitted at any time of prior to the submission of application. Applicant can apply for accelerated assessment procedure if he proves that the medicinal product is in major public health interest and therapeutically effective. Request has to be send within 10 working days in advance of the actual start of the evaluation procedure.

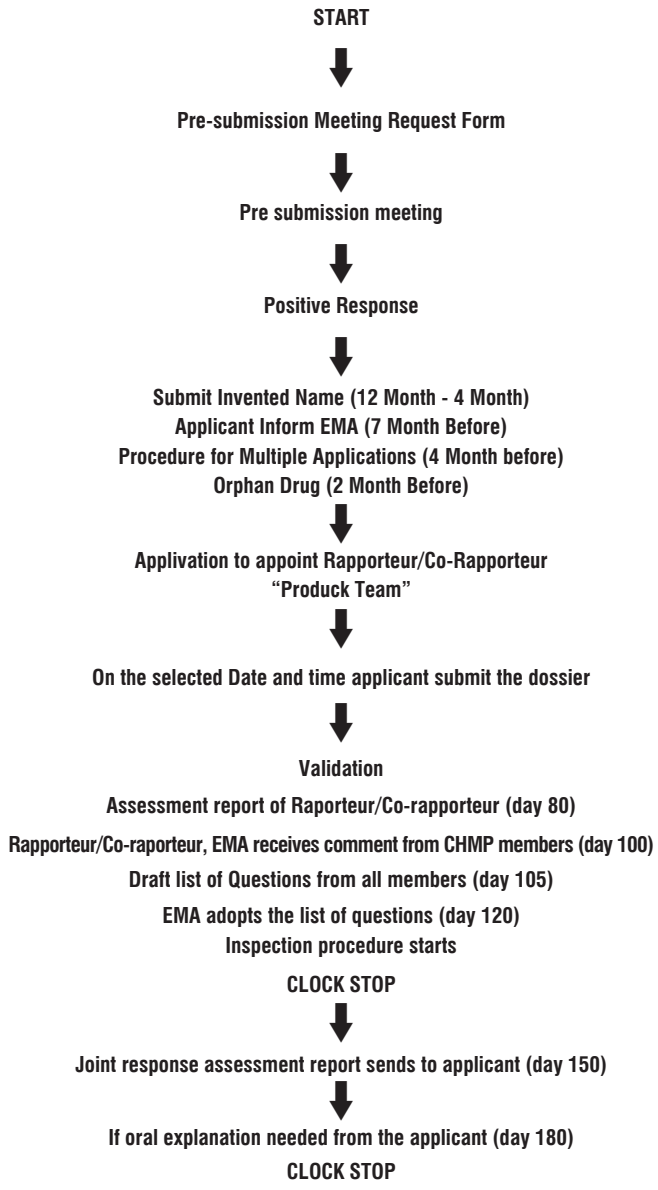
The timetable for the accelerated procedure is reduced to 150 days (6).

Renewal of marketing authorization

After marketing authorization expiry if applicant wants to continue sale the drug into the market then renewal of the marketing authorization is important. For the renewal of the marketing authorization applicant must apply before six month advance of the expiry of medicinal product in market. For this procedure required fees should submit within 45 days of notification date (6).

Schematic representation of Centralized procedure (6):

DAY	ACTION
1	Start of the marketing authorization procedure.
80	Receipt of assessment report from rapporteur and co-rapporteur and EMA send this assessment report to applicant as a preliminary conclusion.
100	Rapporteur, Co-Rapporteur other CHMP members and EMA receive comments from Members of the CHMP (incl. peer reviewers).
115	Receipt of draft list of questions from Rapporteur and Co-Rapporteur, as discussed with the peer reviewers, by CHMP members and EMA.
120	CHMP adopts the list of questions as well as the overall conclusions and review of the scientific data to be sent to the applicant by the EMA.
	CLOCK STOP (for Good Manufacturing Practice (GMP)/Good Laboratory Practice (GLP)/Good Clinical Practice (GCP) inspection)
121	Submission of the responses, including revised summary of product characteristics labeling and package leaflet texts in English, and restart of the clock.



In general the following standard timetable will apply:

DAY	ACTION
150	EMA sends joint Assessment Report to the applicant making it clear that it only their preliminary conclusions and that it is for information only.
170	Deadline for comments from CHMP Members to be sent to Rapporteur and Co-rapporteur, EMA and other CHMP Members.
180	CHMP discussion and decision on the need for adoption of a list of "outstanding issues" and/or an oral explanation by the applicant. If an oral explanation is needed, the clock is stopped to allow the applicant to prepare the oral explanation.
181	Restart the clock and oral explanation (if needed).
181 to 210	Final draft of summary of product characteristics, labeling and package leaflet in English sent by applicant to the rapporteur and Co-rapporteur, EMA and other CHMP members.

After adoption of a CHMP opinion, the preparation of the annexes to the Commission Decision is carried out in accordance with the following timetable:

DAY	ACTION
215 at the latest	Applicant provides the EMA with summary of product characteristics, labeling and package leaflet and Annex A in the 20 languages.
232 at the latest	Applicant provides EMA with final translations of summary of product characteristics, labeling and package leaflet in the 20 languages, taking account comments received from Member States by Day 229.
By 237	Transmission of Opinion and Annexes in all EU languages to applicant, Commission and Members of the Standing Committee, and Norway and Iceland.
By 246	Applicant provides EMA with one final full color 'worst-case' mock-up of outer and inner packaging for each pharmaceutical form.

Flow chart of centralized procedure

Insert Flow char for centralized procedure

2. MUTUAL RECOGNITION PROCEDURE

This procedure is use to obtain marketing authorization in more than one member state where the medicinal product is already authorized in any member state at the time of application.

After first marketing authorization of medicinal product approved by community, applicant may request for one or more member states marketing authorization. After getting first marketing authorization, it is easier to get for further member states because medicinal product is already exist in European market and it helps to prove that product is therapeutic effective.

Action following the submission of the application

- Reference Member State (RMS) prepares and updates assessment report
- Validation of the application by Concerned member states (CMS)
- Start of the 90-day period for approval by the concerned Member States
- Clarification and dialogue - Operating procedure
- Recognition of the marketing authorization (mutual recognition) and granting of national authorizations (10).

Mutual recognition procedure is as follows:

Approx. 90 days before sub. to CMS	Applicant requests RMS to update Assessment Report (AR) and allocate procedure number.
Day -14	Submission the dossier to CMSs and validation. RMS circulates the AR to CMSs.
Day 0	RMS starts the procedure
Day 50	Comments to the RMS and applicant by CMSs.
Day 60	Applicants response document to CMSs and RMS
Until Day 68	RMS send assessment of response document to CMSs.
Day 75	Remaining comments from CMSs to RMS and applicant. A break-out session can be organised between day 73 – 80).
Day 85	CMSs send any remaining comments to RMS and applicant.
Day 90	CMSs notify RMS and applicant of final position. If consensus is reached, the RMS closes the procedure and If not reached then the points for disapproval submitted by CMS(s) are referred to Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMD(h)) by the RMS within 7days
Day 150	For procedures referred to CMD(h): If consensus is reached at the level of CMD(h), procedure closed and if not reached then, RMS refers the matter to CHMP for arbitration
5 days after close of procedure	Applicant sends high quality national translations of SmPC, PL and labeling to CMSs and RMS.
30 days after close of procedure	Granting of national marketing authorizations in the CMSs.

Flow chart of the Mutual Recognition Procedure
Insert Flowchart for Mutual Recognition procedure

3. DECENTRALIZED PROCEDURE

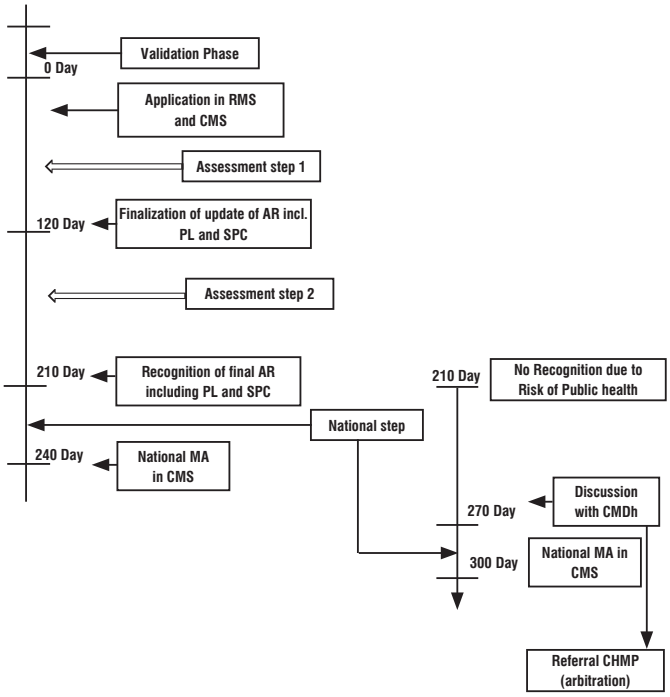
This procedure is used to obtain marketing authorization in more than one member state but at the time of application medicinal product should not be approved in any member state.

Decentralized procedure is consisting of majorly five steps;

1. Pre-procedural step
2. Assessment step I
3. Assessment step II
4. Discussion at coordinal group level
5. National marketing authorisation step (10).

Decentralized procedure is as follows:

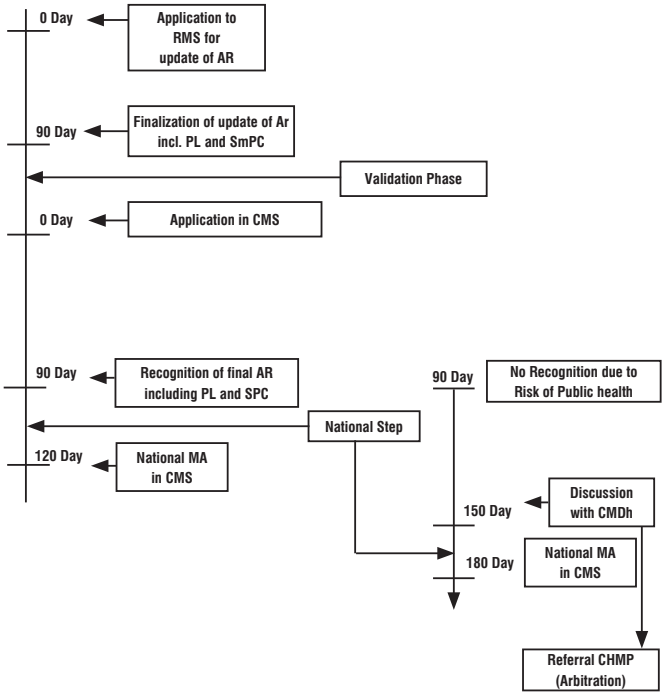
PRE-PROCEDURAL STEP I	
Before Day -14	Applicant discussions with RMS and RMS allocates procedure no.
Day –14	Submission of the dossier to the RMS and CMSs.
Assessment step I	
Day 0	RMS starts the procedure
Day 70	RMS forwards the Preliminary Assessment Report (PrAR) to CMSs
Until Day 100	CMSs send their comments to the RMS
Until Day 105	Consultation between RMS and CMSs and applicant. If consensus not reached RMS stops the clock and ask applicant to respond questions and supplementation to dossier.
Clock-off period	Applicant sends the response document to the RMS and CMSs within a recommended period of 3 months, which could be extended if justified.
Day 106	Valid submission of the response of the applicant received. RMS restarts the procedure.
Day 106 – 120	RMS updates PrAR to prepare Draft Assessment Report (DAR) draft SPC, draft labeling and draft PL to CMSs.
Day 120	If consensus reached procedure closed and start of national step.
ASSESSMENT STEP II	
Day 120 (Day 0)	If consensus not reached RMS sends the DAR, draft SPC, draft labeling and draft PL to CMSs
Day 145 (Day 25)	CMSs sends final comments to RMS
Day 150 (Day 30)	If consensus reached procedure closed.
Until 180 (Day 60)	If consensus is not reached by day 150, RMS to communicate with applicant and ask for additional information.
Until Day 205 (Day85)	Breakout Group of involved Member States reaches consensus on the matter.
Day 210 (Day 90)	Closure of the procedure.
Day 210 (at the latest)	If consensus was not reached at day 210, points of disagreement will be referred to the Co-ordination group for resolution.
Day 270 (at the latest)	Final decision by Co-ordination Group with referral to CHMP/CVMP for arbitration in case of unsolved disagreement.
NATIONAL STEP III	
Day 110/125/155/215/275	Applicant sends high quality national translations of SPC, labeling and PL to CMS and RMS.
Day 135/150/180/240	Granting of national marketing authorisation in RMS and CMSs if no referral to the Co-ordination group.
Day 300	Granting of national marketing authorisation in RMS and CMSs if positive conclusion by the Co-ordination group and no referral to the CHMP/ CVMP.



Flow chart of the Decentralized Procedure
Insert flowchart for decentralized procedure

4. NATIONAL PROCEDURE

If the applicant want to get the marketing authorization in only one member state then application should be made to national competent authority of respective member state where marketing authorization is sought. In this case while taking the national marketing approval, medicinal product should not be approved in other member state under same sponsor.



Approval for the marketing of product is taken directly from the respective member state authority hence sponsor will get approval faster than other procedures (5).

CONCLUSION

A medicinal product can be put in to the European market after getting the marketing authorization issued by the competent authority of member state or it is granted in accordance with Regulation (EC) No 726/2004 for entire community. Holder must follow respective regulation for development of the product and choose the correct procedure to get the marketing authorization for the medicinal product. To get the marketing authorization for medicinal product, holder must be established within the EEA.

PROCESS	USE	PROS	CONS
National Authorization	Individual application for each country.	If rejected still access to other country.	Separate appl. with requirements.
Decentralized Procedure	Product fall outside the scope of CP.	Simultaneous authorization, sponsor can select countries.	Negative decision may affect other countries.
Mutual Recognition Procedure	Individual application to each country + product fall outside scope of CP.	One application, Review by one country other accept same.	Requires time, Negative decision may affect other countries.
Centralized Procedure	Biotech. Products, advanced therapy, orphan drugs, biologic products.	Only one application, fast procedure.	Negative outcome affect access to entire EU.

Avrupa Birliği'nde ilaç ruhsatlandırma süreci

ÖZET

Avrupa Birliği'ne üye 27 ülkeden üçü Avrupa Ekonomik Alanı (European Economic Area, EEA) ve dördü Avrupa Serbest Ticaret Birliği'ne (European Free Trade Association, EFTA) de üyedir. EEA'da piyasada bulunmak isteyen bir firma tıbbi ürünü için pazarlama ruhsatı başvurusunda bulunmak istediğinde tüm üyeler arasında geçerli olan EC726/2004 numaralı mevzuata uymak zorundadır. Avrupa Birliği geniş bir nüfusu kapsamaktadır ve piyasada bulunan ilaçların güvenliliği ve halk sağlığına sonuçları konusunda ciddi yaklaşımlar mevcuttur. Bu makalede Avrupa Birliği'nde pazarlama ruhsatına başvuruda uygulanan prosedürdeki farklı uygulamalar tartışılmıştır.

ANAHTAR SÖZCÜKLER: Avrupa Ekonomik Alanı, İlaç ruhsatlandırması

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